# MATRIX-004

# Phase I Evaluation of the Impact of Vaginal Coitus on the Pharmacokinetics of Tenofovir Alafenamide and Elvitegravir Vaginal Insert

**MATRIX: A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women**

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**Protocol Co-Chair:**
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**Version 1.0**

**18 October 2024**

PEPFAR

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MATRIX
Advancing R&D of Innovative
HIV Prevention Products for Women

**MATRIX-004**

# Phase I Evaluation of the Impact of Vaginal Coitus on the Pharmacokinetics of Tenofovir Alafenamide and Elvitegravir Vaginal Insert

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## LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| ACRO | African Clinical Research Organisation |
| AE | Adverse event |
| AIDS | Acquired immunodeficiency syndrome |
| API | Active pharmaceutical ingredient |
| bNAb | Broadly neutralizing antibodies |
| BV | Bacterial vaginosis |
| BXV | Cervicovaginal biopsy |
| CAPRISA | Centre for the AIDS Programme of Research in South Africa |
| CBC | Complete blood count |
| CDC | Centers for Disease Control and Prevention (US) |
| CFR | Code of Federal Regulations |
| CLIA | Clinical Laboratory Improvement Act |
| CM | Concomitant medication |
| CRA | Clinical Research Associate |
| CRF | Case report form |
| CRM | Clinical Research Manager |
| CRS | Clinical research site |
| CT | *Chlamydia trachomatis* |
| CV | Cervicovaginal |
| CVF | Cervicovaginal fluid |
| CVL | Cervicovaginal lavage |
| CVT | Cervicovaginal tissue |
| DAIDS | Division of AIDS |
| DM | Data Manager |
| DoA | Delegation of Authorities |
| DRA | Drug regulatory authority |
| D2D | Design to Delivery |
| eCRF | Electronic case report form |
| EVG | Elvitegravir (Vitekta®) |
| FDA | U.S. Food and Drug Administration |

| | |
|---|---|
| FDC | Fixed dose combination |
| FTC | Emtricitabine (Emtriva®) |
| FWA | Federal-wide assurance |
| GC | *Neisseria gonorrhea* |
| GCP | Good Clinical Practice |
| GDP | Good Documentation Practice |
| GI | Gastrointestinal |
| GMP | Good Manufacturing Practice |
| HBsAg | Hepatitis B surface antigen |
| HIPAA | The Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| HSV | Herpes Simplex Virus |
| IB | Investigator's Brochure |
| ICH | International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use |
| IDI | In-depth interview |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IND | Investigational New Drug |
| INSTI | Integrase strand transfer inhibitor |
| IRB | Institutional Review Board |
| ISP | Independent Safety Physician |
| IUD | Intrauterine device |
| KOH | Saline/potassium hydroxide |
| KPPB | Kenya Pharmacy and Poisons Board |
| LDMS | Laboratory Data Management System |
| LTFU | Loss-to-follow-up |
| MPA | Multiple Project Assurance |
| NDA | New Drug Application |
| NIH | National Institutes of Health |
| NSAID | Nonsteroidal Anti-inflammatory Drug |
| NOAEL | *No-observed-adverse-effect-level* |
| PBMC | Peripheral blood mononuclear cells |
| PD | Pharmacodynamics |
| PEP | Post-exposure prophylaxis |
| PI | Principal Investigator |

| | |
|---|---|
| PK | Pharmacokinetics |
| PrEP | Pre-exposure prophylaxis |
| QA | Quality assurance |
| QC | Quality control |
| RTI | Reproductive tract infection |
| SAE | Serious adverse event |
| SAHPRA | South African Health Products Regulatory Authority |
| SAP | Statistical analysis plan |
| SEV | Study Exit Visit |
| SOP | Standard operating procedures |
| SSP | Study specific procedures |
| STI | Sexually transmitted infection |
| TAF | Tenofovir alafenamide (Vemlidy®) |
| TAM | Thymidine analog mutation |
| TDF | Tenofovir disoproxil fumarate (Viread®) |
| TEAE | Treatment-emergent adverse effect |
| TESAE | Treatment-emergent serious adverse effect |
| TFV | Tenofovir |
| TV | *Trichomonas vaginalis* |
| UPT | Urine pregnancy test |
| UTI | Urinary tract infection |
| VHS | Virginia Health Sciences |

**MATRIX-004**

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**MATRIX-004**

**Phase I Evaluation of the Impact of Vaginal Coitus on the Pharmacokinetics of Tenofovir Alafenamide and Elvitegravir Vaginal Insert**

## INVESTIGATOR SIGNATURE FORM

**Version 1.0; 18 October 2024**

**A Study of the Microbicide R&D to Advance HIV Prevention Technologies through Responsive Innovation and eXcellence (MATRIX) Collaborative**

**Funded by:**
US Agency for International Development (USAID)

**IND Sponsor:**
CONRAD

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); USAID regulations (22 CFR 200 and 22 CFR 225); applicable U.S. Food and Drug Administration (FDA) regulations; standards of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice Guidance (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., USAID) and institutional policies.

I agree to maintain all study documentation for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. CONRAD will inform the investigator/institution as to when these documents no longer need to be retained.

I have read and understand the information in this protocol and in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Investigator of Record (print)

_____ _____
Signature of Investigator of Record Date

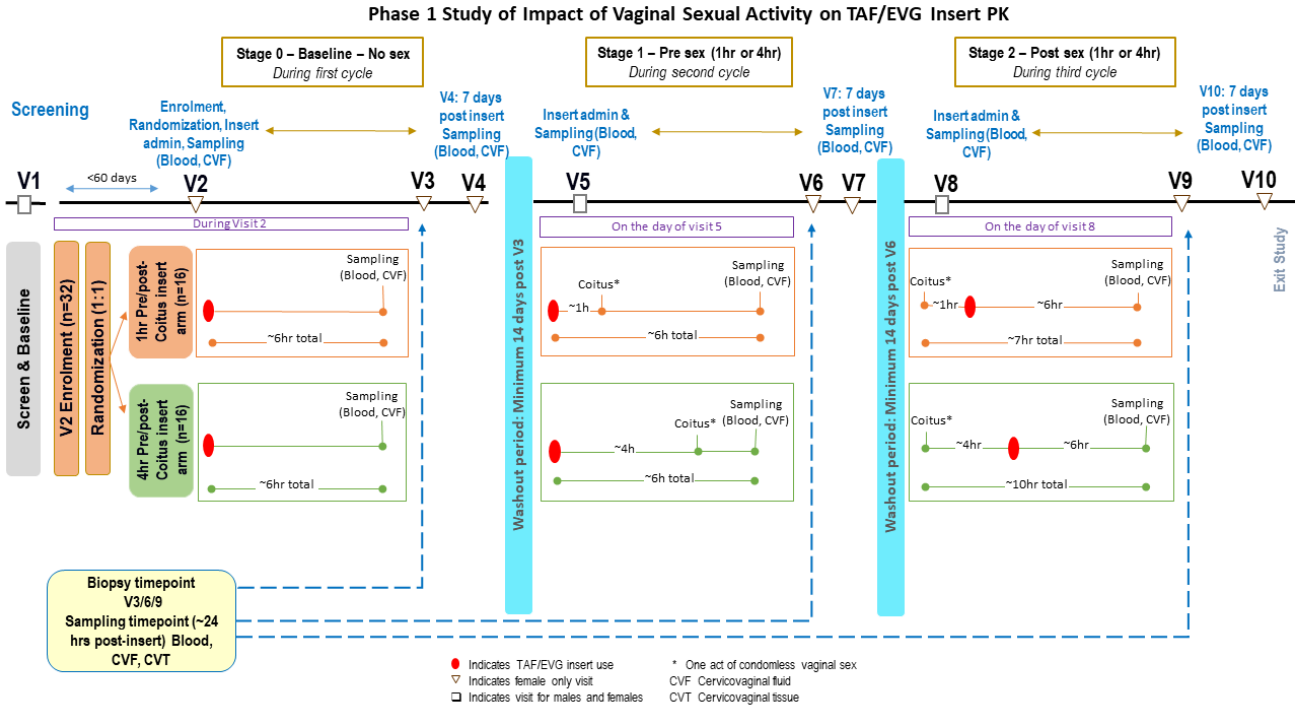
# MATRIX-004

## Phase I Evaluation of the Impact of Vaginal Coitus on the Pharmacokinetics of Tenofovir Alafenamide and Elvitegravir Vaginal Insert

## PROTOCOL SUMMARY

| | |
|---|---|
| **Short Title:** | Impact of Coitus on Tenofovir Alafenamide (TAF) and Elvitegravir (EVG) Vaginal Insert |
| **Clinical Phase:** | Phase 1 |
| **IND Sponsor:** | CONRAD |
| **Funders:** | USAID |
| **Protocol Co-Chair:** | Leila E. Mansoor, B.Pharm, PhD |
| **Protocol Co-Chair:** | Kent Melchiors, MD |
| **Sample Size:** | MATRIX-004 will enroll approximately 32 evaluable couples. |
| **Study Population:** | Healthy, sexually active, non-pregnant, HIV-uninfected adult couples at low risk for HIV acquisition and in a monogamous relationship |
| **Study Sites:** | Two sites:<br>Virginia Health Sciences (VHS) in the United States; and<br>Centre for the AIDS Programme of Research in South Africa (CAPRISA) eThekwini in South Africa |
| **Study Design:** | Phase 1 randomized study evaluating the impact of vaginal sexual intercourse (coitus) on the TAF/EVG insert when administered vaginally before and after coitus |
| **Study Duration:** | The total duration of the study will be approximately 10-12 months at each site. Accrual will occur over approximately 8-10 months, with approximately 8 weeks of follow-up per participant couple. |
| **Study Products:** | Vaginal insert containing TAF and EVG, 20/16 mg |
| **Study Regimen:** | Participants will be randomized 1:1 to vaginally administer the TAF/EVG insert either 1 hour or 4 hours before and after coitus. |

**Figure 1: Study Visit Schedule**




## Primary Objective:

### Pharmacokinetics (PK)

- To assess the impact of coitus on the PK of the TAF/EVG vaginal insert in the female genital tract

## Primary Endpoints:

### PK

- Concentrations of tenofovir (TFV), TAF and EVG in plasma after dosing
- Concentrations of TFV, TAF and EVG in cervicovaginal fluid (CVF) after dosing
- Concentrations of TFV, tenofovir diphosphate (TFV-DP), TAF and EVG in cervicovaginal tissue (CVT) after dosing
- Concentrations of TFV-DP in peripheral blood mononuclear cells (PBMC) after dosing

## Secondary Objectives:

### Acceptability

- To assess the acceptability of the TAF/EVG vaginal insert when used before and after coitus for female and male participants

### Safety

- To assess the safety of the TAF/EVG vaginal insert when used before and after coitus for female and male participants

**Secondary Endpoints:**

**Acceptability**

- Responses to key questions on overall experience (e.g., satisfaction, comfort) with using the TAF/EVG insert before and after coitus

**Safety**

- Any Grade 2 or higher treatment-emergent adverse event (TEAE)

**Exploratory Objectives:**

**Pharmacodynamics (PD)**

- To assess the impact of coitus on the PD of luminal drug by measuring anti-HIV activity in CVF sample

**Impact of coitus on TAF/EVG vaginal insert mucosal safety**

- To determine the impact of coitus on the female genital tract mucosa in the presence of the TAF/EVG vaginal insert

**Exploratory Endpoints:**

**PD**

- Anti-HIV activity in CVF obtained at baseline and after dosing

**Impact of coitus on TAF/EVG vaginal insert mucosal safety**

- Changes in mucosal microenvironment and histology (epithelial integrity and immune cell infiltrate)

# 1 KEY ROLES

## 1.1 Protocol Identification

| | |
|---|---|
| Protocol Title: | Phase I Evaluation of the Impact of Vaginal Coitus on the Pharmacokinetics of Tenofovir Alafenamide and Elvitegravir Vaginal Insert |
| Protocol Number: | MATRIX-004 |
| Short Title: | Impact of Coitus on TAF/EVG Vaginal Insert |
| Date: | 18 October 2024 |

## 1.2 Funding Agency, IND Sponsor and Monitor Identification

| | |
|---|---|
| Funding Agency: | USAID<br>Bureau of Global Health, Office of HIV/AIDS, Research Division<br>500 D Street Southwest<br>Washington, DC 20547 USA |
| IND Sponsor: | CONRAD<br>Virginia Health Sciences (VHS)<br>Old Dominion University<br>601 Colley Avenue<br>Norfolk, VA 23507 USA |
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# 2 INTRODUCTION

## 2.1 Background

Adolescent girls and young women (AGYW) bear the burden of the HIV-1 epidemic, with more than 59% of new infections occurring in women in sub-Saharan Africa (SSA).[1] The daily dosing requirement and systemic side effects, primarily gastrointestinal (GI), of oral pre-exposure prophylaxis (PrEP) have made it difficult, particularly for AGYW, to adhere to daily tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) for HIV-1 prevention.[2, 3]

Although long-acting PrEP regimens, such as injectables and implants, will likely improve adherence over daily pill ingestion, there is clear evidence that many individuals do not want to use continuous systemically administered products and want discreet, **on demand, user-controlled topical** products. In SSA, adolescents and young people desire and even prefer on-demand HIV prevention options.[4] Across multiple end-user studies a subset of women consistently indicate a preference for on-demand HIV and multipurpose prevention technologies (MPT) over daily use and even longer-acting products.[5, 6] Recent acceptability data from the contraceptive field, among AGYW in both high- and low-income countries, indicate that many prefer an on-demand, female controlled, peri-coital contraceptive,[7-12] rather than a daily regimen or even a long-acting product. In stakeholder consultations conducted in 2022 by the MATRIX Design to Delivery (D2D) Hub in Zimbabwe, Kenya, and South Africa, more than 80 percent of the respondents, mostly young women, similarly indicated their support for on-demand HIV prevention products of the kind MATRIX is developing. Specifically, more than 90% of the stakeholders in all three countries expressed support for the vaginal insert to be tested in MATRIX-001 and MATRIX-004.[13]

Topical inserts have the potential for increased adherence as they are easy to store and transport, discreet, and convenient and easy to use. Vaginal administration of HIV prevention products provides local absorption of drug, enhanced bioavailability, high concentration at portals of virus entry, decreased systemic side effects, and reduced dosing frequency, all of which would increase adherence and persistence.[14-18]

One advantage of the tenofovir alafenamide (TAF) and elvitegravir (EVG) vaginal insert is it can be used pericoitally. It is important to understand how condomless vaginal sexual intercourse affects the efficacy of the insert, as the timing of coitus with relation to dosing may affect the insert's pharmacokinetics (PK) and pharmacodynamics (PD), in addition to its acceptability. For example, TAF and/or EVG may be lost due to the mechanical action of sex or diluted in seminal fluid, altering the insert's efficacy. A previous study on the impact of sex on vaginal tenofovir (TFV) gel suggested that the timing of sex with respect to dosing had a significant reduction on TFV levels in the cervicovaginal tract.[19] Couples will be randomized to dose either 1 hour or 4 hours before and after vaginal sex and PK, PD, and mucosal safety will be assessed at specific time points (Stage 1 and 2). This will be compared to dosing without coitus in Stage 0 to help control for baseline factors in the absence of sex.

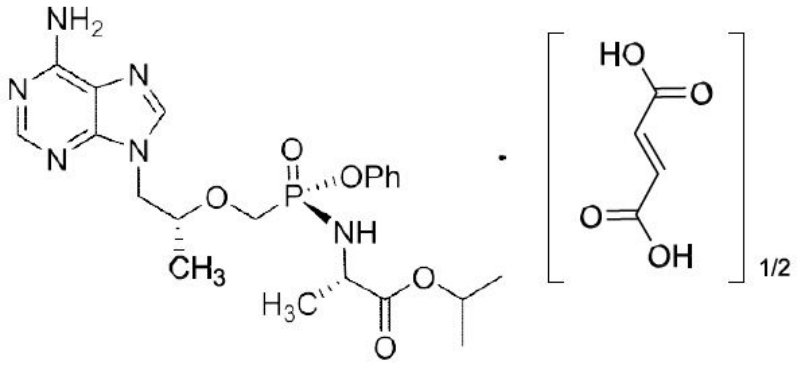
## 2.2 TAF/EVG Vaginal Insert

### 2.2.1 Description

Tenofovir alafenamide (TAF)

Tenofovir alafenamide (TAF) is a nucleotide reverse transcriptase inhibitor and a prodrug of tenofovir. TAF is converted *in vivo* to tenofovir (TFV), an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate, which in turn is converted to the active metabolite, TFV-diphosphate, intracellularly.[20]

The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*- [(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1- methylethyl ester, (2*E*)-2-butenedioate (2:1). It has an empirical formula of C21H29O5N6P•½(C4H4O4) and a formula weight of 534.50. It has the following structural formula:

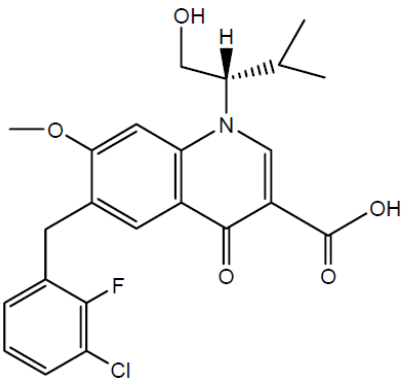



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.[20]

Elvitegravir (EVG)

Elvitegravir (EVG) is a 2nd generation human immunodeficiency virus (HIV) integrase inhibitor. EVG is a white crystalline irregularly shaped material and has an acidic pKa of 6.6 and Log D of 4.5 at pH 6.8. EVG is a poorly water soluble and highly permeable drug. It is considered a BCS class-2 compound. EVG (anhydrous crystalline form γ) is chemically stable in the solid state when exposed to heat, humidity and light.

The chemical name of EVG is (S)-6-(3-chloro-2-fluorobenzyl)-1-(1-hydroxy-3-methylbutan-2-yl)-7methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid. It has a molecular formula of $C_{23}H_{23}ClFNO_5$ and a molecular weight of 447.9 (free acid). It has the following structural formula:




EVG is a white to off-white crystalline powder with a solubility of > 35µg/mL in aqueous buffers at pH 9.0. EVG is stable for at least three years at 30°C.

### 2.2.2 Mechanism of Action

TAF

TAF is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate (TFV-DP). TFV-DP inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

TFV has activity that is specific to human immunodeficiency virus (HIV) and hepatitis B virus (HBV), and herpes simplex virus (HSV). Cell culture studies have shown that tenofovir can be fully phosphorylated when combined in cells. TFV-DP is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity in cell culture based on several assays including mitochondrial DNA analyses.[21]

EVG

EVG is an HIV-1 integrase strand transfer inhibitor (INSTI). Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, which happens around 8-11 hours after infection, blocking the formation of the HIV-1 provirus and propagation of the viral infection. EVG does not inhibit human topoisomerases I or II.[22]

### 2.2.3 Strength of Study Product

Tenofovir alafenamide and elvitegravir (TAF/EVG) inserts have been formulated to contain 20 mg of tenofovir alafenamide free base (equivalent to 22.40 mg tenofovir alafenamide fumarate salt form) and 16 mg of elvitegravir.

## 2.3 Non-Clinical Studies of TAF and EVG

### 2.3.1 Anti-HIV-1 Activity

TAF

The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), primary monocyte/macrophage cells and CD4-T lymphocytes. The EC50 values for TAF ranged from 2.0 to 14.7 nM. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC50 values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 ($EC_{50}$ values ranged from 0.91 to 2.63 nM).[21] TAF also inhibits HSV-2 clinical isolates such as KW strain with an EC50 of 424 nM.[23]

EVG

The antiviral activity of EVG against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cells, monocyte/macrophage cells, and primary peripheral blood lymphocytes. The 50% effective concentration ($EC_{50}$) values ranged from 0.02 to 1.7 nM. EVG displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O ($EC_{50}$ values ranged from 0.1 to 1.3 nM) and activity against HIV-2 ($EC_{50}$ value of 0.53 nM). The antiviral activity of EVG with antiretroviral drugs in two-drug combination studies was not antagonistic when combined with the INSTI raltegravir, NNRTIs (efavirenz, etravirine, or nevirapine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine), Pis (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir), the fusion inhibitor enfuvirtide, or the CCR5 co-receptor antagonist maraviroc. EVG did not show inhibition of replication of HBV or HCV in cell culture.[22]

The antiviral activity of EVG drug substance prepared at varying doses in suspension with insert formulation components was tested in a cervicovaginal tissue (CVT) explant model. Complete protection against HIV-$1_{BAL}$ infection was observed when EVG tissue concentrations were in the range of ~$10^3$-$10^4$ ng/g, whereas only partial protection was observed at ~$10^2$ ng/g. These data suggest that EVG tissue concentration of at least 1000 ng/g will be efficacious prophylactically against HIV infection of CVT and therefore were set as the target benchmark for drug development.[24]

### 2.3.2 Resistance (HIV)

HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.[21]

HIV-1 isolates with reduced susceptibility to EVG were selected in cell culture. Reduced susceptibility to EVG was associated with the primary integrase substitutions T66A/I, E92G/Q, S147G, and Q148R. Additional integrase substitutions observed in cell culture selection included D10E, S17N, H51Y, F121Y, S153F/Y, E157Q, D232N, R263K, and V281M.[22]

### 2.3.3 Cross-resistance (HIV)

TFV resistance substitutions, K65R and K70E, result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. HIV-1 with multiple thymidine analog mutations (TAM) (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R, showed reduced susceptibility to TAF in cell culture.[21]

EVG-resistant viruses showed varying degrees of cross-resistance in cell culture to raltegravir in the INSTI class depending on the type and number of substitutions in HIV-1 integrase.[22]

### 2.3.4 In Vitro Metabolism

TAF is reportedly hydrolyzed within cells to form TFV, which is phosphorylated to the active metabolite, TFV-DP. *In vitro,* TAF is reportedly metabolized to TFV by carboxylestrase 1 in hepatocytes, by cathepsin A in PBMCs and macrophages, with minimal metabolism via CYP3A.[25]

The metabolism of EVG is mediated primarily via intestinal and hepatic cytochrome P450 (CYP) 3A enzymes.[22]

### 2.3.5 Mutagenicity and Carcinogenesis

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice is observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times in mice and 4 times in rats relative to those observed in humans at the 300 mg therapeutic dose of TDF for HIV-1 infection. The TFV exposure in these studies was approximately 167 times in mice and 55 times in rats relative to those observed in humans after administration of Genvoya treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures 10 times (300 mg TDF) and 167 times (10 mg TAF in Genvoya) that in humans. In rats, the study was negative for carcinogenic findings.[21]

TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

EVG was not genotoxic in the reverse mutation bacterial test (Ames test) and the rat micronucleus assay. In an in vitro chromosomal aberration test, EVG was negative with metabolic activation; however, an equivocal response was observed without activation.[22] Long-term carcinogenicity studies of oral EVG were carried out in mice for 104 weeks and in rats for up to 88 weeks in males and 90 weeks in females. No drug-related increases in tumor incidence were found in mice at doses up to 2000 mg per kg per day alone or in combination with 25 mg per kg per day ritonavir at exposures 3- and 14-fold, respectively, the human systemic exposure at the recommended daily dose of 150 mg. No drug-related increases in tumor incidence were found in rats at doses up to 2000 mg per kg per day at exposures 12- to 27-fold, respectively, in male and female, the human systemic exposure.[22]

### 2.3.6 Pregnancy, Teratogenic Effects, and Lactation

Oral EVG studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with EVG during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures (AUC) at the embryo-fetal No Observed Adverse Effects Levels (NOAEL) in rats and rabbits were respectively 23 and 0.2 times higher than the exposure in humans at the recommended daily dose of 150 mg.[22] Studies in rats have demonstrated that EVG is secreted in milk.[22]

Oral TAF studies in animals have shown no adverse embryo-fetal effects at similar exposures in rats and approximately 53 times higher exposures in rabbits to those in the recommended daily dose for humans. Doses of up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 at exposures approximate 14 times higher than the exposures recommended for humans. Studies in rats and monkeys have demonstrated that TAF is secreted in milk. [21]

Prospective pregnancy data from the Antiretroviral Pregnancy Registry (APR) are not sufficient to adequately assess the risk of birth defects or miscarriage in humans. However EVG and TAF use during pregnancy have been evaluated in a limited number of individuals and available data show no statistically significant difference in the overall risk of major birth defects. [21]

### 2.3.7 Reproductive Toxicity

There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.[21]

Oral EVG did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures (AUC), respectively, than in humans at the therapeutic 150 mg daily dose. Fertility was normal in the offspring of rats exposed daily starting in utero and through sexual maturity at daily exposures (AUC) of approximately 18-fold higher than human exposures at the recommended 150 mg daily dose.[22]

## 2.4 Animal Studies of TAF/EVG Insert

### 2.4.1 Anti-HIV-1 Activity

Macaque efficacy studies performed in collaboration with the US Centers for Disease Control and Prevention (CDC) have demonstrated high protection of 90-100% conferred by TAF/EVG inserts against vaginal SHIV infection when administered as PrEP or post-exposure prophylaxis (PEP) 4h before or 4-8h after virus exposure.[26] PEP administration 24h after exposure showed >70% protection.

### 2.4.2 Pharmacokinetics

Macaque Study

CONRAD study 2708 evaluated the PK of TAF and EVG following administration of vaginal inserts containing a combination of TAF/EVG in female pigtailed macaques. Vaginal inserts containing 10/8 mg, 20/16 mg or 40/24 mg of TAF/EVG were administered to groups of 4 female macaques. One insert was administered vaginally to each macaque 5 times over an 8-week period with at least 1 week between doses. Animals were dosed on a single occasion at the 24h PK interval and on two separate occasions for both 2 and 4h PK intervals. Plasma was collected at 0.5 hours post-dose; plasma, vaginal fluid (VF) and vaginal tissue biopsy samples were collected at 2, 4, and 24 hours post-dose. These samples were analyzed for concentrations of TAF, TFV and EVG. Vaginal biopsies were also evaluated for TFV-DP concentrations. The TAF/EVG insert did not result in adverse behavioral changes, physical changes in the vaginal vault or measurable systemic exposure to TAF, TFV or EVG in the macaques.[25] There was minimal dose proportionality between inserts for VF or tissue concentrations. TFV and EVG in VF TAF/EVG (20/16 mg) showed the most favorable PK and resulted in TFV-DP and EVG tissue levels in range with those shown to provide in vivo protection against vaginal SHIV infection in macaques.[27]

Rabbit Study

CONRAD Study 1645-116 evaluated the PK of TAF/EVG following once daily intravaginal administration of TAF/EVG formulated drug substance in female NZW SPF rabbits for 14 consecutive days. 5/4, 15/12 or 25/20 mg TAF/EVG formulated drug substance were administered to 5 groups of 4 female rabbits. Mean Cmax and AUC0-24hr values for TFV appeared to increase with increasing dose in an approximately dose proportional manner across the dose range on Days 1 and 13. Mean TFV maximal concentrations (Cmax) were 264 ng/mL on Day 1 and 354 ng/mL following the highest dose of EVG/TAF (20/25 mg). Systemic exposure (AUC0-24hr) to EVG and TFV did not appear to consistently change following repeated administration of EVG in combination with TAF. TFV mean systemic exposure was 861 hr*ng/mL on Day 1 and 1400 hr*ng/mL following the highest dose of EVG/TAF (20/25 mg).

### 2.4.3 Toxicology

Vaginal Irritation Study in Rabbits

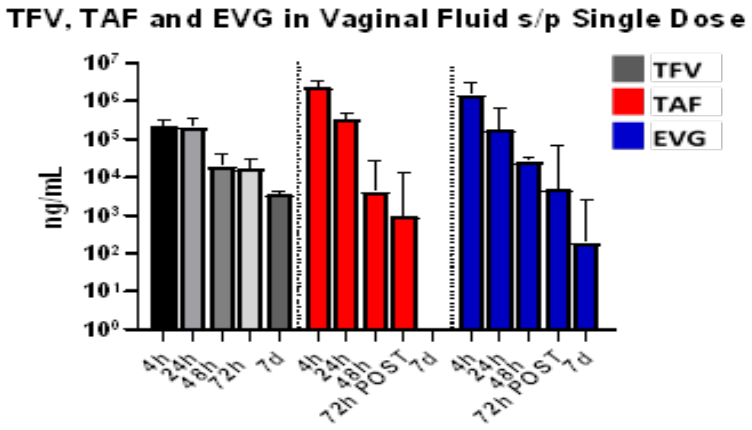
CONRAD Study 1645-116 evaluated potential local irritation and determined the PK following once daily intravaginal administration of EVG and TAF to female rabbits for 14 consecutive days. 24 female rabbits were randomized to 6 groups: vehicle control, placebo control, reference control (N-9), or 4/5, 12/15, or 20/25 mg EVG/TAF. The assessment of toxicity in this study was made based on mortality, clinical observations, body weights, vaginal irritation scoring, micro and macroscopic pathology of reproductive tissues. There were no adverse test article-related effects observed for the following parameters evaluated: bodyweights, clinical observations, vaginal irritation, macroscopic or microscopic pathology of reproductive tissues. Test article-related microscopic observations were present in the vagina and cervix at ≥12/15 mg EVG/TAF, however were not considered adverse due to the reduced severity in comparison with the reference control (Nonoxynol-9). Based upon the results, a no-observable-adverse-effect level (NOAEL) of 20 mg of EVG and 25 mg of TAF per animal administered daily for 14 days was established per the highest dose tested.

## 2.5 Clinical Studies of TAF/EVG Insert

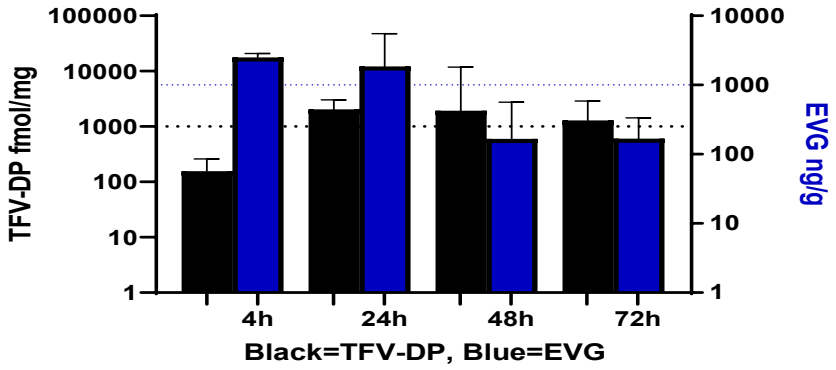
### 2.5.1 Pharmacokinetics

In the first-in-woman study (CONRAD 146),[28] 16 healthy, 18-50 year old, HIV-uninfected women in the US used one TAF/EVG (20/16mg) vaginal insert and were randomized (1:1) to sample collection time groups for up to 7 days post dosing. In Group 1, participants were randomized to have tissue sampling obtained at 4 and 48 hours versus 24 and 72 hours post insert use for Group 2. All participants had plasma, VF and vaginal tissue collected for PK of TAF, EVG, TFV and TFV-diphosphate (TFV-DP).

Systemic plasma exposure was low, consistent with topical delivery. Mucosal concentrations were high and prolonged, with mean and median TFV VF concentrations exceeding 200,000 ng/mL and 1,000 ng/mL for up to 24 hours and 7 days post dosing, respectively. All participants had vaginal tissue EVG concentrations of > 1 ng/mg at 4 and 24 hours post dosing. The majority had tissue TFV-DP concentrations exceeding 1000 fmol/mg by 24 – 72 hours post dosing.




**TFV-DP and EVG concentrations in CV tissue after single dose**




MATRIX-001, a phase I safety and PK study, is currently enrolling 60 healthy 18-50 year old women across 3 sites in Kenya, South Africa, and the US. Participants are randomized (1:1) to

apply a placebo or TAF/EVG insert vaginally for 3 consecutive days then every other day for 14 days. (ClinicalTrials.gov NCT06087913)

### 2.5.2 Safety

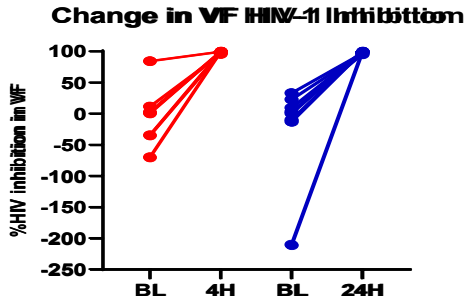
In CONRAD-146, a study conducted in the US, a single dose of TAF/EVG insert administered vaginally to 16 participants was safe and well-tolerated.[28] There were no product related treatment-emergent adverse events (TEAE). There were 8 TEAEs reported by 7 participants (43.8%). The most common TEAE was increased blood glucose, occurring in 3 (18.8%) participants overall. No other TEAE occurred in more than 1 participant. All TEAEs were mild, and none were related to study treatment. TEAEs considered related to genital biopsy procedure occurred in 2 (12.5%) participants overall. All events of increased blood glucose and events related to the genital biopsy procedure occurred in Group 1 (4-hour sample collection), with 3 (37.5%) and 2 (25.0%) respectively, and none occurred in Group 2 (24-hour sample collection). No treatment-emergent serious adverse effects (TESAE), deaths or TEAEs led to dose interruption, discontinuation of study treatment, or premature withdrawal from the study.

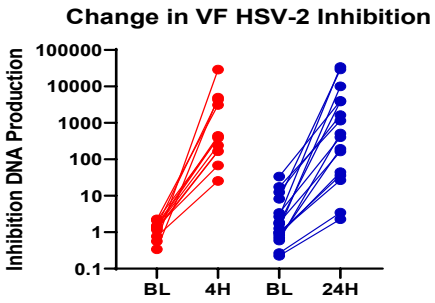
In CONRAD 134, an open-label study conducted in the US that assessed in-vivo disintegration time, safety, and product acceptability of 4 placebo vaginal inserts in 32 women aged 18-50 who were not at risk of pregnancy, placebo inserts were found to be safe, with one mild unrelated AE reported. The optimized insert prototypes were found to disintegrate faster and have higher acceptability over first generation inserts.[24, 29]

CONRAD 117, conducted in the US with 48 participants, was the first-in-human study of vaginal microbicide inserts using TFV and/or FTC containing vaginal inserts. TEAEs were minimal; only one TEAE met the pre-specified criterion for the safety endpoint, but this event was in the placebo group. Colposcopy and physical exam findings were minimal, as were changes in microflora and systemic laboratory values.[24]

### 2.5.3 Pharmacodynamic Assessment

In CONRAD 146, participants in Group 1 had their 4 hour ectocervical tissue biopsies assessed for in vitro p24 antigen production after ex vivo HIV-1BaL infection, while participants in Group 2 had their 24 hour post dosing ectocervical tissue assessed for HSV-2 DNA production after ex vivo HSV-2 infection. PD was then modeled in vitro by quantifying the change in inhibitory activity of VF and vaginal tissue against human immunodeficiency virus (HIV) and HSV-2 from baseline to after treatment. VF inhibition of HIV and HSV-2 *in vitro* significantly increased from baseline and was similarly high at 4 and 24 hours post dosing. Consistent with high tissue TFV-DP concentrations described above, p24 antigen production from ectocervical tissues infected ex vivo with HIV significantly decreased from baseline at 4 hours post dosing. HSV-2 production from tissue also decreased post treatment.




### 2.5.4 In Vivo Disintegration

In CONRAD 146, a single dose of TAF/EVG insert administered vaginally to 16 women was completely dissolved and absorbed into the mucosal tissues, with no remnants visible, for 12 (75%) participants at the earliest assessment (4 or 24 hours). For the remaining 4 participants, the insert was dissolved but there were small gel like areas of spreading observed. No participant had an intact vaginal insert at the first dissolution assessment.

### 2.5.5 Acceptability

In CONRAD 146, a single vaginal dose of the TAF/EVG insert was found to be acceptable overall. At baseline, most participants were very comfortable with inserting the product (13 [81.3%]), despite the fact that most had not previously used vaginal suppositories (12 [75.0%]). All participants expressed either no preference or liked how the insert looked (16 [100%]). Most participants were somewhat or very interested in using the product in the future if it protected against HIV-1 and HSV-2 (14 [87.5%]). At the post treatment visit, most participants found the insert very or somewhat acceptable in size (16 [100%]), ease of insertion (16 [100%]), comfort after insertion (15 [93.8%]), dissolvability (15 [93.8%]), residue (13 [81.3%]), leakage (14 [87.5%]), scent (15 [93.8%]), color (16 [100%]), and discreetness (15 [93.8%]). Just under half of participants overall (7 [43.8%]) reported that using an applicator would make insertion easier. Overall, participants generally were either unsure of the time it took for the insert to dissolve (7 [43.8%]) or reported less than 2 hours (7 [43.8%]). Seven participants overall noticed abnormal leakage/discharge either less than an hour (3 [18.8%]) or 1 to 4 hours after dosing (4 [25.0%]) by feeling it in their underwear (6 [37.5%]). All participants (16 [100%]) reported they thought it could be possible to use the insert without their partner's knowledge. Most participants (15 [93.8%]) reported not feeling anything once the insert was in the vagina.

## 2.6 Study Hypothesis and Rationale for Study Design

### 2.6.1 Primary Study Hypothesis

It is hypothesized that there will be no clinically significant change in PK endpoints from baseline when the TAF/EVG Insert, 20/16 mg, is administered vaginally by healthy, non-pregnant, HIV-uninfected adult women at low risk for HIV acquisition before and after vaginal sexual intercourse (coitus).

### 2.6.2 Rationale for Study Design

MATRIX-004 will examine the PK, PD, general and mucosal safety, and acceptability of inserts containing the combination of TAF and EVG applied vaginally, before and after coitus. The inserts are ultimately intended to be the basis of an event-driven, on-demand method for prevention of HIV sexual infection.

# 3 OBJECTIVES

## 3.1 Primary Objective

**Pharmacokinetics (PK)**

- To assess the impact of coitus on the PK of the TAF/EVG vaginal insert in the female genital tract

## 3.2 Secondary Objectives

**Acceptability**

- To assess the acceptability of the TAF/EVG vaginal insert when used before and after coitus for female and male participants

**Safety**

- To assess the safety of the TAF/EVG vaginal insert when used before and after coitus for female and male participants

## 3.3 Exploratory Objectives

**Pharmacodynamics (PD)**

- To assess the impact of coitus on the PD of luminal drug by measuring anti-HIV activity in cervicovaginal fluid (CVF) sample

**Impact of coitus on TAF/EVG vaginal insert mucosal safety**

- To determine the impact of coitus on the female genital tract mucosa in the presence of the TAF/EVG vaginal insert

# 4 STUDY DESIGN

## 4.1 Identification of Study Design

MATRIX-004 is a Phase 1 randomized study evaluating the impact of vaginal sexual intercourse (coitus) on the TAF/EVG insert when administered vaginally before and after coitus.

## 4.2 Summary of Major Endpoints

**Primary Endpoints:**

**PK**

- Concentrations of TFV, TAF and EVG in plasma after dosing
- Concentrations of TFV, TAF and EVG in CVF after dosing
- Concentrations of TFV, TFV-DP, TAF and EVG in CVT after dosing
- Concentrations of TFV-DP in PBMC after dosing

**Secondary Endpoints:**

**Acceptability**

- Responses to key questions on overall experience (e.g., satisfaction, comfort) with using the TAF/EVG insert before and after coitus

**Safety**

- Any Grade 2 or higher TEAE

**Exploratory Endpoints:**

**PD**

- Anti-HIV activity in CVF obtained at baseline and after dosing

**Impact of coitus on TAF/EVG vaginal insert mucosal safety**

- Changes in mucosal microenvironment and histology (epithelial integrity and immune cell infiltrate)

## 4.3 Description of Study Population

The study population will consist of healthy, sexually active, non-pregnant, HIV-uninfected adult couples at low risk for HIV acquisition and in a monogamous relationship who meet the criteria outlined in Section 5.2 and Section 5.3.

## 4.4 Time to Complete Accrual

The time to complete accrual at each site is anticipated to be approximately 8-10 months.

## 4.5 Study Groups

MATRIX-004 will enroll approximately 32 evaluable couples, randomized (1:1) to vaginally administer the TAF/EVG insert either 1 hour or 4 hours before and after coitus. See Section 10.6 for additional details.

### 4.6 Expected Duration of Participation

Once randomized to dosing either 1 hour or 4 hours before and after coitus, participants will complete approximately 8 weeks of follow-up. The total duration of the study will be approximately 10-12 months at each site.

### 4.7 Sites

The study will be conducted at two sites: VHS in the United States and CAPRISA eThekwini in South Africa.

## 5 STUDY POPULATION

### 5.1 Selection of the Study Population

The inclusion and exclusion criteria in Section 5.2 and Section 5.3 will be used to ensure the appropriate selection of study participants.

#### 5.1.1 Recruitment

Participants will be recruited from a variety of sources across sites including, but not limited to, existing databases (as permitted by local guidelines on protected health information [PHI]), outpatient clinics, universities, and community-based locations. Recruitment will focus on female participants, who would then discuss study participation with their male partner. Recruitment materials will be approved by site Institutional Review Boards/Independent Ethics Committees (IRB/IEC) prior to use per local requirements. Community education strategies, including group sessions, may be employed as part of participant/partner outreach.

#### 5.1.2 Retention

Once a couple is enrolled in MATRIX-004 (i.e., randomized to administer the TAF/EVG insert either 1 hour or 4 hours before and after coitus) study sites will make every effort to retain the participants in follow-up to minimize possible bias associated with loss-to-follow-up (LTFU). An average retention rate of 95% will be targeted across sites.

### 5.2 Inclusion Criteria

Couples must meet all the following criteria to be eligible for inclusion in the study. Unless otherwise specified, the following criteria must be determined prior to the couple's enrollment at Visit 2:

1) Per participant report, in a low risk, sexually active, cis-gender, heterosexual, monogamous relationship with the co-enrolling partner of the opposite sex for at least 6 months prior to Screening and intends to stay in this relationship during study participation. "Monogamous relationship" is defined as both persons being each other's exclusive sexual partner regardless of marital or cohabitation status.

2) Able and willing to have condomless vaginal sexual intercourse before and after intravaginal placement of TAF/EVG insert as instructed per protocol.

### 5.2.1 Females

Female participants must meet all the following criteria to be eligible for inclusion in the study. Unless otherwise specified, the following criteria must be determined prior to the couple's enrollment at Visit 2:

1) Between the ages of 18-50 years old (inclusive at Screening), verified per site standard operating procedures (SOP).

2) Able and willing to provide written informed consent to be screened for and enrolled in MATRIX-004 in one of the study languages, as specified in site SOPs.

3) Able and willing to provide adequate locator information, as defined in site SOPs.

4) General good health per participant history without any evidence of clinically significant systemic disease or reproductive tract disease as determined by Investigator of Record [IoR] or designee.

5) Agrees not to participate in other research studies involving drugs, medical devices, or genital products during study participation, or any other study that could preclude study participation in MATRIX-004 as determined by IoR or designee.

6) HIV-uninfected based on testing performed at Screening and at Enrollment, per protocol algorithm in Appendix III.

7) Per participant report, has had vaginal sex with potentially co-enrolled partner.

8) Has an intact uterus and cervix.

9) Participants over the age of 21 (inclusive) must have documentation of a Grade 0 Pap smear within the past 3 years prior to Enrollment, per the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 (Dated November 2007) to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, or Grade 1 Pap smear at Screening with no treatment required and with no previous history of dysplasia.

10) Currently using effective contraception other than a contraceptive vaginal ring (i.e., oral contraceptive, patch, injectable hormones, subdermal implants, intrauterine device [IUD], sterilization of female partner [e.g., tubal ligation] or male partner [e.g., vasectomy]) for at least six months prior to Screening and intending to use this method for the course of the study.

11) Has a regular and/or predictable bleeding pattern based on the opinion of the investigator, or amenorrhoeic for a minimum of 3 months.

12) Not taking reproductive hormones or gender affirming hormones for reasons other than contraception.

13) Negative urine pregnancy test at Screening and Enrollment.

14) Willing and able to comply with protocol requirements.

### 5.2.2 Males

Male participants must meet all the following criteria to be eligible for inclusion in the study. Unless otherwise specified, the following criteria must be determined prior to the couple's enrollment at Visit 2:

1) 18 years of age or older (inclusive at Screening), verified per site SOPs.

2) Able and willing to provide written informed consent to be screened for and enrolled in MATRIX-004 in one of the study languages, as specified in site SOPs.

3) Able and willing to provide adequate locator information, as defined in site SOPs.

4) General good health per participant history without any evidence of genital disease as determined by IoR or designee at Screening.

5) Agrees not to participate in other research studies involving drugs, medical devices, or genital products during study participation, or any other study that could preclude study participation in MATRIX-004 as determined by IoR or designee.

6) HIV-uninfected based on testing performed at Screening, per protocol algorithm in Appendix III.

7) Willing and able to comply with protocol requirements.

8) Per participant report, has had vaginal sex with potentially co-enrolled partner.

## 5.3 Exclusion Criteria

### 5.3.1 Females

Female participants must not meet any of the following criteria to be eligible for inclusion in the study. Unless otherwise specified, the following criteria must be determined prior to the couple's enrollment at Visit 2:

1) Positive HIV test at Screening or at Enrollment.

2) Participant report of any of the following:
    a. Post-exposure prophylaxis (PEP) for HIV exposure in the past 4 weeks.
    b. Oral PrEP for HIV prevention in the past 4 weeks.
    c. Injectable PrEP for HIV prevention in the past 12 months.
    d. Use of systemic or vaginal antimicrobials in the past 7 days.

3) Participant report of any of the following:
    a. Participation in any other research study or product introduction project involving drugs, medical devices, or genital products within 30 days of Enrollment.
    b. Plans to relocate away from the study site, or to travel away from the study site for a time period that would interfere with study participation.

4) Positive test for *Trichomonas vaginalis* (TV), *Neisseria gonorrhea* (GC), *Chlamydia trachomatis* (CT), *Treponema pallidum* (Syphilis), or Hepatitis B surface antigen (HBsAg) at Screening or (per participant report) treated for STI (diagnosed or suspected) in the past 12 months.

5) Previously received an HIV vaccine or HIV broadly neutralizing antibody (bNAb).

   *NOTE: Individuals may be eligible if they participated in an HIV vaccine or bNAb study but have documentation that they did not receive active product, e.g., placebo recipients.*

6) Per participant report, use of any of the following in the past 12 months: stimulants (cocaine [including crack], methamphetamine, or non-physician prescribed pharmaceutical-grade stimulants), or inhaled nitrates, or illicit injection drug use of any kind.

7) Has any other condition that, based on the opinion of the IoR or designee, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

8) Grade 2 or higher pelvic finding or laboratory abnormality, per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 1 (Female Genital Grading Tables for Use in Microbicide Studies [Dated November 2007]) or clinically significant laboratory abnormality as determined by the clinician.

9) Participant report or clinical finding of any of the following:
   a. Last pregnancy outcome ≤ 90 days prior to Enrollment.
   b. Intends to become pregnant during study participation.
   c. Currently pregnant.
      *NOTE: Self-reported pregnancy is adequate for exclusion from the study. A documented negative pregnancy test performed by study staff is required for inclusion.*
   d. Currently breastfeeding or intends to breastfeed during study participation.

10) Participant report or clinical finding of any of the following:
   a. Gynecologic or genital procedure, e.g., tubal ligation, dilation and curettage, within 30 days prior to Enrollment.
      *NOTE: This does not include biopsy for the evaluation of an abnormal pap result that occurred more than 14 days prior to Enrollment.*
   b. Currently using or planning to use systemic immune modulator(s) during study participation.
   c. History of sensitivity/allergy to any component of the study product, topical anesthetic, cellulose based thrombogenic material, or to both silver nitrate and Monsel's solution.
   d. Chronic or acute vulvar, vaginal or cervical symptoms (e.g., spotting/bleeding other than what would be expected from contraceptive use, pain, irritation, etc.).
   e. Known bleeding/clotting disorder.
   f. Use of anti-coagulants.
   g. Needing to use any contraindicated concomitant medications (as listed in Appendix IV) during study participation.

### 5.3.2 Males

Male participants must not meet any of the following criteria to be eligible for inclusion in the study. Unless otherwise specified, the following criteria must be determined prior to the couple's enrollment at Visit 2:

1) Positive HIV test at Screening.

2) Participant report of any of the following:
    a. Known allergy/sensitivity to the study product (ever).
    b. PEP for HIV exposure in the past 4 weeks.
    c. Oral PrEP for HIV prevention in the past 4 weeks.
    d. Injectable PrEP for HIV prevention in the past 12 months.

3) Participant report of any of the following:
    a. Participation in any other research study or product introduction project involving drugs, medical devices, or genital products within 30 days of Enrollment.
    b. Plans to relocate away from the study site, or to travel away from the study site for a time period that would interfere with study participation.

4) Positive test for TV, GC, CT, Syphilis, or HBsAg at Screening or (per participant report) treated for STI (diagnosed or suspected) in the past 12 months.

5) Previously received an HIV vaccine or HIV bNAb.

    *NOTE: Individuals may be eligible if they participated in an HIV vaccine or bNAb study but have documentation that they did not receive active product, e.g., placebo recipients.*

6) Per participant report, use of any of the following in the past 12 months: stimulants (cocaine [including crack], methamphetamine, or non-physician prescribed pharmaceutical-grade stimulants), or inhaled nitrates, or illicit injection drug use of any kind.

7) Has any other condition that, based on the opinion of the IoR or designee, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

8) Participant report or clinical finding of any of the following:
    a. Penile procedures (e.g. biopsy, circumcision) within 60 days of Enrollment.
    b. Prostatectomy or removal of seminal vesicles (ever).
    c. Chronic or acute genital symptoms (e.g., pain, irritation, discharge, etc.).
    d. Currently untreated erectile or ejaculatory dysfunction.

### 5.4 Co-enrollment Guidelines

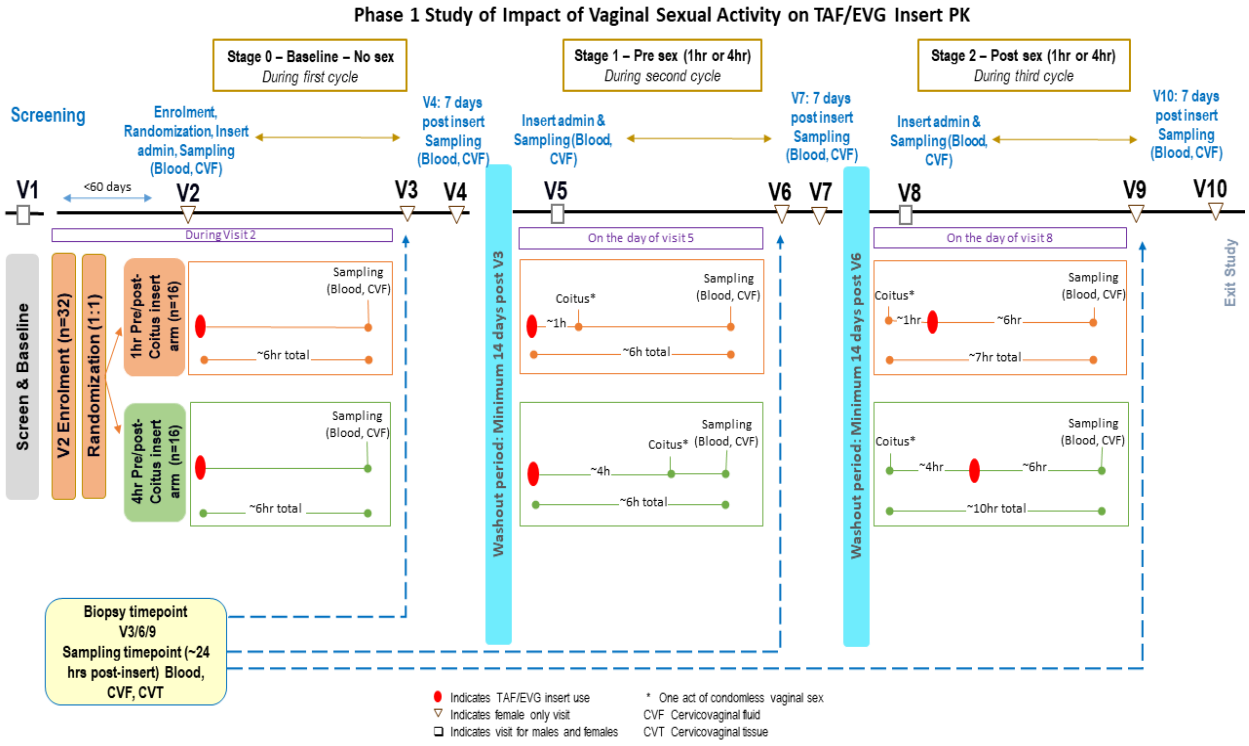
As indicated in Section 5.3, participants must not take part in other research studies involving drugs, medical devices, or genital products while taking part in MATRIX-004, or any other study that could preclude study participation in MATRIX-004 as determined by IoR or designee. Individuals may be eligible if they participated in an HIV vaccine or bNAb study but have documentation that they did not receive active product, e.g., placebo recipients. Should any participant report concurrent participation in contraindicated studies after enrolling in MATRIX-004, the IoR/designee will consult the Protocol Safety Review Team (PSRT) regarding ongoing product use and other potential safety considerations associated with co-enrollment.

# 6 STUDY PRODUCT

## 6.1 Regimen

The product being used in this study is the TAF/EVG Vaginal Insert 20/16 mg. Each insert for vaginal administration contains 20 mg tenofovir alafenamide (TAF) and 16 mg elvitegravir (EVG). At each of the study sites, couples will be randomized (1:1) to receive TAF/EVG vaginal insert either 1 hour or 4 hours before and after vaginal coital activity. Each female participant will self-administer 3 doses of vaginal insert during study participation. At IoR/designee discretion, each stage may be repeated once if the participant is unable to complete the stage as instructed in the protocol. This may include repeat dosing after a minimum 14-day washout period if the participant administers the insert but does not complete the stage.

**Figure 2: Study Product Regimen**




## 6.2 Administration

Each female participant will self-administer the vaginal insert approximately 6 hours prior to sample collection at Visits 2, 5 and 8. The vaginal insert(s) will be placed deep (approximately 4-5 cm) in the vagina.

Participants will self-administer the vaginal insert at the clinic at Visit 2. Participants may self-administer the vaginal insert at the clinic at Visit 5 or outside the clinic prior to Visit 5, i.e., approximately one or four hours before coitus depending on randomization. Participants may self-

administer the vaginal insert at the clinic at Visit 8 or outside the clinic prior to Visit 8, i.e., approximately one or four hours after coitus depending on randomization.

### 6.2.1 TAF/EVG Vaginal Insert

| | |
|---|---|
| Product Name: | Combination vaginal insert containing tenofovir alafenamide (TAF) and elvitegravir (EVG) |
| Dosage Form: | Vaginal Insert |
| Unit Dose: | 20 mg/16 mg (TAF/EVG) |
| Route of Administration: | Intravaginal |
| Physical Description: | White to off-white uncoated bullet shaped inserts |
| Manufacturer: | Patheon Pharma Services (part of Thermo Fisher Scientific, Whitby, ON, Canada |

## 6.3 Study Product Formulation and Storage

Inserts will be packaged in 50 cc, round, white, high-density polyethylene (HDPE) bottles with a child-resistant closure and aluminum, induction-sealed foil liner. Each bottle will contain 20 vaginal inserts and be labeled as per local requirements. Study product will be dispensed for the number of inserts needed for each stage.

Study products should be stored in white induction-sealed HDPE bottle along with polyester coil and a desiccant at room temperature (15° - 30°C) (59° - 86°F) in a locked cabinet or secure area in the clinic prior to dispensing. Consideration should always be given to measures that minimize contact during handling, preparation, and disposal procedures.

### 6.3.1 TAF/EVG Vaginal Insert

The product being used in this study is the TAF/EVG Vaginal Insert 20/16 mg. Each insert for vaginal administration contains 20 mg tenofovir alafenamide (TAF) and 16 mg elvitegravir (EVG). TAF is a nucleotide reverse transcriptase inhibitor (NRTI) and a prodrug of tenofovir and EVG is an integrase inhibitor. Both of the active pharmaceutical ingredients (APIs) are supplied by Gilead Sciences, Inc.

In addition to the APIs, the insert contains the following inactive excipients: Povidone, magnesium stearate, Polaxomer (also known as Kolliphor), polyethylene glycol, mannitol, and lactose anhydrous. The insert dimensions are: length: 1.5 cm, width: 0.7 cm, height: 0.6 cm. Each insert is approximately 500 mg in weight. The insert formulation is manufactured under current Good Manufacturing Practice (cGMP) at Patheon Pharma Services (part of Thermo Fisher Scientific), Whitby, ON, Canada.

## 6.4 Supply and Accountability

CONRAD will oversee the manufacture and analysis/release (Patheon Pharma Services (part of Thermo Fisher Scientific), Whitby, ON, Canada) of the study product under current Good Manufacturing Practices (cGMP).

### 6.4.1 Study Product Supply

The site will manage the distribution of the study product according to Section 6 of the protocol. The site will be provided with sufficient study product for its designated number of participants. Supplies will be distributed by CONRAD or CONRAD designee.

### 6.4.2 Study Product Dispensing

TAF/EVG Inserts will be dispensed to clinic staff on behalf of the participant or directly to the participant, upon receipt of a written prescription from an authorized prescriber. An authorized prescriber includes the IoR or a licensed clinician(s) directly responsible to the IoR as noted on the Form FDA 1572 and the Delegation of Authorities (DoA) Log.

### 6.4.3 Study Product Accountability

Each CRS Pharmacist of Record (PoR) is required to maintain a complete record of all TAF/EVG inserts received and subsequently dispensed. All unused TAF/EVG inserts must be returned to the IND Sponsor, CONRAD, after the study is completed or terminated unless otherwise instructed by the IND Sponsor.

### 6.4.4 Retrieval of Unused Study Products

All undispensed study product remaining at the end of the study will be recorded by the site and reconciled by the study monitor(s). After reconciliation, the sponsor will provide instruction regarding disposal, storage, or return of product.

## 6.5 Concomitant Medications

All concomitant medications used within 7 days of Screening will be recorded on CRFs for participants starting at Screening. Participants may use acetaminophen (paracetamol) on an as-needed basis during the study. Concomitant medications include all prescription medications, over-the-counter preparations, vitamins, nutritional supplements, recreational drugs, and herbal preparations.

## 6.6 Prohibited Medications, Products and Practices

### 6.6.1 Prohibited Medications and Products

Participants should not use the prohibited medications and products as listed in Appendix IV during the study unless instructed by a clinician in which case they should inform study staff.

### 6.6.2 Prohibited Practices

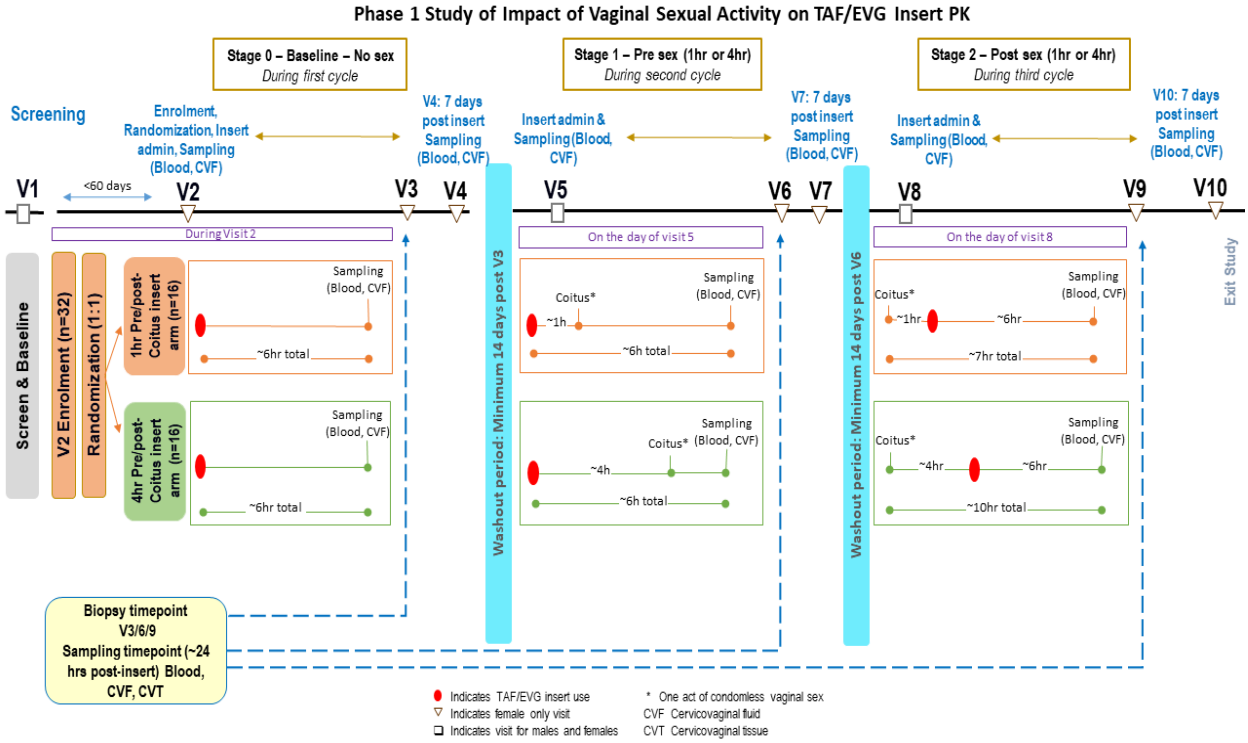
Female participants will be asked to abstain from receptive oral, anal, or vaginal intercourse and other vaginal practices (e.g., masturbation, douching, tampon use, application of lubricants/spermicides or other related practices) 48 hours prior to and after dosing, except for vaginal intercourse when required by protocol, and for at least 10 days after biopsy.

Male participants will be asked to abstain from insertive oral, anal or vaginal intercourse (including with fingers and toys) 48 hours prior to and after dosing, except for vaginal intercourse when required by protocol, and for at least 10 days after the female participant has a biopsy.

# 7 STUDY PROCEDURES

An overview of the study visits and evaluations schedule is provided in Appendix I and Appendix II. Presented in this section is additional information on visit-specific study procedures. Visit procedures may be conducted by phone or (with participant consent) off-site if deemed appropriate by the IoR/designee. Any study procedures, including laboratory tests, can be repeated as clinically indicated. Detailed instructions to guide and standardize procedures across sites as well as to specify the visit windows are provided in the MATRIX-004 Study Specific Procedures (SSP) Manual.

**Figure 3: Study Visit Schedule**




## 7.1 Pre-screening

As part of participant outreach and recruitment strategies, study staff may pre-screen potential study participants in person or over the phone. During these interactions, study staff may explain the study to potential participants and ascertain elements of presumptive eligibility, to be confirmed at an on-site screening visit. Potential participants invited for screening visits may be advised to bring identity documentation and the required locator information. Additionally, they

will be asked to bring documentation of a normal Pap test within 3 years prior to enrollment if available. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at the study site in the absence of written informed consent from potential participants (waivers of consent and HIPAA authorization are for pre-screening purposes only). Procedures and documentation will comply with local IRB/IEC requirements. Sites will be responsible for defining pre-screening procedures in their SOPs prior to initiation.

## 7.2 Screening Visit – Visit 1

Female and male participants will each provide separate written informed consent for screening and enrollment prior to any data collection procedures. Eligibility determination (for female and male participants) will be assessed at Visit 1 and (for female participants) be confirmed at Visit 2. Self-reported elements of eligibility for male participants may be confirmed by phone prior to or during Visit 2, if needed. For female participants, the Screening Visit will include baseline medical history, physical and pelvic examinations, urine pregnancy test (UPT), HIV/STI screening, blood baseline safety tests, and behavioral assessments. For male participants, it will include baseline medical history, directed physical examination (including genital inspection), HIV/STI screening, blood baseline safety tests, and behavioral assessments. Menstruating participants will be scheduled after menstrual flow ceases. Note that if a participant(s) is not able to complete or needs to repeat any of the study procedures conducted at this visit (e.g., blood draw), they may return prior to Visit 2. Labs may be repeated during the screening window per IoR/designee discretion.

*Note: Couples will ideally complete their Screening Visit together. However, if needed and at the discretion of the site IoR/designee, the Screening Visit may be conducted on separate days for the female and male participant to accommodate the participants' schedules.*

*Note: Couples who fail their first screening attempt may be re-screened once at the discretion of the site IoR/designee.*

**Table 1: Screening Visit – Visit 1 – Female Participants**

| **Screening Visit – Visit 1 – Female Participants** | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Informed consent process<br>• Assess eligibility<br>• Assign a unique Participant Identification (PTID) number<br>• Collect locator information<br>• Provide reimbursement<br>• Schedule next visit/contact, if indicated |
| **Behavioral/Counseling** | • Protocol requirements counseling per Section 6.6 and Section 7.10<br>• Pre- and post-test HIV counseling, and risk reduction counselling<br>• Collect demographic information<br>• Baseline behavioral and acceptability questionnaires |

| Screening Visit – Visit 1 – Female Participants | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Clinical** | | • Collect medical history<br>• Collect menstrual history<br>• Assess concomitant medications (CM)<br>• Pelvic (with bimanual) exam<br>• Full physical exam<br>• Vital signs, weight and height<br>• Provide available test results |
| **Laboratory** | **Saliva** | ○ HIV rapid test(s) (only at sites with CLIA certification) |
| | **Urine** | ○ Pregnancy test<br>○ Urine dipstick/urinalysis |
| | **Blood** | ○ HIV rapid test(s) (not required if conducting saliva testing)<br>○ HIV RNA test(s) (not required for sites that conduct saliva testing)<br>○ HBsAg<br>○ Syphilis<br>○ Complete blood count (CBC) with platelets<br>○ Chemistries |
| | **Genital** | ○ TV, GC, CT testing<br>○ Pap smear, if indicated<br>○ Saline/potassium hydroxide (KOH) wet mount for candidiasis and/or bacterial vaginosis (BV), if indicated |

## Table 2: Screening Visit – Visit 1 – Male Participants

| Screening Visit – Visit 1 – Male Participants | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Informed consent process<br>• Assess eligibility<br>• Assign a unique Participant Identification (PTID) number<br>• Collect locator information<br>• Provide reimbursement<br>• Schedule next visit/contact, if indicated |
| **Behavioral/Counseling** | | • Protocol requirements counseling per Section 6.6 and Section 7.10<br>• Pre- and post-test HIV counseling, and risk reduction counselling<br>• Collect demographic information<br>• Baseline behavioral and acceptability questionnaires |
| **Clinical** | | • Collect medical history<br>• Assess concomitant medications (CM)<br>• Directed physical exam, including genital inspection<br>• Vital signs, weight and height<br>• Provide available test results |
| **Laboratory** | **Saliva** | ○ HIV rapid test(s) (only at sites with CLIA certification) |
| | **Urine** | ○ Urine dipstick/urinalysis<br>○ TV, GC, CT testing |
| | **Blood** | ○ HIV rapid test(s) (not required if conducting saliva testing)<br>○ HIV RNA test(s) (not required for sites that conduct saliva testing)<br>○ HBsAg<br>○ Syphilis<br>○ CBC with platelets<br>○ Chemistries |

## 7.3 Stage 0 Visits – Baseline (no sex)

### 7.3.1 Enrollment Visit – Visit 2

Female participants only should be scheduled for the Enrollment Visit within 60 days of Screening/Visit 1 and (if applicable) after their menstrual flow ceases. Female participants will return to the clinic where they will have HIV and pregnancy testing and, provided the HIV and pregnancy test results are negative, couples will then be enrolled and randomized 1:1 to vaginally administer the TAF/EVG insert either 1 hour or 4 hours before and after coitus. Female participants will undergo sample collection of blood for PK and CVF for PK, PD and microbiota, self-administer the TAF/EVG vaginal insert in the clinic (should not coincide with menses or vaginal bleeding), complete a behavioral and acceptability questionnaire, and approximately 6 hours after dosing without coitus will undergo sample collection of blood for PK and CVF for PK and PD.

**Table 3: Enrollment Visit – Visit 2**

| **Enrollment Visit – Visit 2** | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Confirm participation<br>• Confirm eligibility<br>• Conduct randomization (after eligibility confirmation)<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact, if indicated |
| **Behavioral/Counseling** | | • Follow-up 1 (FU1) behavioral and acceptability questionnaire<br>• Protocol requirements counseling per Section 6.6 and Section 7.10<br>• Pre- and post-test HIV counseling, and risk reduction counselling |
| **Clinical** | | • Review/update medical and menstrual history<br>• Assess adverse events (AE) post product use<br>• Assess CM<br>• Pelvic exam<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Laboratory** | **Saliva** | ○ HIV rapid test(s) (only at sites with CLIA certification) |
| | **Urine** | ○ Pregnancy test<br>○ Urine dipstick/urinalysis, if indicated |
| | **Blood** | ○ HIV rapid test(s) (not required if conducting saliva testing)<br>○ HIV RNA test(s) (not required for sites that conduct saliva testing)<br>○ Plasma archive<br>○ Plasma for PK (pre-dose and 6 hrs post-dose)<br>○ PBMC for TFV-DP (pre-dose) |
| | **Genital** | ○ PSA test for semen (pre-dose)<br>○ Vaginal pH (pre-dose)<br>○ Vaginal swab(s) for microbiota (pre-dose)<br>○ Vaginal Gram stain (pre-dose)<br>○ CVF for PK and PD (pre-dose and 6 hrs post-dose)<br>○ TV, GC, CT testing, if indicated<br>○ Saline/KOH wet mount for candidiasis and/or BV, if indicated |
| **Study Product/Supplies** | | • Self-insertion of 1st dose |

### 7.3.2 Post-dose Biopsy Visit – Visit 3

Female participants only will return to the clinic approximately 24 hours after V2 dosing to undergo sample collection of blood for PK, CVT for PK and immunohistochemistry (IHC), and CVF for PK, PD and microbiota.

**Table 4: Post-dose Biopsy Visit – Visit 3**

| **Post-dose Biopsy Visit – Visit 3** | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Confirm participation<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | | • Protocol requirements counseling per Section 6.6 and Section 7.10 |
| **Clinical** | | • Review/update medical and menstrual history<br>• Assess AEs and CM<br>• Pelvic exam<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Laboratory** | **Urine** | ○ Pregnancy test, if indicated<br>○ Urine dipstick/urinalysis, if indicated |
| | **Blood** | ○ Plasma for PK<br>○ PBMC for TFV-DP |
| | **Genital** | ○ PSA test for semen<br>○ Vaginal pH<br>○ Vaginal swab(s) for microbiota<br>○ Vaginal Gram stain<br>○ CVF for PK and PD<br>○ Cervicovaginal biopsies (BXV) for PK<br>○ BXV for IHC<br>○ TV, GC, CT testing, if indicated<br>○ Saline/KOH wet mount for candidiasis and/or BV, if indicated |

### 7.3.3 1-week Post-dose Visit – Visit 4

Female participants only will return to the clinic approximately 7 days after V2 dosing to undergo sample collection of blood for PK and CVF for PK, PD and microbiota.

**Table 5: 1-week Post-dose Visit – Visit 4**

| **1-week Post-dose Visit – Visit 4** | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Confirm participation<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | • Protocol requirements counseling per Section 6.6 and Section 7.10 |

| 1-week Post-dose Visit – Visit 4 | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Clinical** | | • Review/update medical and menstrual history<br>• Assess AEs and CM<br>• Pelvic exam<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Laboratory** | **Urine** | ○ Pregnancy test, if indicated<br>○ Urine dipstick/urinalysis, if indicated |
| | **Blood** | ○ Plasma for PK<br>○ PBMC for TFV-DP |
| | **Genital** | ○ PSA test for semen<br>○ Vaginal pH<br>○ Vaginal swab(s) for microbiota<br>○ Vaginal Gram stain<br>○ CVF for PK and PD<br>○ TV, GC, CT testing, if indicated<br>○ Saline/KOH wet mount for candidiasis and/or BV, if indicated |

## 7.4 Stage 1 Visits – Pre sex

### 7.4.1 Second Dosing Visit – Visit 5

Female and male participants will return to the clinic after a washout period of a minimum of 14 days following V3. Visit 5 should not coincide with menses or vaginal bleeding.

For couples randomized to use the insert 1 hour before and after coitus, female participants will self-administer the TAF/EVG vaginal insert approximately 1 hour prior to coitus and will record both the time of insertion and the time of coitus. The insert may be dispensed at the clinic prior to the scheduled visit and may be self-administered outside the clinic. The couple will return to the clinic and the female participant will undergo sample collection of blood for PK and CVF for PK and PD approximately 6 hours after dosing. Female and male participants will each complete questionnaires after coitus and ideally before sample collection.

For couples randomized to use the insert 4 hours before and after coitus, female participants will self-administer the vaginal insert approximately 4 hours prior to coitus and will record both the time of insertion and the time of coitus. The insert may be dispensed at the clinic prior to the scheduled visit and may be self-administered outside the clinic. The couple will return to the clinic and the female participant will undergo sample collection of blood for PK and CVF for PK and PD approximately 6 hours after dosing. Female and male participants will each complete questionnaires after coitus and ideally before sample collection.

At IoR/designee discretion, the stage may be repeated once if the participant is unable to complete the stage as instructed in the protocol. This may include repeat dosing after a minimum 14-day washout period if the participant administers the insert but does not complete the stage.

## Table 6: Second Dosing Visit – Visit 5 – Female Participants

| Second Dosing Visit – Visit 5 – Female Participants | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Confirm participation<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact, if indicated |
| **Behavioral/Counseling** | | • Follow-up 2 (FU2) behavioral and acceptability questionnaires<br>• Protocol requirements counseling per Section 6.6 and Section 7.10<br>• Pre- and post-test HIV counseling, and risk reduction counselling |
| **Clinical** | | • Review/update medical history<br>• Review/update menstrual history<br>• Assess AEs and CM<br>• Pelvic exam<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Laboratory** | **Saliva** | ○ HIV rapid test(s) (only at sites with CLIA certification) |
| | **Urine** | ○ Pregnancy test<br>○ Urine dipstick/urinalysis, if indicated |
| | **Blood** | ○ HIV rapid test(s) (not required if conducting saliva testing)<br>○ Plasma for PK (6hrs post dose) |
| | **Genital** | ○ PSA test for semen<br>○ Vaginal pH<br>○ CVF for PK and PD (6hrs post dose)<br>○ TV, GC, CT testing, if indicated<br>○ Saline/KOH wet mount for candidiasis and/or BV, if indicated |
| **Study Product/Supplies** | | • Self-insertion of 2nd dose (may occur outside clinic) |

## Table 7: Second Dosing Visit – Visit 5 – Male Participants

| Second Dosing Visit – Visit 5 – Male Participants | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Confirm participation<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact, if indicated |
| **Behavioral/Counseling** | | • Follow-up 2 (FU2) behavioral and acceptability questionnaires<br>• Protocol requirements counseling per Section 6.6 and Section 7.10<br>• Pre- and post-test HIV counseling, and risk reduction counselling |
| **Clinical** | | • Review/update medical history<br>• Assess AEs and CM<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Laboratory** | **Saliva** | ○ HIV rapid test(s) (only at sites with CLIA certification) |
| | **Urine** | ○ Urine dipstick/urinalysis, if indicated<br>○ TV, GC, CT testing, if indicated |
| | **Blood** | ○ HIV rapid test(s) (not required if conducting saliva testing) |

### 7.4.2 Post-dose Biopsy Visit – Visit 6

Female participants only will return to the clinic approximately 24 hours after V5 dosing to undergo sample collection of blood for PK, CVF for PK, PD and microbiota, and CVT for PK and IHC.

**Table 8: Post-dose Biopsy Visit**

| **Post-dose Biopsy Visit – Visit 6** | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Confirm participation<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | | • Protocol requirements counseling per Section 6.6 and Section 7.10 |
| **Clinical** | | • Review/update medical and menstrual history<br>• Assess AEs and CM<br>• Pelvic exam<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Laboratory** | **Urine** | ○ Pregnancy test, if indicated<br>○ Urine dipstick/urinalysis, if indicated |
| | **Blood** | ○ Plasma for PK<br>○ PBMC for TFV-DP |
| | **Genital** | ○ PSA test for semen<br>○ Vaginal pH<br>○ Vaginal swab(s) for microbiota<br>○ Vaginal Gram stain<br>○ CVF for PK and PD<br>○ BXV for PK<br>○ BXV for IHC<br>○ TV, GC, CT testing, if indicated<br>○ Saline/KOH wet mount for candidiasis and/or BV, if indicated |

### 7.4.3 1-week Post-dose Visit – Visit 7

Female participants only will return to the clinic approximately 7 days after V5 dosing to undergo sample collection of blood for PK and CVF for PK, PD and microbiota.

**Table 9: 1-week Post-dose Visit**

| **1-week Post-dose Visit – Visit 7** | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Confirm participation<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | • Protocol requirements counseling per Section 6.6 and Section 7.10 |

| 1-week Post-dose Visit – Visit 7 | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Clinical** | | • Review/update medical and menstrual history<br>• Assess AEs and CM<br>• Pelvic exam<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Laboratory** | **Urine** | ○ Pregnancy test, if indicated<br>○ Urine dipstick/urinalysis, if indicated |
| | **Blood** | ○ Plasma for PK<br>○ PBMC for TFV-DP |
| | **Genital** | ○ PSA test for semen<br>○ Vaginal pH<br>○ Vaginal swab(s) for microbiota<br>○ Vaginal Gram stain<br>○ CVF for PK and PD<br>○ TV, GC, CT testing, if indicated<br>○ Saline/KOH wet mount for candidiasis and/or BV, if indicated |

## 7.5 Stage 2 Visits – Post sex

### 7.5.1 Third Dosing Visit – Visit 8

Female and male participants will return to the clinic after a washout period of a minimum of 14 days following V6. Visit 8 should not coincide with menses or vaginal bleeding. This visit constitutes the male participants' Study Exit Visit (SEV), unless selected for an IDI. The IDI may be conducted at any point between completion of Visits 8 and 10 and is not required to align with a scheduled study visit. See Section 7.5.4 and Section 7.9 for more details about the IDIs.

For couples randomized to use the insert 1 hour before and after coitus, female participants will self-administer the TAF/EVG vaginal insert approximately 1 hour after coitus and will record both the time of insertion and the time of coitus. The insert may be dispensed at the clinic prior to the scheduled visit and may be self-administered outside the clinic. The couple will return to the clinic and the female participant will undergo sample collection of blood for PK and CVF for PK and PD approximately 6 hours after dosing. Female and male participants will each complete questionnaires after coitus and ideally before sample collection.

For couples randomized to use the insert 4 hours before and after coitus, female participants will self-administer the vaginal insert approximately 4 hours after coitus and will record both the time of insertion and the time of coitus. The insert may be dispensed at the clinic prior to the scheduled visit and may be self-administered outside the clinic. The couple will return to the clinic and the female participant will undergo sample collection of blood for PK and CVF for PK and PD approximately 6 hours after dosing. Female and male participants will each complete questionnaires after coitus and ideally before sample collection.

At IoR/designee discretion, the stage may be repeated once if the participant is unable to complete the stage as instructed in the protocol. This may include repeat dosing after a minimum 14-day washout period if the participant administers the insert but does not complete the stage.

## Table 10: Third Dosing Visit – Visit 8 – Female Participants

| Third Dosing Visit – Visit 8 – Female Participants | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Confirm participation<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact, if indicated |
| **Behavioral/Counseling** | | • Follow-up 2 (FU2) behavioral and acceptability questionnaires<br>• Protocol requirements counseling per Section 6.6 and Section 7.10<br>• Pre- and post-test HIV counseling, and risk reduction counselling |
| **Clinical** | | • Review/update medical history<br>• Review/update menstrual history<br>• Assess AEs and CM<br>• Pelvic exam<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Laboratory** | **Saliva** | ○ HIV rapid test(s) (only at sites with CLIA certification) |
| | **Urine** | ○ Pregnancy test<br>○ Urine dipstick/urinalysis, if indicated |
| | **Blood** | ○ HIV rapid test(s) (not required if conducting saliva testing)<br>○ Plasma for PK (6hrs post dose) |
| | **Genital** | ○ PSA test for semen<br>○ Vaginal pH<br>○ CVF for PK and PD (6hrs post dose)<br>○ TV, GC, CT testing, if indicated<br>○ Saline/KOH wet mount for candidiasis and/or BV, if indicated |
| **Study Product/Supplies** | | • Self-insertion of 3rd dose (may occur outside clinic) |

## Table 11: Third Dosing Visit – Visit 8 – Male Participants

| Third Dosing Visit – Visit 8 – Male Participants | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact, if indicated |
| **Behavioral/Counseling** | | • Follow-up 2 (FU2) behavioral and acceptability questionnaires<br>• Protocol requirements counseling per Section 6.6 and Section 7.10<br>• Pre- and post-test HIV counseling, and risk reduction counselling |
| **Clinical** | | • Review/update medical history<br>• Assess AEs and CM<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Laboratory** | **Saliva** | ○ HIV rapid test(s) (only at sites with CLIA certification) |
| | **Urine** | ○ Urine dipstick/urinalysis, if indicated<br>○ TV, GC, CT testing, if indicated |
| | **Blood** | ○ HIV rapid test(s) (not required if conducting saliva testing)<br>○ CBC with platelets<br>○ Chemistries |

### 7.5.2 Post-dose Biopsy Visit – Visit 9

Female participants only will return to the clinic approximately 24 hours after V8 dosing to undergo sample collection of blood for PK, CVF for PK, PD and microbiota, and CVT for PK and IHC.

**Table 12: Post-dose Biopsy Visit**

| **Post-dose Biopsy Visit – Visit 9** | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Confirm participation<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | | • Protocol requirements counseling per Section 6.6 and Section 7.10 |
| **Clinical** | | • Review/update medical and menstrual history<br>• Assess AEs and CM<br>• Pelvic exam<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Laboratory** | **Urine** | ○ Pregnancy test, if indicated<br>○ Urine dipstick/urinalysis, if indicated |
| | **Blood** | ○ Plasma for PK<br>○ PBMC for TFV-DP |
| | **Genital** | ○ PSA test for semen<br>○ Vaginal pH<br>○ Vaginal swab(s) for microbiota<br>○ Vaginal Gram stain<br>○ CVF for PK and PD<br>○ BXV for PK<br>○ BXV for IHC<br>○ TV, GC, CT testing, if indicated<br>○ Saline/KOH wet mount for candidiasis and/or BV, if indicated |

### 7.5.3 Study Exit Visit – Visit 10

Female participants only will return to the clinic approximately 7 days after V8 dosing to undergo sample collection of blood for PK and CVF for PK, PD and microbiota. This visit constitutes the female participants' SEV.

**Table 13: Study Exit Visit**

| **Study Exit Visit – Visit 10** | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Review/update locator information<br>• Provide reimbursement |

| Study Exit Visit – Visit 10 | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Clinical** | | • Review/update medical and menstrual history<br>• Assess AEs and CM<br>• Pelvic exam<br>• Directed physical examination, if indicated<br>• Vital signs and weight<br>• Provide available test results |
| **Behavioral/Counseling** | | • Pre- and post-test HIV counseling, and risk reduction counselling |
| **Laboratory** | **Saliva** | ○ HIV rapid test(s) (only at sites with CLIA certification) |
| | **Urine** | ○ Pregnancy test, if indicated<br>○ Urine dipstick/urinalysis, if indicated |
| | **Blood** | ○ HIV rapid test(s) (not required if conducting saliva testing)<br>○ Plasma for PK<br>○ PBMC for TFV-DP<br>○ CBC with platelets<br>○ Chemistries |
| | **Genital** | ○ PSA test for semen<br>○ Vaginal pH<br>○ Vaginal swab(s) for microbiota<br>○ Vaginal Gram stain<br>○ CVF for PK and PD<br>○ TV, GC, CT testing, if indicated<br>○ Saline/KOH wet mount for candidiasis and/or BV, if indicated |

### 7.5.4 Participant In-depth Interview (IDI) Visit

A subset of male and female participants will be invited to participate in an IDI at any point between completion of visit 8 and visit 10. If they agree, study staff will schedule an IDI visit that may align with the date of the third dosing visit (V8), female participants' SEV (V10), or any point in between. Female and male participants will have the option of completing up to one IDI each as individuals or completing one IDI together as a couple.

**Table 14: Participant IDI Visit**

| IDI Visit | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Confirm participation<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact (as needed) |
| **Behavioral/Counseling** | • IDI |

## 7.6 Follow-up Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product

### 7.6.1 Participants Who Become Infected with HIV

Potential participants who test positive for HIV prior to eligibility confirmation will be excluded from participating in the study. If a participant (female or male) tests positive for HIV after eligibility confirmation, the participant will be referred to local care and treatment services and

may return to the research clinic for additional counseling and other support services, as needed. Continued study participation would be of no added benefit and thus follow-up visits will be discontinued for both participants, study product use will cease for the female participant, and the participant couple will be considered terminated from the study. Participants who become infected after eligibility confirmation will be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), if clinically indicated per discussions between IoR/designee and MATRIX. Please reference the MATRIX-004 SSP Manual for additional details (www.matrix4prevention.org).

### 7.6.2 Participants Who Become Pregnant

Participants must be protected from pregnancy as described in Section 5.2.1. A pregnancy test will be performed at clinic visits per Appendix I. A pregnancy test will be done at other visits, if indicated. If pregnancy is confirmed, the female participant will be referred for antenatal care and discontinued from use of study product (if initiated) and the participant couple will be considered terminated from the study. Every reasonable effort will be made to follow the pregnancy to outcome and to collect information on the infant(s) up to approximately one year after delivery for those pregnancies that result in live birth. Pregnancy outcomes will be reported on relevant CRFs. See Section 9.5 for more details.

Any pregnancy that occurs while a participant is taking study drug product will be recorded in the Antiretroviral Pregnancy Registry (APR) online at http://www.apregistry.com/. The Investigator must register the pregnancy within fifteen (15) calendar days of first becoming aware of the pregnancy and maintained through to pregnancy outcome. A copy of the report will be provided to the sponsor and reported to the IRB/IEC, as needed, in accordance with local requirements.

### 7.6.3 Participants Who Temporarily Hold or Permanently Discontinue Study Product Use

If a participant (female or male) experiences a clinically significant AE where short-term resolution is possible, the female participant may have study product held temporarily per IoR/designee discretion. Both participants will continue their scheduled follow-up visits and have all protocol-specified study procedures for the current dosing stage unless the IoR/designee determines that collection of samples would not be anticipated to yield analyzable data. The PSRT may be consulted if necessary; see Note below for more details.

Ideally, participants will complete the current dosing stage as described in the protocol and the temporary product hold will resolve prior to the start of the next dosing stage. If it is determined that participants are unable to complete the current dosing stage, the stage may be repeated after a minimum 14-day washout period (if participant already administered the insert) and upon resolution of the AE which prompted the temporary product hold. Provision of vaginal insert, product use instructions, and product use adherence counseling will be withheld from their next scheduled dosing visit if the AE does not resolve prior to dosing, and per IoR/designee discretion, the start of the next dosing stage may be postponed until the AE resolves. The PSRT may be consulted if necessary; see Note below for more details.

Participants who permanently discontinue study product use for any clinician-initiated reason other than HIV infection or pregnancy will discontinue study follow-up visits and procedures.

Participants will, however, be asked to complete all the procedures scheduled to occur at their respective SEV (Visit 8 for males, Visit 10 for females), if willing. Every effort will be made to bring both participants for a final visit.

*Note: If the male partner is discontinued from the study after coitus during stage 1 or 2, the female partner may continue the remaining follow-up visits for that stage, if willing. Refer to the MATRIX-004 SSP Manual for additional details.*

Participants who permanently discontinue study product use due to a product-related AE must continue to be followed in the study, if they are willing, until resolution (return to baseline) or stabilization of the AE is documented, per clinical discretion. See Section 8.3.1 for more details regarding follow-up of product-related AEs leading to permanently discontinuation.

*Note: The MATRIX-004 Management Team, in consultation with CONRAD, may provide guidance to the site regarding a modified study visit schedule to ensure PK samples are collected at the appropriate time points and/or omitted if the collection of samples would not be anticipated to yield analyzable data. Participants' duration of use and timing of study product hold/permanent discontinuation will be factored into a modified schedule. Refer to the MATRIX-004 SSP Manual for additional details.*

## 7.7 Interim Visits/Contacts

Interim visits may be performed at participant(s) request or as deemed necessary by the investigator at any time during the study, including to conduct point-of-care testing or dispense study product prior to Visits 5 and 8. Male and female participants will be instructed to contact the site at any time during the study if they experience moderate to severe urogenital symptoms (e.g., genital burning, irritation, stinging, pressure, rash, itching, discharge, urgency, dysuria, or hematuria). Female participants will be instructed to contact the site if they experience pelvic/lower abdominal pain or moderate to heavy menstrual bleeding (more than she would have during a normal period). The participant(s) will be asked to come in for an evaluation, as indicated.

Interim visits or procedures (e.g., pregnancy test, physical and/or pelvic examination, blood laboratory assessments, urine dipstick, microscopy, culture, STI testing, wet prep, and/or pH) may be performed as deemed necessary by the investigator. The participant(s) will be asked to come in for an evaluation, as indicated. Interim visits after baseline sampling that require examination or interview due to symptoms will be recorded on CRFs.

When an interim visit occurs in response to an AE experienced by a participant(s), study staff will assess the reported event clinically and provide treatment or refer the participant(s) to appropriate medical care, as necessary. All AEs will be evaluated and follow-up of any observed abnormalities will proceed according to Section 8.3.

## 7.8 Final Contact

Since participants' SEV (i.e., Visit 8 for males, Visit 10 for females) may include laboratory testing for HIV and STI/RTI, additional contacts after their respective SEV may be required to provide them additional study test results, and post-test counseling, if needed. In addition, for participants

who become pregnant during study participation, additional contacts may be required to ascertain the participant's pregnancy and infant outcome (see Section 7.6.2 for details). Study sites may complete these contacts by phone, at the study clinic or at community-based locations, depending on site capacities and site and participant preferences. All final contacts will be documented in participant study records.

## 7.9 Behavioral Evaluations

Participants will respond to interviewer- or self-administered questionnaires at Screening, Enrollment, Visit 5, and Visit 8. Questionnaire data will be complemented by data captured through IDIs (as a standalone visit) with a subset of participants after completing product use. Participants will have the option of completing the IDI individually or as a couple. The content of the behavioral evaluations is informed by a recent systematic review of the Theoretical Framework of Acceptability (Sekhon)[30], published by Ortblad et al.,[31] and an extensive review of socio-behavioral and acceptability assessments in clinical trials research.

Additionally, select CRS staff at each MATRIX-004 site (which are also study sites for MATRIX-001, a study of the same product) will be invited to complete an IDI to further understand their experiences providing the fast-dissolving insert to participants in a clinical setting.

### 7.9.1 Quantitative Behavioral Assessments

Behavioral questionnaires at enrollment and during follow-up will measure key dimensions of acceptability pertinent to the vaginal insert in its current phase of development alongside female and male participant's experiences in using the vaginal insert during the study. Questions will draw on multiple acceptability domains (e.g., affective attitude, usability, and self-efficacy), and other factors that may be correlated with vaginal insert acceptability and user experiences.

### 7.9.2 Qualitative Behavioral Assessments

Participant IDIs will be conducted with a subset of participants (6-10 female and 6-10 male participants per site) who will be selected and invited after completing at least Stage 1 of the study. The IDI will take place after V8 and before being terminated from the study. Selection of couples to invite for individual or couples IDI will be purposive so that timing of use relative to coitus, study site, and a breadth of perspectives and experiences are represented. Selection criteria and procedures are further described in the MATRIX-004 SSP Manual.

We will explore participant experiences using the vaginal insert, acceptability of different attributes of the insert, impacts on sex, views of any side effects experienced, and social factors influential to attitudes toward the vaginal insert as a future HIV prevention option.

IDIs will be conducted with participants jointly (as a couple) or separately, based on site discretion and/or participant preferences. IDIs will include, but not be limited to, the following topics:

- Views of vaginal insert use before and after coitus (including timing of insertion prior to/post coitus).
- Descriptions of any changes experienced by either partner during coitus.

- Other factors (e.g., situational, relationship, trial-specific, social/cultural/economic, sex and menstruation related, vaginal practices,) influencing vaginal insert acceptability and use experience.
- Perspectives and attitudes regarding on-demand vaginal insert use for HIV prevention.

IDIs will also be conducted with purposively selected CRS staff at each MATRIX-004 site (4-8 CRS staff total) with the goal of understanding their experiences with the study product in this study and its predecessor (MATRIX-001). Between approximately 4 and 8 CRS staff across the 2 study sites will be invited to take part in a single IDI after more than half of the couples have completed all study visits at their respective site and before their site closes the study with its IRB/IEC. Members of the protocol team and site leadership will collaboratively determine which CRS staff would be appropriate to invite for an IDI. Information will be collected about experiences with the FDI in clinical trial settings, and staff's understanding of participant experiences and perceptions of the products used in MATRIX-001 and/or MATRIX-004. These IDIs could provide early information about hands-on provider experiences with the study product, their training needs, preferences, their perspectives on how those products compare to current and future offerings, and thoughts about how these products might integrate into future implementation, roll-out, and choice counseling.

Semi-structured IDI guides will be developed by qualified social scientists and administered by trained interviewers. Guides will contain key research questions relating to the main topics of interest and suggested probes. Interviews and discussion sessions will be audio-recorded and transcribed. They are anticipated to last approximately 60-90 minutes. The interview notes, recordings and transcripts from the IDIs will be considered as source documentation. The IDIs may be conducted in-person or remotely over a secure digital platform.

## 7.10 Protocol and Product Adherence Counseling

Contraception counseling will be provided to participants of childbearing potential at all visits beginning at the Screening Visit. HIV/STI risk reduction counseling will be provided to participants at all visits when HIV testing is conducted, beginning at the Screening Visit. Protocol adherence counseling will be provided at all visits beginning at the Screening Visit. Participants will have the option of having counseling individually or as a couple. Counseling will be provided by different site staff than those conducting the behavioral assessments in accordance with standard study methods and as specified in site SOPs.

Counseling also will include reminders regarding concomitant medication, sexual activity (including timing of coitus in relation to product use and that protocol-required coitus is defined as one act of condomless vaginal sexual intercourse), intravaginal product use and practices, and behavioral restrictions during study participation. Female participants will be asked to abstain from vaginal, oral and anal sexual activity, douching, and use of all intravaginal objects and products as specified in Section 6.6.2.

## 7.11 Clinical Evaluations and Procedures

**Medical History and Physical Examination**

A comprehensive medical history for all participants will be taken at screening, followed by a directed history at all visits they attend thereafter. Participants will be asked about

medications/therapies at every visit they attend, including Visit 1. A full physical examination for female participants and a directed physical examination including genital inspection for male participants will be conducted at screening and will include general appearance and evaluation of body systems as outlined in the MATRIX-004 SSP Manual. A directed physical exam for female participants will be conducted at the enrollment visit and, as clinically indicated, for all participants at all follow-up visits they attend to assess any complaints or symptoms. In addition, vital signs and weight will be checked for all participants at all visits they attend. Height will be measured at screening only. Adverse events will be recorded for all participants at all visits they attend after the start of product use at Visit 2.

**Pelvic Examination**

Pelvic exams will be performed for female participants using visual inspection of external genitalia and using a speculum for examination of the cervix and vagina. Bimanual exam may be performed as needed (required at Screening Visit). Pelvic exams will be conducted at each visit for PK, PD and subclinical safety specimen collection and as indicated based on participant reports. CVF will be collected using swabs. Further specimen collection procedures will be detailed in the MATRIX-004 SSP Manual. Biopsy areas will be checked for healing at applicable visits and as indicated.

**Specimen Collection (CVT, CVF and Blood)**

CVT will be obtained at Visits 3, 6 and 9 to assess PK and IHC.

The study site should carefully record the date and time of each collection of blood, CVF, and CVT biopsies. The time of sampling will be based on the time the first sample is taken (when multiple sample types are being collected at a time point, all samples should be collected within a short period). Samples collected outside the sampling windows below will be considered a protocol deviation:

- ± 1 hour outside of the 6-hour post-dose time point at V2, V5 and V8
- ± 4 hours outside of the 24-hour post-dose time point at V3, V6 and V9
- ± 2 days outside of the 7-day post-dose time point at V4, V7 and V10

*Note: Detailed information regarding the genital examination, as well as the associated procedures required for collecting specimens at each visit, can be found in the MATRIX-004 SSP Manual.*

Additional clinical assessments/procedures may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam/procedure.

## 7.12 Laboratory Evaluations

Local Laboratory – Females

- Saliva (only at sites with CLIA certification)
  - HIV rapid test(s)

- Urine
  - Pregnancy
  - Urine dipstick, with microscopy and culture (microscopy and culture done per local standard of care)

- Blood
    - HIV rapid test(s) (not required if conducting saliva testing)
    - HIV RNA test(s) (not required for sites that conduct saliva testing)
    - For anyone with a positive blood or saliva HIV rapid result, HIV confirmatory testing as needed
    - HBsAg
    - Syphilis serology
    - CBC with platelets
    - Chemistries

- Genital
    - NAAT for GC/CT/TV
    - PSA test for semen
    - Pap smear (if indicated)
    - Gram stain for Nugent score
    - Vaginal pH
    - Saline/KOH wet mount for candidiasis and/or BV (if indicated)

<u>Local Laboratory – Males</u>

- Saliva (only at sites with CLIA certification)
    - HIV rapid test(s)

- Urine
    - Urine dipstick, with microscopy and culture (microscopy and culture done per local standard of care)
    - NAAT for GC/CT/TV

- Blood
    - HIV rapid test(s) (not required if conducting saliva testing)
    - HIV RNA test(s) (not required for sites that conduct saliva testing)
    - For anyone with a positive blood or saliva HIV rapid result, HIV confirmatory testing as needed
    - HBsAg
    - Syphilis serology
    - CBC with platelets
    - Chemistries

<u>Designated Laboratory(ies) – Females only</u>

- Blood
    - Plasma for archive
    - Plasma for PK for TFV, TAF, EVG
    - PBMC for TFV-DP

- CVF
    - CVF for PD – anti-HIV
    - CVF for PK for TFV, TAF, EVG
    - Vaginal swab(s) for microbiota

- CVT
    - BXV for PK for TFV, TFV-DP, TAF, EVG
    - BXV for IHC

Only Local Laboratory test results will be provided to the participant, except for test results collected solely for research purposes, i.e., PSA and Nugent score. Once all required study analyses of collected specimens are complete, any remaining samples may be shipped to the Sponsor for use in study-related quality assurance and quality control testing. Once all study-related quality assurance and quality control testing is complete, all remaining samples will be destroyed upon Sponsor approval; this could be 5-10 years after completion of the study.

## 7.13 Pharmacokinetics (PK) and Pharmacodynamics (PD)

**Table 15: Specimens Collected to Assess Safety, PK and Ex Vivo Antiviral Activity**

| Study Visit | Specimens collected for PK, PD and subclinical safety – Females only | | |
|---|---|---|---|
| | Blood | CVF | CVT |
| Visit 2 | • Plasma for PK (pre-dose & 6hr post-dose)<br>• PBMC for TFV-DP (pre-dose) | • CVF for PK (pre-dose & 6hr post-dose)<br>• CVF for PD (pre-dose & 6hr post-dose) | |
| Visit 3 | • Plasma for PK<br>• PBMC for TFV-DP | • CVF for PK<br>• CVF for PD | • 2 BXV for PK<br>• 1 BXV for IHC |
| Visit 4 | • Plasma for PK<br>• PBMC for TFV-DP | • CVF for PK<br>• CVF for PD | |
| Visits 5 (6hr post-dose) | • Plasma for PK | • CVF for PK<br>• CVF for PD | |
| Visit 6 | • Plasma for PK<br>• PBMC for TFV-DP | • CVF for PK<br>• CVF for PD | • 2 BXV for PK<br>• 1 BXV for IHC |
| Visit 7 | • Plasma for PK<br>• PBMC for TFV-DP | • CVF for PK<br>• CVF for PD | |
| Visit 8 (6hr post-dose) | • Plasma for PK | • CVF for PK<br>• CVF for PD | |
| Visit 9 | • Plasma for PK<br>• PBMC for TFV-DP | • CVF for PK<br>• CVF for PD | • 2 BXV for PK<br>• 1 BXV for IHC |
| Visit 10 | • Plasma for PK<br>• PBMC for TFV-DP | • CVF for PK<br>• CVF for PD | |

## 7.14 Specimen Management

Study sites will adhere to the standards of good clinical laboratory practice, in accordance with the MATRIX-004 SSP Manual and site-specific SOPs for proper collection, processing, labeling,

transport, and storage of specimens. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, or out of range and the site IoR/designee determines that it is reasonable to repeat, the site is permitted to re-draw specimens. No genetic testing (limited or genome-wide) is planned on leftover samples.

### 7.15 Laboratory Oversight

All laboratories participating in this study will adhere to MATRIX's Laboratory Policy (www.matrix4prevention.org).

### 7.16 Biohazard Containment

As the acquisition of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC, National Institutes of Health (NIH), and all other applicable national regulatory authorities. All biological specimens will be transported using packaging mandated by Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

## 8 ASSESSMENT OF SAFETY

### 8.1 Safety Monitoring

Site IoRs/designees are responsible for continuous close safety monitoring of all study participants, and for alerting the Management Team and/or PSRT if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Co-Chairs, Protocol Safety Physician, Clinical Research Manager(s) (CRM), Data Manager(s) (DM) and CONRAD representatives will serve as the PSRT. The DM prepares routine AE and clinical data reports for review by the PSRT, which meets via conference call approximately once per month or more frequently as needed throughout the period of study implementation to review safety data, discuss product use management, and address any potential safety concerns.

### 8.2 Clinical Data and Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The site IoRs/designees are responsible for the initial evaluation and reporting of safety information at the participant level and for alerting the PSRT if unexpected concerns arise. Participant safety is also monitored at the project level through routine reviews conducted by the PSRT and study sponsors. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

The DM(s) will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. To ensure prompt review of AEs of concern (e.g., serious adverse events [SAE] and Related Grade 3+ AEs), such AEs submitted in the clinical database can be forwarded to the PSRT for review within 72 hours of entry.

The PSRT will meet approximately every month, or as needed, via conference call to review clinical data reports generated by the DM(s). The content, format and frequency of the clinical data reports will be agreed upon by the PSRT and the DM(s) in advance of study implementation. In addition to the routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to MATRIX representing expertise in the fields of microbicides, biostatistics, HIV acquisition and medical ethics may be invited to join the PSRT safety review. A recommendation to pause or stop the trial may be made by the PSRT at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

The Independent Safety Physician (ISP) will review participant safety data as part of their regular reviews (see Section 10.7.1), since no Data and Safety Monitoring Board (DSMB) oversight is planned for MATRIX-004. These reviews will take place approximately every 3 months, or as needed. The ISP will be an independent investigator(s) with no interest (financial or otherwise) in the outcomes of this study. At the time of these reviews, or at any other time, the ISP or PSRT may convene a panel (composed of the ISP, PSRT and protocol statistician[s]) to review study findings. This panel may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. If at any time a decision is made to discontinue enrollment and/or study product use in all participants, CONRAD will notify USAID, the US Food and Drug Administration (FDA), Gilead, and any investigators conducting studies under the same IND, and the site IoRs/designees will notify the responsible IRBs/IECs and applicable national drug regulatory authorities (DRA) expeditiously per local guidelines.

## 8.3 Adverse Events Definitions and Reporting Requirements

### 8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition is applied to all study participants and is applied beginning after product use at the enrollment visit. The term "investigational products" for this study refers to the TAF/EVG vaginal insert, 20/16 mg. AEs should be assessed for relatedness to investigational product and to study procedures.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience. In cases of potentially life-threatening events, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where a study clinician is based. With appropriate permission of the participant(s), whenever possible, records from all

non-study medical providers related to untoward medical occurrences may be sought if necessary to obtain clinically relevant information for the study and required data elements will be recorded on study CRFs. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes, per clinical discretion.

Study site staff will document in source documents and in the study database all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 1 (Female Genital Grading Tables for Use in Microbicide Studies [Dated November 2007].

For any SAEs that are continuing at SEV, the IoR/designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the SAE must be re-assessed by study staff within 30 days after the SEV; additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the SEV, for any new AEs found at the SEV, and for participants who permanently discontinue study product use due to a product-related AE. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant(s) while the study is ongoing, per IoR/designee discretion. For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE CRFs based on the re-assessments; see Section 9.5 for exceptions related to updating CRFs post-SEV to document pregnancy outcomes, should they occur during the study.

After the study has ended, the PSRT may advise study staff on a case-by-case basis as to whether any additional follow-up may be indicated for AEs that have not resolved or stabilized.

### 8.3.2 Serious Adverse Events

As per the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidance (ICH E6; https://www.ich.org/page/efficacy-guidelines), SAEs are defined as AEs occurring at any dose that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization

  *NOTE: Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event. Thus, hospitalization in the absence of an AE is not regarded as an AE. The following are examples of hospitalization that are not considered to be AEs:*
  - Protocol-specified admission (e.g., for procedure required by study protocol)
  - Admission for treatment of target disease of the study, or for pre-existing condition (unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator)

- Diagnostic admission (e.g., for a work-up of an existing condition such as persistent pretreatment lab abnormality)
- Administrative admission (e.g., for annual physical)
- Social admission (e.g., placement for lack of place to sleep)
- Elective admission (e.g., for elective surgery)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any SAE including those listed in the protocol, investigator brochure, or package insert must be reported to CONRAD within 24 hours of discovery. If there is any question whether the event meets the criteria for "serious" it should be reported anyway. In addition, a completed SAE form must be emailed to CONRAD (conradsafety@odu.edu) as soon as possible.

### 8.3.3 Adverse Event Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. The PSRT will review and confirm relatedness. The relationship categories that will be used for this study are:

- Related: There is a reasonable possibility that the AE may be related to the study agents
- Not Related: There is not a reasonable possibility that the AE is related to the study agents

## 8.4 Pregnancy and Infant Outcomes

Pregnant women are excluded from this study.

A participant who is pregnant after enrollment will continue to be followed until the pregnancy outcome is ascertained, and information collected on the infant(s) up to approximately one year after delivery for those pregnancies that result in live birth. A participant who becomes pregnant during the study will have study product discontinued (if initiated) and will be terminated from the study. Please see Section 9.5 for additional details.

## 8.5 Regulatory Requirements

AEs reported on CRFs will be included in reports to the FDA and other applicable national DRA. Site IoRs/designees will submit AE information in accordance with local and national regulatory agencies' or other local and national authorities' requirements. Site IoRs/designees also will submit AE information and any other relevant safety information to their IRBs/IECs and national DRA in accordance with IRB/IEC/DRA requirements.

## 8.6 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. For example, participants could be treated unfairly, or could have problems

being accepted by their families, partners and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the PSRT and responsible site IRBs/IECs according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. While maintaining participant confidentiality, study sites may engage their community advisory boards (CABs) in exploring the social context surrounding instances of social harm.

# 9 CLINICAL MANAGEMENT

Guidelines for clinical management and temporary product hold/permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to hold study product temporarily at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. Unless otherwise specified below, the IoR/designee should immediately consult the PSRT for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs.

## 9.1 Grading System

AE severity grading is described in Section 8.3.

## 9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

## 9.3 General Criteria for Temporary Hold and Permanent Discontinuation of Study Product

A participant will be permanently discontinued from product use by the IoR/designee for any of the following reasons:

- Failure to follow protocol requirements that is judged severe enough by the investigator to significantly affect study outcomes
- HIV or STI acquisition
- Pregnancy or expresses a desire to become pregnant
- SAEs or other serious medical reasons, as judged by the IoR/designee to clinically warrant permanent discontinuation

A participant will be temporarily held from product use by the IoR/designee for any of the following reasons:

- Grade 2 related or higher AE/SAE where short-term resolution is possible, if assessed by the IoR/designee to clinically warrant a product hold

The IoR/designee must consult the PSRT on all temporary product holds for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent

discontinuation. If product use is temporarily held/permanently discontinued at IoR/designee discretion, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time. All AEs are defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, as outlined in Section 8.3.

## 9.4 HIV Infection

Potential participants who test positive for HIV prior to eligibility confirmation will be excluded from the study but will be referred to HIV care and management without delay. Participants who test positive for HIV after eligibility confirmation must have study product permanently discontinued by the IoR/designee. A participant who is confirmed to be HIV positive during the study will have all follow-up visits discontinued and the participant will be considered terminated from the study as per Section 7.6.1. Participants identified as infected with HIV are managed or referred for management according to the local standard of care. Guidance regarding management and referral for participants confirmed to be HIV-positive can be found in Section 13.10. Sites will not be responsible for paying for HIV-related care.

## 9.5 Pregnancy

Pregnancy testing will be performed at designated study visits and participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The IoR/designee will counsel any participant who becomes pregnant regarding possible risks to the fetus. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

Potential participants who test positive for pregnancy prior to eligibility confirmation will be excluded from the study but will be referred to all applicable services. Participants who test positive for pregnancy after eligibility confirmation will have study product discontinued and will be terminated from the study as per Section 7.6.2. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Pregnancy outcomes will be reported on relevant CRFs; outcomes meeting criteria for SAE reporting also will be reported on the Adverse Event CRF. The study site will make every reasonable effort to contact participants and collect information on the infant(s) up to approximately one year after delivery for those pregnancies that result in live birth.

## 9.6 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. IoRs/designees also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if CONRAD, USAID, MATRIX, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs/IECs/DRAs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of both participants if one or both withdraw or are withdrawn from the study prior to completing follow-up (see details regarding the Early Termination Visits for male and female participants in Section 7.5.1 and Section 7.5.3, respectively). Study staff members will record the reason(s) for all withdrawals in participants' study records.

# 10 STATISTICAL CONSIDERATIONS

## 10.1 Overview and Summary of Design

MATRIX-004 is a Phase 1 randomized study evaluating the impact of vaginal sexual intercourse (coitus) on the TAF/EVG insert when administered vaginally before and after coitus. MATRIX-004 will examine the PK, PD, general and mucosal safety, and acceptability of inserts containing the combination of TAF and EVG applied vaginally, before and after coitus.

## 10.2 Study Endpoints

**Primary Endpoints**

**PK**

- Concentrations of TFV, TAF and EVG in plasma after dosing
- Concentrations of TFV, TAF and EVG in CVF after dosing
- Concentrations of TFV, TFV-DP, TAF and EVG in CVT after dosing
- Concentrations of TFV-DP in PBMC after dosing

**Secondary Endpoints**

**Acceptability**

- Responses to key questions on overall experience (e.g., satisfaction, comfort) with using the TAF/EVG insert before and after coitus

**Safety**

- Any Grade 2 or higher TEAE

**Exploratory Endpoints**

**PD**

- Anti-HIV activity in CVF obtained at baseline and after dosing

**Impact of coitus on TAF/EVG vaginal insert mucosal safety**

- Changes in mucosal microenvironment and histology (epithelial integrity and immune cell infiltrate)

## 10.3 Primary Study Hypothesis

It is hypothesized that there will be no clinically significant change in PK endpoints from baseline when the TAF/EVG Insert, 20/16 mg, is administered vaginally by healthy, non-pregnant, HIV-uninfected adult women at low risk for HIV acquisition before and after vaginal sexual intercourse (coitus).

## 10.4 Sample Size and Power Calculations

Based on previous findings on the impact of sex on TFV vaginal gel from MTN-011[18] and focusing on observed differences in TFV-DP concentrations in vaginal tissue, we would need about 20 female participants (10 per group) to detect a similar effect size (~65%) with 80% power at a 0.05 significance level. We are planning to enroll 32 couples to complete at least 28 to provide sufficient power to analyze effect differences per site. Altogether, this sample size will provide 80% power to detect a minimum of 55% difference in TFV-DP concentration (effect size) at 5% level of significance.

### Qualitative data collection

Up to 40 study participants (6-10 female and 6-10 male per site) will be purposively selected and invited to complete an IDI after V8 but before exiting the study.

## 10.5 Randomization Procedures

Couples will be randomized (1:1) to receive the combination TAF/EVG vaginal insert either 1 hour or 4 hours before and after coitus.

| Couples | Randomization Group |
|---|---|
| *16* | 1 hour before and 1 hour after coitus |
| *16* | 4 hours before and 4 hours after coitus |

## 10.6 Participant Accrual, Follow-up and Retention

A sufficient number of couples may be consented and undergo assessment procedures in order to have approximately 32 (16 in each site) evaluable couples, i.e., couples that complete all study visits. All participants that undergo baseline sampling will be included in the analysis. Participants who initiate product use but discontinue the study prior to completion may not re-enroll. If either partner (female or male) discontinues the study early, the couple will be discontinued from the study early. Participants who discontinue the study early may be replaced to reach the target of having approximately 32 couples with complete study data. Replacement participants will be assigned to the same group (1hr or 4hr) as the withdrawn participants to avoid bias.

*NOTE: Per Section 10.4, a maximum of 4 couples across the 2 study sites (up to 2 per randomization group) may discontinue the study early without requiring that the participants be replaced while still achieving sufficient power to analyze effect differences per site.*

## 10.7 Data and Safety Monitoring and Analysis

### 10.7.1 Study Monitoring

DSMB oversight is not planned for this study. The MATRIX Clinical Trials Hub will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, and study or laboratory issues. The ISP will conduct interim review of a closed safety data report. These reviews will take place approximately every

three months, or as needed. At the time of these reviews, or at any other time, the ISP or PSRT may convene a panel (composed of the ISP, PSRT and protocol statistician[s]) to review study findings. This panel may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Safety monitoring will be done by the PSRT.

### 10.7.2 Primary Analysis(es)

PK and PD:
PK analysis will include descriptive statistics by sample time point of EVG, TFV, and TAF concentrations for all plasma, CVT, and CVF sample types, in addition to TFV-DP concentrations from CVT samples.

PD endpoints will be summarized using descriptive statistics by time point as well as changes from baseline. Estimates and 95% confidence intervals will be provided.

Comparisons:

- At baseline: Compare the 1-hour pre/post coitus and 4-hour pre/post coitus groups to ensure groups are comparable
- At stage 1 (pre coitus)
    - For the 1-hour group: comparing 5 hours after coitus (6 hours after insert) to the 6 hours after insert at baseline
    - For the 4-hour group: comparing 2 hours after coitus (6 hours after insert) to the 6 hours after insert at baseline
- At stage 2 (post coitus)
    - For the 1-hour group: comparing 7 hours after coitus (6 hours after insert) to the 6 hours after insert at baseline
    - For the 4-hour group: comparing 10 hours after coitus (6 hours after insert) to the 6 hours after insert at baseline

Statistical Analysis plan:

Categorical variables will be summarized by frequencies and percentages. Continuous variables will be summarized by mean (SD) when found normally distributed. Median (IQR) will be used otherwise. Normality will be assessed graphically by Q-Q plots and statistically by Shapiro-Wilk test for normality.

To assess for the comparability between the two groups of the study at baseline, t-test or Mann-Whitney test will be used (based on the normality assumptions) to assess for the differences in continuous variables. Chi-squared test for independence or Fisher's exact test will be used for categorical variables as appropriate.

For the 1-hour pre/post coitus insert group, Paired analysis will be conducted for each endpoint at 6 hours post insert for stage 1 and stage 2 to compare to the baseline separately. For this analysis paired t-test or Wilcoxon signed rank test will be used as appropriate. Similar analysis will be conducted for the 4-hour pre/post coitus insert group.

To assess for the change on TFV-DP and other PK parameters over time, repeated measure ANOVA or Friedman test will be used (based on the normality assumptions) to compare all PK parameters of tissue, blood, or vaginal fluid samples at V3, V6, and V9 for the 1-hour pre/post coitus group and the 4-hour pre/post coitus group separately; pairwise comparison will then be conducted using Bonferroni or Sidak correction as needed.

Finally, Mixed Effect Model will be used to compare the PK parameters between the 1-hour pre/post coitus and 4-hour pre/post coitus groups and within each group compared to baseline.

### 10.7.3 Secondary and Exploratory Analyses

Acceptability:
Acceptability endpoints will be summarized by assessment time point using descriptive statistics (e.g., frequencies, means), as appropriate. We will compare ratings of key acceptability measures over time (e.g., prior to use, after Stage 1, and after Stage 2 use), assessing whether they changed with increased experience with product insertion using a one-sample t test. In addition, we will examine differences based on the assigned timing of insert use (i.e., 1 hour vs. 4 hours; pre coitus vs. post coitus) and between females and males, overall and within-couples.

Qualitative Analysis:
Qualitative analyses from the MATRIX-004 study will use a variety of techniques to provide an in-depth characterization of the contextual factors that affected participants' experience with product use during sex. The primary source of qualitative data used in the analysis will consist of raw textual data. Qualitative data will be audio-recorded, translated and transcribed in English, and coded for thematic analyses using Dedoose or a similar qualitative software. Data coding will be used as a primary analytical approach for data reduction; that is, to summarize, extract meaning, and condense the data. Whenever possible, we will also compare study sites and explore differences or similarities related to product use experiences due to different socioeconomic, cultural and geographical contexts, with a particular focus on male and female perspectives. The findings and interpretations of the data will be critically discussed until there is group consensus on the dominant themes and meanings contained in the data. Whenever possible, site staff will be involved to corroborate findings from the analysis team.

### 10.7.4 Missing Data

All attempts will be made to avoid missing data. However, missing values will remain as missing, i.e., no attempt will be made to impute. In general, only observed values will be used in data analyses and presentations. The one exception to this is summarizing concentration data; values that are detectable but below the lower limit of quantification (LLOQ) will be set to one-half the value LLOQ; concentrations below the limit of detection will be set to 0. Otherwise, no imputation is anticipated. No transformation will be applied.

# 11 DATA HANDLING AND RECORDKEEPING

## 11.1 Data Management Responsibilities

Data collection tools will be developed by the DM(s) in conjunction with the protocol team. Quality control and data integrity are managed manually and systematically with reports and queries routinely generated and provided by the DM(s) to the study sites for verification and resolution. As part of the study activation process, each study site will identify all CRFs to be used as source documents. Study CRF data will be entered and cleaned using a data management system compliant with the ICH Good Clinical Practices (GCP) and US CFR guidelines for electronic data capture.

IDI files generated in the field will be electronically transferred to RTI International using a secure File Transfer Protocol (FTP) site, where they will be uploaded and managed using a qualitative software package. RTI International will act as a hub and manage all qualitative data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. Transcripts will be transferred to RTI International as they are completed. RTI International will save all versions of all files on a secure, password-protected server in the US.

## 11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with MATRIX's Good Documentation Practice (GDP) guidelines (www.matrix4prevention.org).

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, for the investigational products tested, IoRs/designees will maintain all study documentation for at least two years following the date of marketing approval for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued, or longer as per local regulatory requirements, and the US FDA is notified.

Study records must be maintained on site for the entire period of study implementation. Thereafter, instructions for record storage will be provided by CONRAD. No study records may be moved to an off-site location or destroyed prior to receiving approval from CONRAD.

## 11.3 Quality Control and Quality Assurance

Study sites will conduct quality control and quality assurance procedures in accordance with MATRIX's Quality Management Plan (www.matrix4prevention.org).

# 12 CLINICAL SITE MONITORING

Study monitoring will be carried out by ACRO for African sites and by CRA Resources for US sites. Study monitors will do the following:

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, ICH GCP guidelines, and applicable regulatory requirements (US and non-US), including US Code of Federal Regulations (CFR) Title 45 Part 46 and Title 2 Parts 200 and 225
- Perform source document verification to ensure the accuracy and completeness of study data
- Verify proper collection and storage of biological specimens
- Verify proper storage, dispensing, and accountability of investigational study products
- Assess implementation and documentation of internal site quality management procedures

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose. Remote monitoring visits may be performed in place of or in addition to onsite visits to ensure the safety of study participants and data integrity.

For on-site visits, the IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of MATRIX, CONRAD, USAID, FDA, OHRP, IRBs/IECs/DRAs and other local, US, or international regulatory authorities. A site visit log will be maintained at the study site to document all visits.

# 13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, IoRs/designees will have obtained IRB/IEC approval and the protocol will have been submitted to the FDA and other applicable national drug regulatory authorities. IoRs/designees will permit audits by USAID, the FDA, OHRP, MATRIX, IRBs/IECs/DRAs, and other local, US, or international regulatory authorities or any of their appointed agents.

Changes to this protocol may be implemented by investigators prior to IRB/IEC approval, if those changes are required to eliminate apparent immediate hazards to the study participant; see 45 CFR 46.108(a)(3)(iii) under the 2018 Requirements (https://www.ecfr.gov). These changes must be documented as Protocol Deviations and reported to the Protocol Team and IRBs/IECs as soon as possible; see ICH E6(R2), Good Clinical Practice, Section 4.5.4 (https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/ich-guidance-documents). In the event of a public health emergency, investigators should adhere to the recommendations of their local institutions, IRBs/IECs and local health departments. When conflicts exist between local directives, MATRIX, Protocol Team and/or USAID policies or guidance, sites should follow the requirement that is most protective of study participants and site staff.

## 13.1 Institutional Review Boards/Ethics Committees

The participating institution is responsible for assuring that this protocol, the associated site-specific informed consent forms (ICFs), and study-related documents (such as participant education and recruitment materials) are reviewed by an IRB/IEC responsible for oversight of research conducted at each study site and, as required, by applicable national DRA. Any amendments to the protocol must be approved by the responsible IRBs/IECs and (if applicable) national DRA prior to implementation.

Subsequent to the initial review and approval, the responsible IRBs/IECs must review the study at least annually. Each IoR/designee will make safety and progress reports to the IRBs/IECs at least annually and within three months after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. In addition, the results of all ISP reviews of the study will be provided to the IRBs/IECs.

## 13.2 Protocol Implementation

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local IRBs/IECs and any other applicable regulatory entities. Upon receiving final approval, sites will submit copies of all relevant protocol/amendment documents (i.e., IRB/IEC approval letters with a detailed list of approved documents, approved ICF documents, etc.) to the MATRIX Clinical Trials Hub Regulatory team.

The MATRIX CRM(s) will review the submitted document packet to ensure receipt of all required protocol/amendment documents prior to study activation at the sites. Sites will receive a Study Activation Notification from the MATRIX CRM(s) that indicates successful completion of the protocol readiness process. A copy of the Study Activation Notification should be retained in the site's regulatory files.

Upon receiving final IRB/IEC and any other applicable approval(s) for a protocol/amendment, sites are required to submit copies of all relevant protocol/amendment documents (i.e., IRB/IEC submission letters, IRB/IEC approval letters with a detailed list of approved documents, related correspondence with IRB/IEC, approved ICF documents, etc.) to CONRAD prior to study activation. Upon receiving final IRB/IEC and any other applicable approval(s) for an amendment, activated sites should implement the amendment immediately but are still required to submit copies of all relevant amendment documents to CONRAD.

## 13.3 Study Coordination

CONRAD holds the Investigational New Drug (IND) application for this study. Delegation of any sponsor responsibilities for this study will be specified in writing between CONRAD and MATRIX.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Co-Chairs and Protocol Team representatives from MATRIX and USAID. Study implementation will also be guided by a common SSP Manual that provides

further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to sites by the MATRIX CRM(s) and other designated members of the Protocol Team.

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The PSRT will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team as well as the ISP and the MATRIX Clinical Trials Hub.

## 13.4 Risk Benefit Statement

### 13.4.1 Risks

General
The study may cause an inconvenience to daily life due to visit scheduling and study participation requirements, including refraining from vaginal practices and sexual activity at specified timepoints.

Phlebotomy
Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling, having a blood clot, excessive bleeding, and/or infection.

Pelvic Examination and Procedures
The pelvic examination with speculum insertion may cause discomfort, redness, itching, and/or irritation in the external genital and vaginal area.

CVF Collection
Collection of CVF may cause discomfort or pressure in the vagina or genital area.

CVT Biopsy Collection
There is a risk of mild pain and/or sharp pinch when biopsies are taken. Bleeding sometimes occurs after biopsy collection and can usually be stopped with pressure or medication to the biopsy area. If medicine is used, it may cause temporary dark-colored discharge from the vagina. In rare cases, a stitch might need to be placed to stop the bleeding. Soreness and discomfort in the vagina may occur for one to two days after the procedure along with some vaginal spotting. There is a small risk of infection and heavier bleeding. Participants will be instructed to contact the clinic if symptoms are bothersome, if heavy bleeding is noted or if the participant develops any abnormal odor or discharge from the vagina. Participants will be counselled to refrain from NSAIDs or aspirin use 3 days before and after CVT biopsy sample collection.

Other Risks
Disclosure of HIV and STI status may cause worry, sadness or depression. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial as well as social isolation. Trained study staff will be available to help participants deal with these feelings.

Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions when discussing sexual behaviors.

Sexual partner notification in response to diagnosed STI or HIV infection could cause problems in participants' relationships.

Site staff will make every effort to protect participant privacy while in the study. Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-positive or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their partners, families and/or communities.

Risks Associated with vaginal inserts
The inserts may cause irritation of the female and male genitalia, including pain, itching, irritation, rash, or vaginal discharge. The insert may also cause female urinary symptoms including dysuria, frequency, or urgency.

Risks Associated with oral TAF and oral EVG
There is a low probability of adverse events associated with systemic levels of TAF and EVG. Those include: headache, nausea, fatigue, diarrhea, abdominal pain, back pain, cough, arthralgia, and dyspepsia. These side effects may or may not be associated with the use of TAF or EVG when the drugs are administered vaginally.

### 13.4.2 Benefits

Information learned from this study may contribute to the development of safe and effective options to prevent HIV acquisition and transmission. We believe that the potential public health benefit compares favorably against the minimal risks to participants. Participants may enjoy sharing their opinions about the insert and other HIV prevention methods with the research team. Participants may appreciate being part of a research effort that will contribute to the development of HIV prevention methods and that aims to curb the epidemic. However, there are no direct benefits to participants for participating in the proposed research aside from those described below.

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical and pelvic exams, and laboratory testing related to blood, liver, and kidney function. Participants will be provided STI treatment at no cost, and referrals may be provided if needed. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some participants may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals.

## 13.5 Informed Consent Process

Written informed consent will be obtained from each member of the participant couple prior to screening. Written informed consent also will be obtained from each member of the participant

couple for the IDI, although consent for the IDI is not required for study participation. Written informed consent also will be obtained from each CRS staff member selected for an IDI (see Section 7.9 for more details). In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with MATRIX's GDP guidelines (www.matrix4prevention.org). Participants will be provided with copies of the ICF if they are willing to receive them.

In addition to the ICF, the Protocol Team will work with study staff and community representatives to develop appropriate materials about the study and a standardized approach to the informed consent process to be implemented at study sites, which will be detailed in the MATRIX-004 SSP Manual.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process specifically will address the following topics of importance to this study:

- The unknown safety and unproven efficacy of the study product
- The need to practice safer sex behaviors (except when required by protocol to engage in condomless vaginal sex)
- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The limited benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

### 13.6 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Study staff will not share participant information or test results with their co-enrolled partner unless necessary to comply with local reporting requirements (see Section 13.9 for details). Study sites will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them.

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded participant number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and ICFs, will be stored separately from study records identified by code number. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers to identifying information will be stored in a separate, locked file in an area with limited access.

Audio files will be translated (when applicable) and transcribed in English. Audio files and resulting transcripts may contain personal identifiers and will be securely stored in line with local guidelines and sites' practices for confidentiality protection. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the FDA, OHRP, USAID, and/or contractors of USAID, and other local, US, or international regulatory authorities
- CRA Resources and ACRO representatives
- CONRAD representatives
- MATRIX designees/representatives
- Study staff
- Site IRBs/IECs/DRAs

## 13.7 Special Populations

### 13.7.1 Pregnant Women

Couples who test positive for pregnancy at the Screening or Enrollment Visit will not be eligible to participate in this study. Should a female participant test positive for pregnancy after Enrollment, a product discontinuation will be implemented. Follow-up will be completed and data collected per Section 7.6.2. During the informed consent process, couples will be informed that the TAF/EVG vaginal insert is not an effective method of contraception and the effects of TAF/EVG on a developing human fetus are unknown.

### 13.7.2 Children

The US NIH has mandated that children, defined as younger than 18 years old, be included in research trials when appropriate. This study meets "Justifications for Exclusion" criteria for younger children as set forth by the NIH (specifically, "insufficient data are available in adults to judge potential risk in children" and "children should not be the initial group to be involved in research studies"). As such, this study does not plan to enroll children.

## 13.8 Compensation

Pending IRB/IEC approval, participants will be compensated for time, inconvenience and travel in this Phase 1 study. Site-specific reimbursement amounts will be determined per local IRB/IEC/DRA guidelines and will be specified in the study ICFs of each individual site.

If a participant becomes ill or injured as a result of participation in this trial, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer the participant for ongoing treatment for the injury, if needed. Where required, clinical trial insurance is provided by CONRAD and will be responsible for compensating the study participant for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation.

### 13.9 Reporting

#### 13.9.1 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV identified among study participants to health authorities. Participants will be made aware of reporting requirements during the informed consent process.

#### 13.9.2 Other Reporting

Study staff will comply with local requirements to report cases of sexual assault or of sexual activity involving a person below the age of consent identified in the study.

### 13.10 Access to HIV-related Care

#### 13.10.1 HIV Counseling and Testing

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV testing time point. Testing will be performed in accordance with the algorithm in Appendix III. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will emphasize the unknown efficacy of the study products in preventing HIV infection. Participants will be given the option to have counseling individually or as a couple. Participants must receive their HIV test results to take part in this study. Condoms will be available to participants as part of standard risk reduction counselling.

#### 13.10.2 Care for Participants Identified as HIV-Positive

An individual who has been identified as infected with HIV will be referred for management according to the local standard of care. Should a participant test positive for HIV after Enrollment Visit, follow-up procedures will be performed as per Section 7.6.1.

### 13.11 Study Discontinuation

This study may be discontinued at any time by USAID, MATRIX, CONRAD, the US FDA, the OHRP, site IRBs/IECs/DRAs, and other local, US or international regulatory authorities.

## 14 PUBLICATION POLICY

USAID and MATRIX policies and a written agreement between CONRAD and MATRIX will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to USAID, MATRIX and CONRAD for review prior to submission.

## 15 APPENDICES

## APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS – FEMALES

| STUDY PROCEDURES | | SCR Visit 1 | Stage 0 (No sex) | | | Stage 1 (1hr/4hrs Pre sex) | | | Stage 2 (1hr/4hrs Post sex) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ENR Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 | SEV Visit 10 |
| **ADMINISTRATIVE AND REGULATORY** | | | | | | | | | | | |
| Informed consent process | | X | | | | | | | | | |
| Assign a unique PTID | | X | | | | | | | | | |
| Assess/confirm eligibility | | X | X | | | | | | | | |
| Collect/review/update locator information | | X | X | X | X | X | X | X | X | X | X |
| Provide reimbursement | | X | X | X | X | X | X | X | X | X | X |
| Schedule next visit/contact | | * | * | X | X | X | X | X | X | X | |
| Randomization (1:1) to receive insert 1 hr or 4 hrs pre and post sex (after eligibility confirmation) | | | X | | | | | | | | |
| **BEHAVIORAL/COUNSELING** | | | | | | | | | | | |
| Protocol adherence counseling per Section 6.6 and Section 7.10 | | X | X | X | X | X | X | X | X | X | |
| HIV pre and post/ risk reduction counselling | | X | X | | | X | | | X | | X |
| Demographic information | | X | | | | | | | | | |
| Baseline behavioral and acceptability questionnaire | | X | | | | | | | | | |
| Follow-up (FU1) behavioral and acceptability questionnaire | | | X | | | | | | | | |
| Follow-up (FU2) behavioral and acceptability questionnaire | | | | | | X | | | X | | |
| IDI (subset) | | | | | | | | | X◊ | X◊ | X◊ |
| **CLINICAL** | | | | | | | | | | | |
| Physical exam (directed after Screening) | | X | * | * | * | * | * | * | * | * | * |
| Vital signs, weight and (at Screening only) height | | X | X | X | X | X | X | X | X | X | X |
| Collect/review/update medical and menstrual history | | X | X | X | X | X | X | X | X | X | X |
| Pelvic exam (bimanual exam at Screening) | | X | X | X | X | X | X | X | X | X | X |
| Assess AEs | | | X (post use) | X | X | X | X | X | X | X | X |
| Assess CMs | | X | X | X | X | X | X | X | X | X | X |
| **LABORATORY** | | | | | | | | | | | |
| SALIVA | HIV rapid test(s) (only at sites with CLIA certification) | X | X | | | X | | | X | | X |
| URINE | Pregnancy test | X | X | * | * | X | * | * | X | * | * |
| | Urine dipstick/urinalysis | X | * | * | * | * | * | * | * | * | * |

| STUDY PROCEDURES | | SCR Visit 1 | Stage 0 (No sex) | | | Stage 1 (1hr/4hrs Pre sex) | | | Stage 2 (1hr/4hrs Post sex) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ENR Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 | SEV Visit 10 |
| BLOOD | HIV rapid test(s) (not required if conducting saliva testing) | X | X | | | X | | | X | | X |
| | HIV RNA test(s) (not required for sites that conduct saliva testing) | X | X | | | | | | | | |
| | HBsAg | X | | | | | | | | | |
| | Syphilis | X | | | | | | | | | |
| | CBC with platelets | X | | | | | | | | | X |
| | Chemistries | X | | | | | | | | | X |
| | Plasma for archive | | X | | | | | | | | |
| | PK (Plasma): TAF, TFV, EVG | | X (pre- & 6hr post dose) | X | X | X (6hr post dose) | X | X | X (6hr post dose) | X | X |
| | PBMC for TFV-DP | | X (pre-dose) | X | X | | X | X | | X | X |
| GENITAL | GC, CT, TV testing | X | * | * | * | * | * | * | * | * | * |
| | Saline/KOH wet mount for candidiasis &/or BV | * | * | * | * | * | * | * | * | * | * |
| | PSA (semen marker) | | X (pre-dose) | X | X | X | X | X | X | X | X |
| | Pap smear | * | | | | | | | | | |
| | Vaginal pH | | X (pre-dose) | X | X | X | X | X | X | X | X |
| | Vaginal swab(s) for microbiota | | X (pre-dose) | X | X | | X | X | | X | X |
| | Vaginal Gram stain | | X (pre-dose) | X | X | | X | X | | X | X |
| | CVF for PK – TAF, TFV, EVG | | X (pre- & 6hr post dose) | X | X | X (6hr post dose) | X | X | X (6hr post dose) | X | X |
| | CVF for PD – anti-HIV | | X (pre- & 6hr post dose) | X | X | X (6hr post dose) | X | X | X (6hr post dose) | X | X |
| | BXV for PK – TAF, TFV, EVG, TFV-DP | | | X | | | X | | | X | |
| | BXV for IHC | | | X | | | X | | | X | |
| **STUDY PRODUCT SUPPLY** | | | | | | | | | | | |
| Study product self-insertion (may occur outside clinic at V5 and V8) | | | X | | | X | | | X | | |

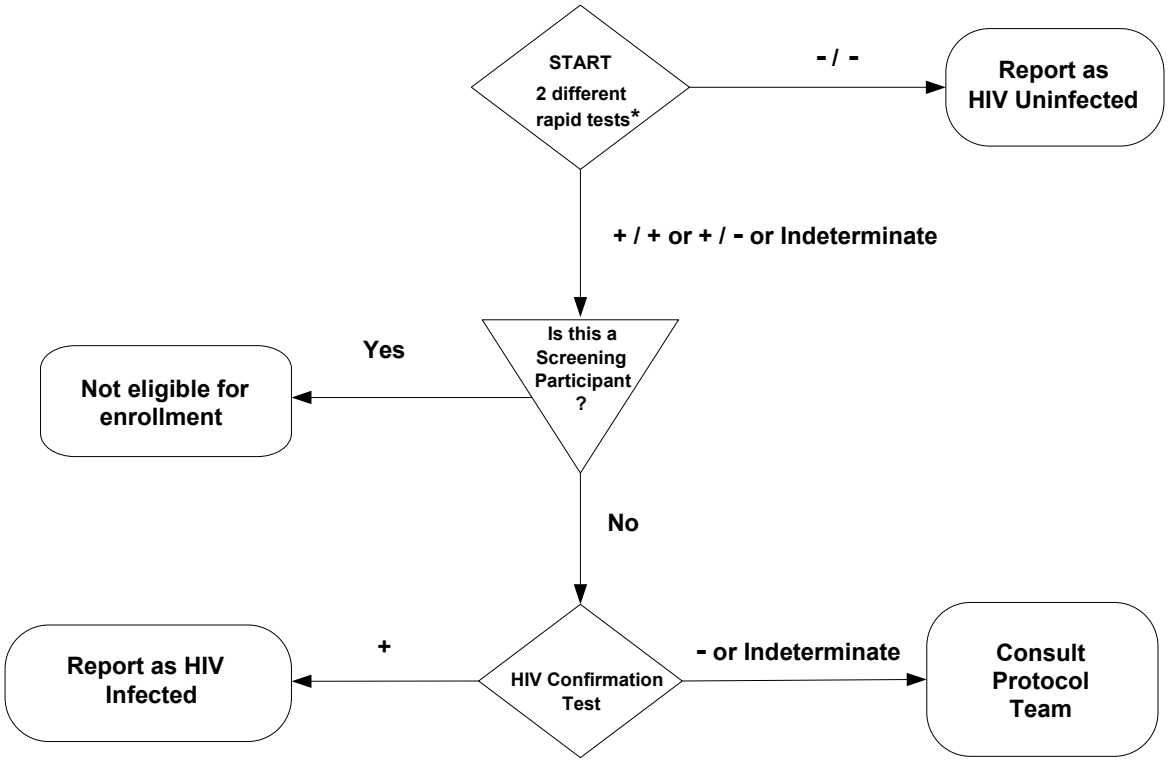
X = required
* = If indicated
◊ = IDI may be conducted at any point between V8 and V10, and is not required to align with a scheduled clinical study visit
*Note: Any study procedures, including laboratory tests, can be repeated at any visit if clinically indicated.*

## APPENDIX II: SCHEDULE OF STUDY VISITS AND EVALUATIONS – MALES

| STUDY PROCEDURES | | SCR Visit 1 | Stage 1 (1hr/4hrs Pre sex) Visit 5 | Stage 2 (1hr/4hrs Post sex) Visit 8 |
|---|---|---|---|---|
| **ADMINISTRATIVE AND REGULATORY** | | | | |
| Informed consent process | | X | | |
| Assign a unique PTID | | X | | |
| Assess/confirm eligibility | | X | | |
| Collect/review/update locator information | | X | X | X |
| Provide reimbursement | | X | X | X |
| Schedule next visit/contact | | * | X | X |
| **BEHAVIORAL/COUNSELING** | | | | |
| Protocol adherence counseling per Section 6.6 and Section 7.10 | | X | X | X |
| HIV pre and post/ risk reduction counselling | | X | X | X |
| Demographic information | | X | | |
| Baseline behavioral and acceptability questionnaire | | X | | |
| Follow-up (FU2) behavioral and acceptability questionnaire | | | X | X |
| IDI (subset) | | | | X◊ |
| **CLINICAL** | | | | |
| Physical exam (directed) (including genital inspection) | | X | * | * |
| Vital signs, weight and (at Screening only) height | | X | X | X |
| Collect/review/update medical history | | X | X | X |
| Assess AEs | | | X | X |
| Assess CMs | | X | X | X |
| **LABORATORY** | | | | |
| SALIVA | HIV rapid test(s) (only at sites with CLIA certification) | X | X | X |
| URINE | Urine dipstick/ urinalysis | X | * | * |
| | GC, CT, TV testing | X | * | * |
| BLOOD | HIV rapid test(s) (not required if conducting saliva testing) | X | X | X |
| | HIV RNA test(s) (not required for sites that conduct saliva testing) | X | | |
| | HBsAg | X | | |
| | Syphilis | X | | |
| | CBC with platelets | X | | X |
| | Chemistries | X | | X |

X = required
* = If indicated
◊ = IDI may be conducted at any point between V8 and V10, and is not required to align with a scheduled clinical study visit
*Note: Any study procedures, including laboratory tests, can be repeated at any visit if clinically indicated.*

## APPENDIX III: ALGORITHM FOR HIV TESTING – SCREENING/ENROLLING/FOLLOW-UP



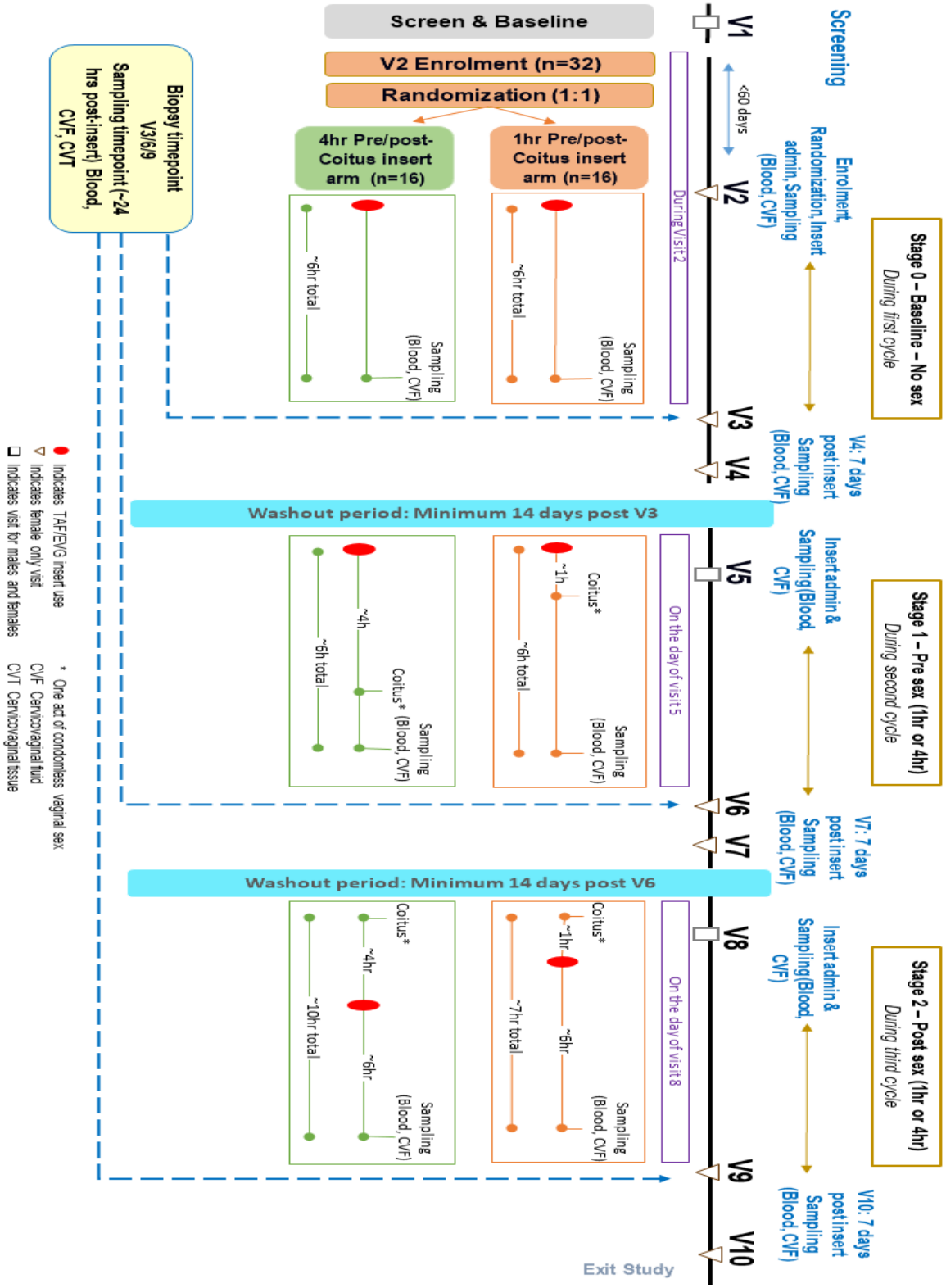

*CLIA certified labs may perform 1 rapid test

## APPENDIX IV: PROHIBITED MEDICATIONS AND PRODUCTS

The following medications and products should not be used by female participants during the study:
Vaginal corticosteroids (e.g., dexamethasone)
Antibiotics (vaginal)
Anticonvulsants (e.g., carbamazepine, oxcarbazepine, phenobarbital, phenytoin)
Antimycobacterials (rifbutin, rifampin, rifapentine)
Anticoagulants or other drugs known to prolong bleeding and/or prevent clotting
Antifungals (vaginal) (e.g., ketoconazole)
Systemic or vaginal antivirals (e.g., acyclovir, valacyclovir, Paxlovid™)
Antiretrovirals (e.g., tenofovir, emtricitabine)
St. John's Wort
Other drugs that may interact with TAF or EVG as specified in the Vitekta and Vemlidy package inserts (e.g., systemic dexamethasone, bosentan)
Over-the-counter medications that may alter the genital mucosa/bacteria (e.g., topical vaginal probiotics)

The following medications and products should not be used by male participants during the study:
Antiretrovirals (e.g., tenofovir, emtricitabine)
Genital topical products (e.g., antifungal creams, antiviral creams) on the day of sexual activity

## APPENDIX V: STUDY VISIT FIGURE



## APPENDIX VI: SAMPLE INFORMED CONSENT FORM (SCREENING and ENROLLMENT)

## SAMPLE INFORMED CONSENT FORM – FEMALES

## MATRIX-004
## Phase I Evaluation of the Impact of Vaginal Coitus on the Pharmacokinetics of Tenofovir Alafenamide and Elvitegravir Vaginal Insert

## USAID

## Version 1.0
## 18 October 2024

**PRINCIPAL INVESTIGATOR:** *[SITES TO INSERT]*
**INSTITUTION:** *[SITES TO INSERT]*
**AFTER HOURS CONTACT DETAILS:** *[SITES TO INSERT]*
**STUDY SITE CONTACT DETAILS:** *[SITES TO INSERT]*
**SHORT TITLE:** Impact of Coitus on TAF/EVG Vaginal Insert

**INFORMED CONSENT**

[*SITES TO INSERT APPROPRIATE GREETING*] You and your partner are invited to take part in this research study because you are an adult female 18-50 years old in a monogamous relationship with an adult male partner. Approximately thirty-two (32) couples will take part in this study across two sites in the United States and South Africa. This study is funded by the US Agency for International Development (USAID) and conducted by CONRAD as part of the MATRIX (Microbicide R&D to Advance HIV Prevention Technologies through Responsive Innovation and eXcellence) Collaborative. The study products are supplied by CONRAD. At this site, the person in charge of this study is [*SITES TO INSERT NAME OF CRS PI/IOR*].

**KEY INFORMATION**

- The study product in this clinical trial is a vaginal insert that contains tenofovir alafenamide (TAF) and elvitegravir (EVG). The vaginal insert is in a solid form that looks like a tablet that is made to dissolve quickly in the vagina. It contains 20 mg TAF and 16 mg EVG. Both drugs are used to treat HIV in oral form. This study will focus on how the vaginal insert containing TAF and EVG works when used before and after sex.
- The purposes of this study are:
    - To better understand how TAF and EVG enter and exit the body when the vaginal insert is used before and after sex.
    - To find out if it is safe to use the vaginal insert before and after sex.
    - To understand whether you find it acceptable to use the vaginal insert before and after sex.
- If you and your partner are eligible and choose to participate, you will receive 3 doses of the TAF/EVG vaginal insert, 20/16 mg. During the study, you will have laboratory tests for research purposes and to make sure you do not have any side effects.

- You will be asked to attend 10 clinic visits at this research clinic and will be followed for approximately 8 weeks. The total length of your participation in this study will be about 2-3 months.
- [*SITES TO DELETE IF NOT REQUIRED BY IRB/IEC:* At some of the clinic visits, the following will occur (other things may happen that are not listed here but are in the detailed descriptions of the study procedures):
    - A physical and/or pelvic exam will be performed.
    - Blood will be obtained to test for HIV and/or other sexually transmitted infections (STI) and for research purposes.
    - Urine will be collected to test for pregnancy and infections (if applicable).
    - Vaginal fluids will be collected for research purposes and to test for STIs (if applicable). At 3 of the 10 visits, cervicovaginal tissue will also be collected.
    - You will be asked to complete questionnaires about the vaginal insert, vaginal products, and/or vaginal hygiene practices.
    - We may also ask you and/or your partner to do one in-depth interview (IDI) with a staff member before or at your final visit. You will have the option to complete the interview individually or as a couple. We will audio-record the interview(s). It is your choice if you want to do the interview.]
- Some common risks from the use of TAF and/or EVG in oral forms include headache, diarrhea, nausea, fatigue, abdominal pain, cough, back pain, vomiting and rash. Uncommon adverse reactions include depression, insomnia and suicidal thought and attempt in patients with a history of depression or psychiatric illness.
- You and your partner may not experience any direct benefit from participation in this study, but information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive HIV/STI risk reduction counseling, HIV and STI testing, physical and pelvic examinations, and routine laboratory testing. You will have the option to receive HIV/STI counseling individually or as a couple.
- Taking part in this research study is voluntary. You and your partner do not have to participate, and you can stop your participation in the study at any time.

Please take the time to read this entire form and ask questions before deciding to join the study. If you and your partner are willing to take part in the study, you will sign this form. A copy of this form will be offered to you. Signing this form does not mean you will be able to join the study. You and your partner must first complete the screening tests and clinical examinations to see if you are eligible. It is important to know that your and your partner's participation in this research study is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

**WHY IS THIS RESEARCH BEING DONE?**

This study is being done to assess how TAF and EVG enter and exit the female body when the vaginal insert is used before and after sex.

**WHO WILL BE IN THIS RESEARCH STUDY?**

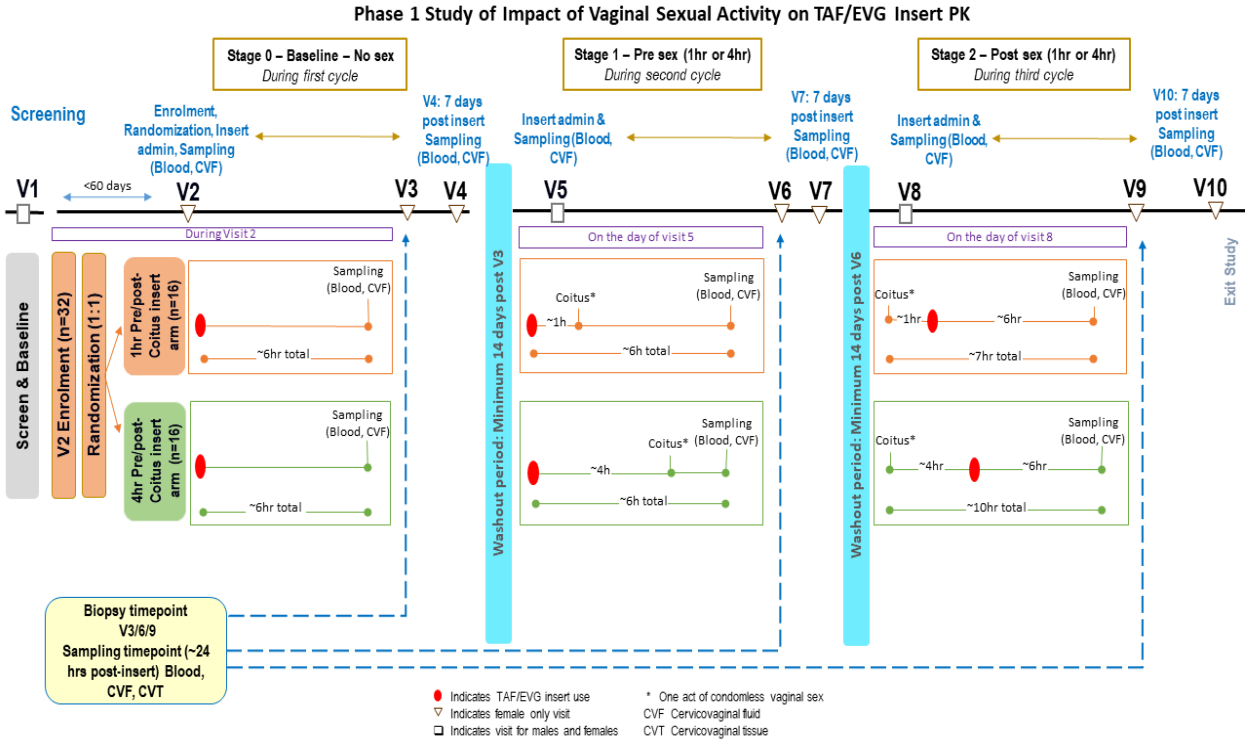
Approximately thirty-two (32) women who are 18-50 years old and their adult male partners will be enrolled in the study across two sites in the United States and South Africa.

**DO I HAVE TO BE IN THIS STUDY?**

You and your partner do not have to be in this study. You and your partner can still get the care you need at your local healthcare facility even if you do not join the study. If you and your partner decide to join the study, you can change your mind later.

**WHAT WILL I BE ASKED TO DO IF I JOIN THIS RESEARCH STUDY?**

Site investigators will assess if you and your partner are eligible for the study at this visit. If eligible, your partner will have a total of three (3) visits and you will have a total of ten (10) visits over approximately 2-3 months. You will be required to use an acceptable method of contraception. You will be randomized to use the TAF/EVG insert either 1 hour or 4 hours before and after sex. You and your partner will be sent reminders by phone and/or text regarding the timing of insert use and sex. You will be asked to use one vaginal insert at 3 of the 10 visits, beginning at Enrollment. You will have blood collected, pelvic exams done, vaginal swabs collected, and cervicovaginal biopsies taken. You are also asked to agree to not use vaginal products or engage in vaginal, oral and/or anal sexual activity for 48 hours before and after dosing (at Visits 2, 5 and 8) and for at least 10 days after biopsies are taken (at Visits 3, 6 and 9).




If you are randomized to use the insert 1 hour before and after sex, you will be required to use the insert 1 hour before sex in Stage 1 and 1 hour after sex in Stage 2. The necessary samples will be taken 6 hours after you have used the insert, which will be 5 hours after sex in Stage 1 and 7 hours after sex in Stage 2.

If you are randomized to use the insert 4 hours before and after sex, you will be required to use the insert 4 hours before sex in Stage 1 and 4 hours after sex in Stage 2. The necessary samples

will be taken 6 hours after you have used the insert, which will be 2 hours after sex in Stage 1 and 10 hours after sex in Stage 2.

**WHAT WILL HAPPEN DURING THE STUDY VISITS?**

The study includes a total of ten (10) clinic visits, including the Screening Visit today. The procedures done at the Screening Visit will let us know if you and your partner can join this study. It may be necessary to conduct more than one clinic visit to complete all required screening procedures. All visits will take place at this research clinic. The table below outlines procedures that will be conducted at these visits. Note, the cross (X) is a required procedure and the star (*) represents procedures that are only done if indicated. Study staff may contact you and/or your partner by phone to complete some of the visit procedures, if needed.

Also note that the IDI may be conducted at any point between Visit 8 and Visit 10 and is not required to align with a scheduled clinical study visit.

| STUDY PROCEDURES | SCR V1 | Stage 0 (No sex) | | | Stage 1 (1hr/4hrs Pre sex) | | | Stage 2 (1hr/4hrs Post sex) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | ENR V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | SEV V10 |
| **ADMINISTRATIVE AND REGULATORY** | | | | | | | | | | |
| Conduct informed consent process to confirm you are willing and able to join the study. | X | | | | | | | | | |
| Assess / confirm your and your partner's eligibility to join the study. | X | X | | | | | | | | |
| Collect / review / update your contact information (i.e., where you live and how we can get in touch with you). | X | X | X | X | X | X | X | X | X | X |
| Reimburse you for your visit. | X | X | X | X | X | X | X | X | X | X |
| Schedule your next visit / contact, if applicable. | * | * | X | X | X | X | X | X | X | |
| Randomly assign you to use TAF/EVG vaginal insert either 1 hour or 4 hours before and after sex (1:1). | | X | | | | | | | | |
| **BEHAVIORAL/COUNSELING** | | | | | | | | | | |
| Talk with you about and/or review the requirements of the study, including the importance of completing clinic visits, study activities and procedures according to the study schedule. | X | X | X | X | X | X | X | X | X | |
| Conduct individual / couple HIV pre- and post-test risk reduction counselling. | X | X | * | * | X | * | * | X | * | X |
| Collect your demographic information. | X | | | | | | | | | |
| Administer behavioral and/or acceptability questionnaires (asking you questions about your thoughts on using the study product). | X | X | | | X | | | X | | |
| Ask you to discuss in greater detail your experiences using the vaginal insert, if selected for a longer interview and you agree to participate (see In-Depth Interview Subset section for details). | | | | | | | | X | X | X |
| **CLINICAL** | | | | | | | | | | |
| Perform a full physical examination at screening and then a directed physical exam, if needed at other visits. | X | * | * | * | * | * | * | * | * | * |
| Collect vital signs, weight and (at Screening only) height. | X | X | X | X | X | X | X | X | X | X |
| Ask you questions about and/or review your medical health (including what medications you are taking and the method of family planning you are using) and menstrual history. May also ask to view your medical records, with your permission. | X | X | X | X | X | X | X | X | X | X |
| Perform a pelvic examination (bimanual examination at Screening) to check your vagina and cervix for signs of infection and other problems. | X | X | X | X | X | X | X | X | X | X |

| STUDY PROCEDURES | SCR V1 | Stage 0 (No sex) | | | Stage 1 (1hr/4hrs Pre sex) | | | Stage 2 (1hr/4hrs Post sex) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | ENR V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | SEV V10 |
| Ask you about any health or medical problems you may be currently experiencing or that have occurred since your last visit, including any bad or harmful events. | | X (post use) | X | X | X | X | X | X | X | X |
| **SAMPLE COLLECTION** | | | | | | | | | | |
| Collect your saliva to test for HIV (only at sites with CLIA certification) | X | X | * | * | X | * | * | X | * | X |
| Test your urine for pregnancy and/or infections. | X | X | * | * | X | * | * | X | * | * |
| Take a blood sample *[SITES TO INSERT AMOUNT]* to test for HIV and/or in case there is a question about your HIV test results at a later time. | X | X | * | * | X | * | * | X | * | X |
| Take a blood sample *[SITES TO INSERT AMOUNT]* to test for infections typically passed through sex, including Hepatitis B. | X | * | * | * | * | * | * | * | * | * |
| Take a blood sample *[SITES TO INSERT AMOUNT]* to test the health of your blood, liver and kidneys. | X | * | * | * | * | * | * | * | * | X |
| Take a blood sample *[SITES TO INSERT AMOUNT]* for storage. | | X | | | | | | | | |
| Take a blood sample *[SITES TO INSERT AMOUNT]* for research purposes, including to measure the amount of study drug present in your body when using the vaginal insert. | | X | X | X | X | X | X | X | X | X |
| Collect a small amount of vaginal fluid via swab(s), like a Q-tip, to test for sexually transmitted infections and diseases (commonly known as STIs or STDs) and other problems. | X | * | * | * | * | * | * | * | * | * |
| May collect samples from your cervix for a “Pap test” or “Pap smear”. | * | | | | | | | | | |
| Collect vaginal fluid for research purposes, including to measure the amount of study drug present in your body when using the vaginal insert, measure changes in the vagina during use, and test for the presence of semen in the vagina. | | X | X | X | X | X | X | X | X | X |
| Perform a biopsy to collect small tissue samples from your vagina [*US SITE ONLY:* and cervix] for research purposes, including to measure the amount of study drug present in your body when using the vaginal insert. | | | X | | | X | | | X | |
| **STUDY PRODUCT SUPPLY** | | | | | | | | | | |
| Give you 1 vaginal insert to self-insert (<u>without</u> sex at the Enrollment Visit / V2 and either 1 hour <u>or</u> 4 hours before and after sex at Visits 5 and 8, depending on which study group you were assigned to). | | X | | | X | | | X | | |
| **APPROXIMATE DURATION OF EACH VISIT** | | | | | | | | | | |
| Approximate time in hours *[SITES TO INSERT APPROXIMATE DURATION UNDER EACH VISIT]* | *XX* | *XX* | *XX* | *XX* | *XX* | *XX* | *XX* | *XX* | *XX* | *XX* |

The next table gives you more details about some of the procedures listed above.

| Procedure or Test | Description / Additional Information |
|---|---|
| Physical examination | Includes general appearance and evaluation of the abdomen, heart and lungs. |
| Pelvic examination | The study clinician will use a speculum (a plastic or metal instrument inserted in the vagina). Study staff will ask if you are experiencing symptoms of an infection. |
| Pap test / Pap smear | Study staff will inform you of the results of your Pap test when available. It takes about *[SITES TO INSERT AMOUNT OF TIME]* before Pap test results are ready. |

| Procedure or Test | Description / Additional Information |
|---|---|
| | If you have a written report confirming a normal Pap test in the past 3 years, you will not need to have a Pap test taken at this screening visit. The results of your Pap test may affect whether you can join the study. |
| Cervicovaginal biopsy | The study clinician will take approximately *[XXX]* adequate samples from your vagina, each about the size of a grain of rice.<br><br>It is important that you do not put anything in your vagina for at least 10 days after the biopsy tissue collections, which includes avoiding sexual intercourse, because you may be at higher risk for getting or spreading an infection until the biopsy sites have healed.<br><br>It is also important that you do not take any aspirin or NSAIDs for 3 days before and after the biopsy tissue collections, because you may be at higher risk of bleeding. |
| Individual / couple HIV post-test risk reduction counselling | You will be told your test results as soon as they are available. You will talk with the study staff about the meaning of your results, how you feel about them, and learn about ways to prevent HIV and other STIs.<br><br>Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we are sure of your status.<br>To participate in the study, you must receive the results of your HIV test. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any. |
| Assess and/or review your method of family planning | Study staff will talk with you about ways to avoid becoming pregnant. You will answer questions about whether you are using an effective method of contraception and intend to use this method for the entire time that you are in this study. Effective methods include:<br>• Sterilization by you or your partner (tubal ligation, vasectomy, etc.).<br>• Use of hormonal methods except contraceptive vaginal rings for at least 6 months before enrollment.<br>• Intrauterine devices (IUDs) inserted at least 6 months before enrollment. |
| Behavioral and acceptability questionnaires | Study staff will ask you questions such as your prior experience with and comfort using vaginal products, your initial thoughts on the study product and your thoughts on the vaginal insert after using it before and after sex. It is important that you know that you will answer these questions in private and your responses will be kept confidential. |
| Randomization | You will be randomly assigned to use the vaginal insert either 1 hour or 4 hours before and after sex. |
| Self-insertion of study product | Study staff will talk with you about what to do if you have any problems or symptoms while using the vaginal insert. |

If you enroll in the study, you will be asked to abstain from the following activities for specified periods of time prior to your clinic visits. See stated length of time below:

- 48 hours before and after dosing (at Visits 2, 5 and 8) and at least 10 days after biopsy tissue collections (at Visits 3, 6 and 9):
    - Vaginal, oral and/or anal intercourse (except vaginal intercourse when required at Visits 5 and 8)
    - Finger stimulation
    - Insertion of any objects into the vagina or rectum including
        - Sex toys
        - Female condoms, diaphragms, or other vaginal barrier methods

        - Menstrual cups and tampons
- 3 days before and after biopsy tissue collections:
    - Use of aspirin or NSAIDs
- For the duration of the study:
    - Use of any drugs which could prolong bleeding and/or clotting or otherwise interfere with study results per study criteria (i.e., St. John's Wort, blood thinners, etc.)
    - Use of vaginal products including
        - Spermicides, lubricants, douches, medications, or moisturizers
        - Contraceptive vaginal rings

If you do not join the study, blood and other samples collected at the Screening visit(s) will not be kept or used for any tests other than those listed above. If you do join the study, test results from samples collected for research purposes throughout the study will not be shared with you.

**Additional Visits and Procedures**
In addition to the procedures listed above, a study doctor may ask you to make additional visits to have study procedures repeated. Any study procedure may be repeated if needed, including giving you an additional insert dose to use.

It is also possible that study clinicians may need to perform additional tests, if necessary (e.g., if you report having symptoms of a urinary, genital, or other infection and/or other issues). These tests might include the following:

- Physical exam
- Pelvic exam
- Test vaginal swab samples for STIs
- Test your urine for STIs or other infections
- Test your blood for STIs
- Test your blood to check the health of your blood, liver and kidneys
- Give you treatment or refer you for treatment of STIs or other issues, if needed.

You may be asked to make additional visits so we can do more laboratory tests. We will do this if there are abnormal test results or problems/mistakes during the collection, processing and/or shipping of your samples.

It is important for you to come to every study visit. If you cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

It is important that you remember that at any time during the study, study staff can answer any questions you may have about the procedures mentioned above or any other aspect of this study. We may also contact you and/or your partner to follow up about your health during and after the study.

**In-depth Interview Subset:**
You and/or your partner may be asked to participate in an interview with a trained staff member to discuss your experiences during study participation. You and your partner will be given the option of completing the interview individually or as a couple, if both of you agree and are selected

to participate in the interview. The interview would take place sometime between Visit 8 and Visit 10, depending on your preference and availability. Up to 20 couples across two sites will be interviewed. If you are asked to participate in this interview, you will be asked questions about your experiences during the study, including using the vaginal insert, your preferences and opinions, any problems you may have had using the insert, and whether you used the vaginal insert as instructed or not. This interview may take approximately 60-90 minutes and may take place in the clinic or at an alternate location, as schedules permit and as approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). An IRB/IEC is a committee that watches over the safety and rights of study participants. The interviews will be audio-recorded to make sure to record your words exactly how you said them. The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or fake names, and the hardware will be physically protected in a locked area. This means that no one other than the study team will have access to your responses. The information that links you to the research materials will be kept in a secure location that will be accessed only by members of the study team for the purposes of this research. [*SITES TO MODIFY WITH THEIR SITE-SPECIFIC SOURCE DOCUMENTATION STORAGE DURATION REQUIREMENTS IF REQUIRED BY THEIR IRB/IEC:* The audio recordings, notes, and transcripts from these materials will be kept for at least two years after the vaginal insert is approved for marketing or two years after all developmental research on the vaginal insert is stopped.]

[*NON-US SITES TO INCLUDE/AMMEND THE FOLLOWING PER LOCAL REGULATIONS/GUIDELINES:*

**WHAT WILL HAPPEN TO MY SAMPLES?**

During this study, samples of your blood, urine, vaginal fluids and cervicovaginal tissue will be taken to the site laboratory for the tests mentioned in this consent form. Some of the tests will be done right away. For other tests, the samples will be stored in the site laboratory during the study and tested in batches at the end of the study. But, not all of the tests will be done in [*Insert country*]; some of the samples of your blood, vaginal fluid and cervicovaginal tissue will be shipped to the study laboratory outside the country for testing. Only the study tests mentioned in this consent form will be done on your samples in that external laboratory. Your identity on these samples will be indicated by a number rather than by your name, and the information linking these numbers with your name will be kept separate from the samples. When the researchers are certain none of those tests must be repeated, any samples leftover in the external laboratory will be destroyed.]

**WHAT IF I BECOME INFECTED WITH HIV?**

We do not know if the vaginal insert will prevent HIV infection. Persons living with HIV will not be included in this study. Being in this study will not cause HIV infection. But there is always a chance that you or your partner can get HIV through unprotected sex or other activities. If you become HIV-positive, you will stop using the study products. The study staff will refer you for medical care and other available services. The study does not pay for this care. If you get HIV, it is possible that the virus is resistant to some drugs. This means that some drugs may not work well to treat your HIV. We will do a blood test to find out if you have drug resistance. These results can help us know which drugs would be best to treat your HIV. [*SITES TO INCLUDE/AMMEND THE FOLLOWING IF APPLICABLE:* If you are interested, study staff will inform you of other available research studies you may be eligible for.]

Depending on local and national health requirements, the study staff may need to report certain diseases, including HIV. The reportable diseases at this site are [*SITES TO INSERT*]. We must inform the following [*SITES TO INSERT MORE DETAILED INFORMATION REGARDING WHO WILL BE INFORMED OF THE REPORTABLE DISEASES*]. [*SITES TO INCLUDE/AMMEND THE FOLLOWING*]: Outreach workers from the [*LOCAL HEALTH AUTHORITY*] may then contact you about informing your partner/s, since they also should be tested. If you do not want to inform your partner/s yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [*LOCAL HEALTH AUTHORITY*].

**WHAT IF I BECOME PREGNANT?**

The TAF/EVG vaginal inserts are not family planning methods and will not prevent pregnancy. We do not know what effect the study products have on pregnancy, including any effect on the unborn babies. Because of this, pregnant women cannot join this study. Also, you must use an effective family planning method (e.g., birth control pills, hormonal-based methods, intrauterine device [IUD], etc.) other than a vaginal ring, unless your partner has had a vasectomy.

If you become pregnant during the study, study staff will refer you to available medical care and other services. The study does not pay for this care. You will stop using the study product. We may contact you to find out about the health of your pregnancy and baby. [*SITES TO INCLUDE/AMMEND THE FOLLOWING IF APPLICABLE:* If you and/or your partner are interested, study staff will inform you of other available research studies you may be eligible for.]

**RISKS AND/OR DISCOMFORTS**

**Risks of Blood Draws**

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, small clot, or infection where the needle goes into your hand or arm.

**Risks of Pelvic Exams**

You may feel discomfort or pressure during the pelvic exam and vaginal fluid collection. You may have a small amount of vaginal bleeding or spotting which should stop shortly after the exam.

**Risks of Cervicovaginal Tissue Collection Procedures**

Cervicovaginal tissue biopsies carry the risk of discomfort or pain during the procedure and for a few hours afterwards. You may have spotting (bleeding) for one or two days. There is also a small risk of infection and heavier bleeding. You may also be at increased risk for STIs and HIV acquisition, if exposed. You will be encouraged to call the clinic to report any problems after the collection, especially if heavy bleeding is noted (soaking through a pad in an hour or less) or if you develop any abnormal odor or discharge. Note: You are also asked to agree to not use vaginal products or engage in vaginal, oral and/or anal sexual activity for at least 10 days post-biopsy.

**Risks of Vaginal Inserts**

The vaginal inserts may cause irritation of the vagina and external genitalia, including pain, itching, irritation, vaginal discharge, or rash. The insert may also cause urinary symptoms including dysuria, frequency, or urgency.

**Risks of TAF/EVG**
The following side effects have been associated with the use of EVG in participants in other studies in which the drug was taken by mouth. These side effects may or may not be associated with the use of EVG when the drug is taken vaginally. The most common adverse reactions (i.e., occurring in 10% or more of participants receiving EVG by mouth) were: headache, diarrhea, nausea, and tiredness. Other common adverse reactions (i.e., occurring in between 1% and 10% of participants receiving EVG by mouth) were: depression, inability to sleep, pain in abdomen, vomiting, indigestion, and rash. Uncommon adverse reactions (i.e., occurring in between 0.1% and <1% of participants receiving EVG by mouth) were: depression, inability to sleep, and suicidal thoughts and suicide attempt in patients with a history of depression or psychiatric illness.

The following side effects have been associated with the use of TAF in participants in other studies in which the drug was taken by mouth. These side effects may or may not be associated with the use of TAF when the drug is taken vaginally. The most common adverse reactions (i.e., occurring in 5% or more of participants receiving TAF) were: headache, abdominal pain, cough, back pain, fatigue, nausea, joint pain, diarrhea, and dyspepsia. Other common adverse reactions (i.e., occurring in between 1% and 5% of participants receiving TAF) were: vomiting, rash, and flatulence.

There is a theoretical risk of the development of HIV drug resistance to tenofovir or EVG if the participant acquires HIV infection around the time of study drug administration.

It is also possible that you may have an allergic reaction to the study product. Signs of allergic reaction may include: rash, dizziness, itching, muscle aches, nausea, fainting, facial flushing, chest tightness, cough, hives, fever, and shortness of breath.

**Risks of HIV and Sexually Transmitted Infection (STI) Testing**
HIV and STI testing may make you feel anxious regardless of the test results. Finding out your HIV status may also cause problems with your family, friends, or partner.

**Other Possible Risks**
You may feel embarrassed and/or worried when talking about sexual activities, your living situation, ways to protect against HIV and STIs, and your test results. You can choose not to answer questions at any time. Trained study staff will help you with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. Reports via computer will be stored on computers that are password-protected and will not include personal information that could identify or link information to you; only your study ID number will be recorded. However, it is possible that others may learn of your participation in this study, and because of this, may treat you unfairly or discriminate against you. If you have any problems, study staff will talk with you and try to help you.

If you and your partner are selected for an in-depth interview and you agree, the interview may be performed [*SITES TO SPECIFY MECHANISM:* at the clinic / remotely]. The interview will be audio recorded and questions of a personal nature may be asked. Responding to these questions may make you uncomfortable. The audio files will be put into writing by the person interviewing

you or by another person who does not know you and does not have your personal information. You should NOT identify anyone in the interviews and any names that might be mentioned on the recording will only be noted in the transcript using a generic description. The audio files will be stored on computers that are password protected.

**BENEFITS**

Though you and your partner may not experience any direct benefit from participation in this study, information learned from this study may help us develop more options to prevent the spread of HIV in the future. You may enjoy sharing your opinions about the insert and other HIV prevention methods with the study team. You will receive medical exams and counseling and testing for HIV and STIs. You will also have tests to check your overall health.

This study cannot give you or your partner general medical care, but study staff will refer you to another medical provider for care, if needed. If you have an STI diagnosed, you will receive medicine or a referral, if you need it.

**NEW INFORMATION**

You and your partner will be told about any new information learned during this study that may affect your willingness to stay in the study. For example, we will let you know if we learn that the study products may be causing bad side-effects. We will also tell you when study results may be available, and how to learn about them.

**WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE ASKED TO LEAVE THE STUDY**

You and your partner may need to leave the study early without your permission if:

- The study is cancelled by the US Food and Drug Administration (FDA), USAID, CONRAD, the US Office for Human Research Protections (OHRP), MATRIX, the local government or medicines regulatory agency, or the IRB/IEC.
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully.

The study doctor will ask you to stop using the study products if:

- You or your partner are found to be infected with HIV (see "What If I Become Infected With HIV" section).
- You become pregnant or are breastfeeding (see "What If I Become Pregnant" section).
- You or your partner acquire an STI.
- You or your partner experience a serious adverse event while on study.
- You or your partner fail to follow study requirements in a manner judged by the study doctor to significantly put you at risk of an adverse reaction or otherwise affect study outcomes.
- A study clinician decides that using the study product would be harmful to you or your partner, for example, you have a bad reaction to the vaginal insert(s).

If a study doctor asks you to stop using study product, we will ask you and your partner to come in for an interim visit during which the procedures scheduled to occur on the Study Exit Visit (Visit 10 for you and Visit 8 for your partner) will be completed. You will then be exited from the study, unless otherwise informed by study staff. We may contact you and/or your partner to follow up about your health.

If you and/or your partner are removed from the study or choose to leave, we will ask you and your partner to come back for one final clinic visit and to return any study products you may have. If you do not have the study products with you when you come to the clinic, staff members will make every effort to assist you in returning them as soon as possible. [*SITES TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES*]

**ALTERNATIVES TO BEING IN THE STUDY**

There are methods to prevent sexually transmitted HIV, including condom use during sex and/or HIV pre-exposure prophylaxis (PrEP). PrEP is an HIV prevention method where people who do not have HIV take a medication to reduce their risk of becoming infected. Study staff can provide you with additional information about PrEP if you are interested in learning more, and where to access PrEP.

[*SITES TO INCLUDE/AMEND THE FOLLOWING, IF APPLICABLE*: You may be able to join other studies here or in the community. There may be other places where you can go for HIV counseling and testing and family planning. We will tell you about those studies and those places if you wish.]

**COSTS TO YOU**

[*SITES TO COMPLETE ACCORDING TO SITE CAPACITY*] There is no cost to you or your partner for study visits, study products, physical/clinical exams, laboratory tests or other procedures. We can give you treatments for STIs (other than HIV) at no cost while you are in the study, or we can refer you for available treatment.

**REIMBURSEMENT**

[*SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT:*] You will receive [*SITES TO INSERT AMOUNT $XX*] for your time, inconvenience, and travel to and from the clinic for each scheduled study visit. You may receive [*SITES TO INSERT AMOUNT $XX*] for any extra study visits requested by the study doctor/study team. If you are chosen to take part in the in-depth interview, you will receive [*SITES TO INSERT AMOUNT $XX*].

**CONFIDENTIALITY**

We will make every effort to keep your information private and confidential. But we cannot guarantee it.

Study visits will take place in private. We will keep the information about your study visits in a secure place that only certain people can access for the purposes of this study. We will only enter your information into computers protected by passwords and will not include information that could identify you or your partner. Your identity on these records will be indicated by a number rather than by your name, and the information linking these numbers with your name will be kept separate from the research records. You can choose not to answer questions at any time. If you are selected to do the in-depth interview, you can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names. We will store the original records, including the audio recordings, for at least two years after either the study insert is approved for use or research on the insert is stopped. These records will be stored in a secure, locked location.

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff must take steps to keep you and others safe. This means that we have to share any information with the authorities (hospital, police, or social services) that tells us you or your partner may be in danger. For example, if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you.

The study staff may use your personal information to verify that you and your partner are not in any other research studies. This study will not use your name or identify you personally in any publication.

[*SITES TO INSERT INFORMATION ABOUT SYSTEMS CURRENTLY IN PLACE TO ENSURE PARTICIPANTS ARE NOT PART OF OTHER CONFLICTING STUDIES, INCLUDING BIOMETRIC IDENTIFICATION SYSTEMS; SEE EXAMPLE BELOW FOR SOUTH AFRICA SITE:*

In clinical studies where drugs, vaccines or medical devices (study products) are being assessed, it is important that you are enrolled in only one clinical study at a time. Using more than one study product at the same time may lead to drug interactions and side effects. It may affect your health and the outcome of the study.

The Biometric Co-Enrollment Prevention System (BCEPS) is a web-based system developed by the South African Medical Research Council's IT (Information Technology) department, for the prevention of co-enrolment (being enrolled in more than one study at a time). It is a secure system that is used to ensure your safety, as well as study data integrity.

Authorized study staff will enter your South African Identification number (SA ID) or SA/foreign Passport Number into the system to check if you are enrolled in any study within any of the organizations using BCEPS in South Africa. During screening for a study at a CAPRISA clinic/site, your SA ID number or SA/foreign Passport Number and fingerprints are captured onto the system. At every visit thereafter, your SA ID number or SA/foreign Passport Number and fingerprints will be checked.]

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US OHRP, USAID and/or USAID contractors, the local government or medicines regulatory agency, and other local, national, or international regulatory authorities
- [*SITES TO INSERT APPLICABLE LOCAL AND NATIONAL AUTHORITIES*]
- CONRAD representatives
- MATRIX representatives
- Study monitors
- Site IRBs/IECs
- Study staff

[*US SITE TO INCLUDE/AMEND THE FOLLOWING:* Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form, you provide your authorization for the use and disclosure of information protected by the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. This includes things learned from the procedures

described in this consent form. Study staff may also collect other information including your name, address, date of birth, and information from your medical records.]

[*NON-US SITES TO INCLUDE/AMEND THE FOLLOWING:* As part of your participation in this research study, your personal information may be sent to the United States for analysis or storage. This includes things learned from the procedures described in this consent form. Study staff may also collect other information including your name, address, date of birth, and information from your medical records. There are laws in the U.S. to protect your personal information when in that country.]

[*SOUTH AFRICA SITE TO INCLUDE/AMEND THE FOLLOWING:* The Protection of Personal Information Act (POPIA) ensures that all South African institutions collect, process, store, and share your personal information in a responsible manner and that they will be held accountable should they abuse or compromise your personal information.]

People outside the study team may need to see or receive your information for this study, such as those listed above. We cannot do this study without your authorization to use and give out your information to them. You do not have to give us this authorization. If you do not, then you may not join this study.

The use and disclosure of your information has no time limit. You may cancel your authorization to use and disclose your information at any time by notifying the Principal Investigator of this study in writing. If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

**RESEARCH-RELATED INJURY**

[*SITES TO SPECIFY INSTITUTIONAL POLICY:* It is unlikely that you will be injured by being in this study. If you are injured or get sick from being in this study, please tell study staff immediately.

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. If you become ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you for ongoing treatment for the injury, if needed. Clinical trial insurance is provided by CONRAD and will be responsible for compensating you for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research center or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because you used other medicine during the study that you did not tell us about.
- Any injury that happens because you did not follow instructions given by the study doctor or nurse.
- Any injury that happens because of negligence on your part.]

[*SITES TO SPECIFY ANY ADDITIONAL POLICY RELATED TO EMERGENCY MEDICAL ATTENTION*]

[*US SITE TO INCLUDE/AMEND THE FOLLOWING:* To pay these medical expenses, the sponsor will need to know some information about you, like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.]

You are not giving up any legal rights by signing this form.

**CLINICALTRIALS.GOV**
A description of this research study will be available on https://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

[*SOUTH AFRICA SITE TO INCLUDE LANGUAGE RELATED TO SOUTH AFRICAN NATIONAL CLINICAL TRIALS REGISTER*]

**YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER**
[*SITES TO SPECIFY INSTITUTIONAL POLICY:*] Being in this study is completely voluntary. You or your partner may choose not to join this study or leave this study at any time. If you or your partner choose not to join or to leave the study, you can still join other studies and you can still access non-study services you would normally get at this or another clinic. If you leave the study, your specimens will be destroyed when all protocol-specified testing has been completed and your study records may be kept for at least two years after either the vaginal insert is approved for use or research on the insert is stopped. If you want the results of the study after it is over, let the study staff members know.

**PROBLEMS OR QUESTIONS**
If you or your partner ever have any questions about the study, or if you have a research-related injury, you should contact [*SITES TO INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF*] at [*SITES TO INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS*].

If you or your partner have questions about your rights as a research participant, you should contact [*SITES TO INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE*] at [*SITES TO INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER*].

*[SITES TO OMIT THE FOLLOWING IF A SEPARATE CONSENT IS REQUIRED FOR IDI]*

**CONSENT TO PARTICIPATE IN AN IN-DEPTH INTERVIEW**

We would like to ask your and your partner's permission to participate in an in-depth interview (IDI) at the end of the study to gather more feedback about the vaginal insert. If you agree and are selected to participate in the IDI, trained study staff will ask you questions about your experiences using the product, about product design, packaging and delivery, and other topics related to product use during sex. The IDI may be conducted at the study site, over a secure digital platform, or an agreed upon location. If both you and your partner agree and are selected to participate in the interview, you will be given the option of completing the interview individually or as a couple.

The IDI is anticipated to last approximately 60-90 minutes. Study staff will take notes and record the interview. You can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names to identify them. These materials will be stored in a secure, locked location for at least two years after either the study insert is approved for use or research on the insert is stopped.

Please read the following statement carefully and initial and date one option. We will reconfirm the decision you and your partner make today at later study visits should you change your mind about participating in the IDI.

**You can still enroll in this study if you or your partner decide not to participate in the IDI. You can withdraw your consent to participate in the IDI at any time.**

| | | |
|---|---|---|
| _____ Initials | _____ Date | I DO agree to participate in an in-depth interview. I understand the interview will be recorded and notes will be taken. |
| _____ Initials | _____ Date | I DO NOT agree to participate in an in-depth interview. |

*[SITES TO OMIT THE FOLLOWING IF NOT APPLICABLE]*

**CONSENT FOR OFF-SITE VISITS**

If the site determines that an off-site visit is appropriate and with your permission, members of the research team at this clinic may be able to schedule off-site visits with you and/or your partner at your home or at another location as part of the study. Some of the scheduled study visits and some of the study procedures may take place at your home or other location(s) outside of the research clinic. For example, if you need to receive vaginal inserts or to have a urine or blood sample collected but you are unable to come into the clinic. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the time it will take) and the procedures in place to maintain your information in a confidential manner. However, it is important that you know that off-site visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

We will only conduct visits outside of the clinic if you give us permission to do so. Please read the following statement carefully and initial and date one option. Choosing not to have study visit procedures outside of the study clinic will not affect your participation in this study. Even if you agree today, you can withdraw your consent for off-site visits at any time by providing your request in writing to the person in charge of this study. In addition, before each off-site visit, we will confirm with you that you still agree and remember today's discussion.

| | | |
|---|---|---|
| _____<br>Initials | _____<br>Date | I DO agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary. |
| _____<br>Initials | _____<br>Date | I DO NOT agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary. |

**SIGNATURE PAGE**

*[SITES TO INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/IEC:]*
All of the above has been explained to me and all of my current questions have been answered. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form or their representatives.

Any questions I have about my rights as a research participant will be answered by *[SITES TO INSERT LOCAL IRB/IEC INFORMATION].*

I voluntarily agree to be in this research study. A copy of this permission form will be given to me.

_____
Participant's Name (Print)

_____ _____
Participant's Signature Date

_____
Study Staff's Name Conducting
Consent Discussion (Print)

_____ _____
Study Staff Conducting Date
Consent Discussion (Signature)

_____
Witness Name (Print), if required

_____ _____
Witness Signature, if required Date

## APPENDIX VII: SAMPLE INFORMED CONSENT FORM (SCREENING and ENROLLMENT)

## SAMPLE INFORMED CONSENT FORM – MALES

## MATRIX-004
## Phase I Evaluation of the Impact of Vaginal Coitus on the Pharmacokinetics of Tenofovir Alafenamide and Elvitegravir Vaginal Insert

## USAID

## Version 1.0
## 18 October 2024

**PRINCIPAL INVESTIGATOR:** *[SITES TO INSERT]*
**INSTITUTION:** *[SITES TO INSERT]*
**AFTER HOURS CONTACT DETAILS:** *[SITES TO INSERT]*
**STUDY SITE CONTACT DETAILS:** *[SITES TO INSERT]*
**SHORT TITLE:** Impact of Coitus on TAF/EVG Vaginal Insert

**INFORMED CONSENT**

[*SITES TO INSERT APPROPRIATE GREETING*] You and your partner are invited to take part in this research study because you are an adult male over 18 years old in a monogamous relationship with an adult female partner. Approximately thirty-two (32) couples will take part in this study across two sites in the United States and South Africa. This study is funded by the US Agency for International Development (USAID) and conducted by CONRAD as part of the MATRIX (Microbicide R&D to Advance HIV Prevention Technologies through Responsive Innovation and eXcellence) Collaborative. The study products are supplied by CONRAD. At this site, the person in charge of this study is [*SITES TO INSERT NAME OF CRS PI/IOR*].

**KEY INFORMATION**

- The study product in this clinical trial is a vaginal insert that contains tenofovir alafenamide (TAF) and elvitegravir (EVG). The vaginal insert is in a solid form that looks like a tablet that is made to dissolve quickly in the vagina. It contains 20 mg TAF and 16 mg EVG. Both drugs are used to treat HIV in oral form. This study will focus on how the vaginal insert containing TAF and EVG works when used before and after sex.
- The purposes of this study are:
    - To better understand how TAF and EVG enter and exit the body when the vaginal insert is used before and after sex.
    - To find out if it is safe to use the vaginal insert before and after sex.
    - To understand whether you find it acceptable for your partner to use the vaginal insert before and after sex.
- If you and your partner are eligible and choose to participate, your partner will receive 3 doses of the TAF/EVG vaginal insert, 20/16 mg.

- You will be asked to attend 3 clinic visits at this research clinic and will be followed for approximately 8 weeks. The total length of your participation in this study will be about 2-3 months.
- [*SITES TO DELETE IF NOT REQUIRED BY IRB/IEC:* At some of the clinic visits, the following will occur (other things may happen that are not listed here but are in the detailed descriptions of the study procedures):
    - Blood will be obtained to test for HIV and/or other sexually transmitted infections (STI) and for research purposes.
    - You will be asked to complete questionnaires about the vaginal insert and/or its use around sex.
    - We may also ask you and/or your partner to do one in-depth interview (IDI) with a staff member before or at your partner's final visit. You will have the option to complete the interview individually or as a couple. We will audio-record the interview(s). It is your choice if you want to do the interview.]
- You and your partner may not experience any direct benefit from participation in this study, but information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive HIV/STI risk reduction counseling, HIV and STI testing, and physical exams. You will have the option to receive HIV/STI counseling individually or as a couple.
- Taking part in this research study is voluntary. You and your partner do not have to participate, and you can stop your participation in the study at any time.

Please take the time to read this entire form and ask questions before deciding to join the study. If you and your partner are willing to take part in the study, you will sign this form. A copy of this form will be offered to you. Signing this form does not mean you will be able to join the study. You and your partner must first complete the screening tests and clinical examinations to see if you are eligible. It is important to know that your and your partner's participation in this research study is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

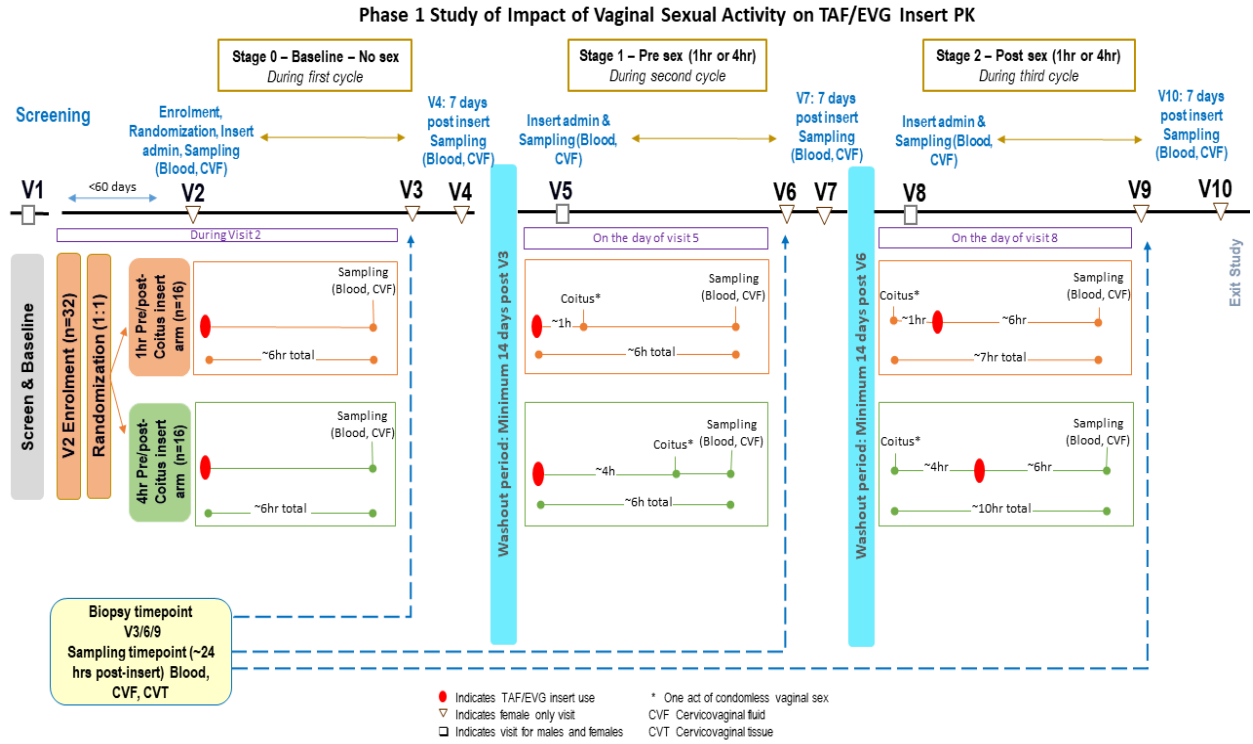
**WHY IS THIS RESEARCH BEING DONE?**
This study is being done to assess how TAF and EVG enter and exit the female body when the vaginal insert is used before and after sex.

**WHO WILL BE IN THIS RESEARCH STUDY?**
Approximately thirty-two (32) men who are over 18 years old and their adult female partners will be enrolled in the study across two sites in the United States and South Africa.

**DO I HAVE TO BE IN THIS STUDY?**
You and your partner do not have to be in this study. You and your partner can still get the care you need at your local health care facility even if you do not join the study. If you and your partner decide to join the study, you can change your mind later.

**WHAT WILL I BE ASKED TO DO IF I JOIN THIS RESEARCH STUDY?**
Site investigators will assess if you and your partner are eligible for the study at this visit. You and/or your partner may be contacted by phone after this visit to confirm your eligibility before your partner's next visit. If eligible, your partner will have a total of ten (10) visits and you will have a total of three (3) visits over approximately 2-3 months. Your partner will be required to

use an acceptable method of contraception. Your partner will be randomized to use the TAF/EVG insert either 1 hour or 4 hours before and after sex at 2 of the 3 visits. You and your partner will be sent reminders by phone or text regarding the timing of insert use and sex. You and your partner will also be asked to agree to not engage in vaginal, oral and/or anal sexual activity for 48 hours before and after dosing (at Visits 2, 5 and 8) and for at least 10 days after your partner's cervicovaginal biopsies are taken (at Visits 3, 6 and 9).




If your partner is randomized to use the insert 1 hour before and after sex, she will be required to use the insert 1 hour before sex in Stage 1 and 1 hour after sex in Stage 2. Samples from your partner will be collected 6 hours after she has used the insert, which will be 5 hours after sex in Stage 1 and 7 hours after sex in Stage 2.

If your partner is randomized to use the insert 4 hours before and after sex, she will be required to use the insert 4 hours before sex in Stage 1 and 4 hours after sex in Stage 2. Samples from your partner will be collected 6 hours after she has used the insert, which will be 2 hours after sex in Stage 1 and 10 hours after sex in Stage 2.

**WHAT WILL HAPPEN DURING THE STUDY VISITS?**

The study includes a total of ten (10) clinic visits, including the Screening Visit today, although you would only need to attend a minimum of three (3) of the visits. All visits will take place at this research clinic. The table below outlines procedures that will be conducted at these visits. Note, the cross (X) is a required procedure and the star (*) represents procedures that are only done if indicated. Study staff may contact you and/or your partner by phone to complete some of the visit procedures, if needed.

Also note that the IDI may be conducted at any point between Visit 8 and your partner's final study visit and is not required to align with a scheduled clinical study visit.

| STUDY PROCEDURES | SCR V1 | Stage 1 (1hr/4hrs Pre sex) V5 | Stage 2 (1hr/4hrs Post sex) V8 |
|---|---|---|---|
| **ADMINISTRATIVE AND REGULATORY** | | | |
| Conduct informed consent process to confirm you are willing and able to join the study. | X | | |
| Assess / confirm your and your partner's eligibility to join the study. | X | | |
| Collect / review / update your contact information (i.e., where you live and how we can get in touch with you). | X | X | X |
| Reimburse you for your visit. | X | X | X |
| Schedule next visit / contact, if applicable. | * | X | X |
| **BEHAVIORAL/COUNSELING** | | | |
| Talk with you about and/or review the requirements of the study, including the importance of completing clinic visits, study activities and procedures according to the study schedule. | X | X | X |
| Conduct individual / couple HIV pre- and post-test risk reduction counselling. | X | X | X |
| Collect your demographic information. | X | | |
| Administer behavioral questionnaires (asking you questions about your thoughts on your partner using the study product). | X | X | X |
| Ask you to discuss in greater detail your experiences of your partner using the vaginal insert, if selected for a longer interview and you agree to participate (see In-Depth Interview Subset section for details). | | | X |
| **CLINICAL** | | | |
| Perform a directed physical exam. | X | * | * |
| Collect vital signs, weight and (at Screening only) height. | X | X | X |
| Ask you questions about and/or review your medical health (including what medications you are taking). May also ask to view your medical records, with your permission. | X | X | X |
| Ask you about any health or medical problems you may be currently experiencing or that have occurred since your last visit, including any bad or harmful events. | | X | X |
| **SAMPLE COLLECTION** | | | |
| Collect your saliva to test for HIV (only at sites with CLIA certification) | X | X | X |
| Test your urine for sexually transmitted infections and diseases (commonly known as STIs or STDs) and other problems. | X | * | * |
| Take a blood sample *[SITES TO INSERT AMOUNT]* to test for HIV and/or in case there is a question about your HIV test results at a later time. | X | X | X |
| Take a blood sample *[SITES TO INSERT AMOUNT]* to test for infections typically passed through sex, including Hepatitis B. | X | * | * |
| Take a blood sample *[SITES TO INSERT AMOUNT]* to test the health of your blood, liver and kidneys. | X | * | X |
| **APPROXIMATE DURATION OF EACH VISIT** | | | |
| Approximate time in hours *[SITES TO INSERT APPROXIMATE DURATION UNDER EACH VISIT]* | *XX* | *XX* | *XX* |

The next table gives you more details about some of the procedures listed above.

| Procedure or Test | Description / Additional Information |
|---|---|
| Directed physical examination | Includes general appearance and evaluation of the abdomen, heart, lungs and genital area. |
| Individual / couple HIV post-test risk reduction counselling | You will be told your test results as soon as they are available. You will talk with the study staff about the meaning of your results, how you feel about them, and learn about ways to prevent HIV and other STIs.<br><br>Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we are sure of your status.<br>To participate in the study, you must receive the results of your HIV test. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any. |
| Behavioral questionnaires | Study staff will ask you questions about your experiences with your partner using the study product before and after sex, as well as your opinions on the study product. It is important that you know that you will answer these questions in private and your responses will be kept confidential. |

If you enroll in the study, you will be asked to abstain from the following activities for specified periods of time prior to your clinic visits. See stated length of time below:

- 48 hours before and after dosing (at Visits 2, 5 and 8) and at least 10 days after your partner has biopsy tissue collections (at Visits 3, 6 and 9):
    - Vaginal, oral and/or anal intercourse (except vaginal intercourse when required at Visits 5 and 8)
    - Finger stimulation of your partner
    - Insertion of sex toys into your partner's vagina or rectum
- On the days when sexual activity is required by the protocol (at Visits 5 and 8):
    - Topical genital products (e.g., antifungal creams and antiviral creams)

If you do not join the study, blood and other samples collected at the Screening visit(s) will not be kept or used for any tests other than those listed above.

**Additional Visits and Procedures**

In addition to the procedures listed above, a study doctor may ask you to make additional visits to have study procedures repeated if needed.

It is also possible that study clinicians may need to perform additional tests, if necessary (e.g., if you report having symptoms of a urinary, genital, or other infection and/or other issues). These tests might include the following:

- Physical exam (including genital inspection)
- Test your urine for STIs or other infections
- Test your blood for STIs
- Test your blood to check the health of your blood, liver and kidneys
- Give you treatment or refer you for treatment of STIs or other issues, if needed.

You may be asked to make additional visits so we can do more laboratory tests. We will do this if there are abnormal test results or problems/mistakes during the collection, processing and/or shipping of your samples.

It is important for you to come to all 3 of your scheduled study visits. If you cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

It is important that you remember that at any time during the study, study staff can answer any questions you may have about the procedures mentioned above or any other aspect of this study. We may also contact you and/or your partner to follow up about your health during and after the study.

**In-depth Interview Subset:**
You and/or your partner may be asked to participate in an interview with a trained staff member to discuss your experiences during study participation. You will be given the option of completing the interview individually or as a couple, if both of you agree and are selected to participate in the interview. The interview would take place sometime between Visit 8 and your partner's final study visit, depending on your preference and availability. Up to 20 couples across two sites will be interviewed. If you are asked to participate in this interview, you will be asked questions about your partner's experiences using the vaginal insert, your preferences and opinions, and any problems you may have had with your partner's use of the insert. This interview may take approximately 60-90 minutes and may take place in the clinic or at an alternate location, as schedules permit and as approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). An IRB/IEC is a committee that watches over the safety and rights of study participants. The interviews will be audio-recorded to make sure to record your words exactly how you said them. The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or fake names, and the hardware will be physically protected in a locked area. This means that no one other than the study team will have access to your responses. The information that links you to the research materials will be kept in a secure location that will be accessed only by members of the study team for the purposes of this research. [*SITES TO MODIFY WITH THEIR SITE-SPECIFIC SOURCE DOCUMENTATION STORAGE DURATION REQUIREMENTS IF REQUIRED BY THEIR IRB/IEC:* The audio recordings, notes, and transcripts from these materials will be kept for at least two years after the vaginal insert is approved for marketing or two years after all developmental research on the vaginal insert is stopped.]

**WHAT IF I BECOME INFECTED WITH HIV?**
We do not know if the vaginal insert will prevent HIV infection. Persons living with HIV will not be included in this study. Being in this study will not cause HIV infection. But there is always a chance that you or your partner can get HIV through unprotected sex or other activities. If you become HIV-positive, your partner will stop using the study products. The study staff will refer you for medical care and other available services. The study does not pay for this care. If you get HIV, it is possible that the virus is resistant to some drugs. This means that some drugs may not work well to treat your HIV. We will do a blood test to find out if you have drug resistance. These results can help us know which drugs would be best to treat your HIV. [*SITES TO INCLUDE/AMMEND THE FOLLOWING IF APPLICABLE:* If you are interested, study staff will inform you of other available research studies you may be eligible for.]

Depending on local and national health requirements, the study staff may need to report certain diseases, including HIV. The reportable diseases at this site are [*SITES TO INSERT*]. We must inform the following [*SITES TO INSERT MORE DETAILED INFORMATION REGARDING WHO WILL BE INFORMED OF THE REPORTABLE DISEASES*]. [*SITES TO INCLUDE/AMMEND THE*

*FOLLOWING*]: Outreach workers from the [*LOCAL HEALTH AUTHORITY*] may then contact you about informing your partner/s, since they also should be tested. If you do not want to inform your partner/s yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [*LOCAL HEALTH AUTHORITY*].

**WHAT IF MY PARTNER BECOMES PREGNANT?**

The TAF/EVG vaginal inserts are not family planning methods and will not prevent pregnancy. We do not know what effect the study products have on pregnancy, including any effect on the unborn babies. Because of this, pregnant women cannot join this study. Also, your partner must use an effective family planning method (e.g., birth control pills, hormonal-based methods, intrauterine device [IUD], etc.) other than a vaginal ring, unless you have had a vasectomy.

If your partner becomes pregnant during the study, study staff will refer her to available medical care and other services. The study does not pay for this care. Your partner will stop using the study product. We may contact your partner to find out about the health of the pregnancy and baby. [*SITES TO INCLUDE/AMMEND THE FOLLOWING IF APPLICABLE:* If you and/or your partner are interested, study staff will inform you of other available research studies you may be eligible for.]

**RISKS AND/OR DISCOMFORTS**

**Risks of Blood Draws**

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, small clot, or infection where the needle goes into your hand or arm.

**Risks of HIV and Sexually Transmitted Infection (STI) Testing**

HIV and STI testing may make you feel anxious regardless of the test results. Finding out your HIV status may also cause problems with your family, friends, or partner.

**Risks of Vaginal Inserts**

The vaginal inserts may cause irritation of the male genitalia, including pain, itching, irritation, or rash.

**Other Possible Risks**

You may feel embarrassed and/or worried when talking about sexual activities, your living situation, ways to protect against HIV and STIs, and your test results. You can choose not to answer questions at any time. Trained study staff will help you with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. Reports via computer will be stored on computers that are password-protected and will not include personal information that could identify or link information to you; only your study ID number will be recorded. However, it is possible that others may learn of your participation in this study, and because of this, may treat you unfairly or discriminate against you. If you have any problems, study staff will talk with you and try to help you.

If you and your partner are selected for an in-depth interview and you agree, the interview may be performed [*SITES TO SPECIFY MECHANISM:* at the clinic / remotely]. The interview will be audio recorded and questions of a personal nature may be asked. Responding to these questions may make you uncomfortable. The audio files will be put into writing by the person interviewing you or by another person who does not know you and does not have your personal information. You should NOT identify anyone in the interviews and any names that might be mentioned on the recording will only be noted in the transcript using a generic description. The audio files will be stored on computers that are password protected.

**BENEFITS**

Though you and your partner may not experience any direct benefit from participation in this study, information learned from this study may help us develop options to prevent the spread of HIV in the future. You may enjoy sharing your opinions about the insert and other HIV prevention methods with the study team. You and your partner will receive medical exams and counseling and testing for HIV and STIs. Your partner will also have tests to check her overall health.

This study cannot give you or your partner general medical care, but study staff will refer you to another medical provider for care, if needed. If you have an STI diagnosed, you will receive medicine or a referral, if you need it.

**NEW INFORMATION**

You and your partner will be told about any new information learned during this study that may affect your willingness to stay in the study. For example, we will let you know if we learn that the study products may be causing bad side-effects. We will also tell you when study results may be available, and how to learn about them.

**WHY YOUR PARTNER MAY STOP TAKING THE STUDY DRUG EARLY OR YOU MAY BE ASKED TO LEAVE THE STUDY**

You and your partner may need to leave the study early without your permission if:

- The study is cancelled by the US Food and Drug Administration (FDA), USAID, CONRAD, the US Office for Human Research Protections (OHRP), MATRIX, the local government or medicines regulatory agency, or the IRB/IEC.
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully.

The study doctor will ask your partner to stop using the study products if:

- You or your partner are found to be infected with HIV (see "What If I Become Infected With HIV" section).
- Your partner becomes pregnant or is breastfeeding (see "What If My Partner Becomes Pregnant" section).
- You or your partner acquire an STI.
- You or your partner experience a serious adverse event while on study.
- You or your partner fail to follow study requirements in a manner judged by the study doctor to significantly put your partner at risk of an adverse reaction or otherwise affect study outcomes.
- A study clinician decides that using the study product would be harmful to you or your partner, for example, your partner has a bad reaction to the vaginal insert(s).

If a study doctor asks your partner to stop using study product, we will ask you and your partner to come in for an interim visit during which the procedures scheduled to occur on the Study Exit Visit (Visit 8 for you and Visit 10 for your partner) will be completed. You and your partner will then be exited from the study, unless otherwise informed by study staff. We may contact you and/or your partner to follow up about your health.

If you and/or your partner are removed from the study or choose to leave, we will ask you and your partner to come back for one final clinic visit and return any study products you may have. If you do not have the study products with you when you come to the clinic, staff members will make every effort to assist you in returning them as soon as possible. [*SITES TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES*]

**ALTERNATIVES TO BEING IN THE STUDY**

There are methods to prevent sexually transmitted HIV, including condom use during sex and/or HIV pre-exposure prophylaxis (PrEP). PrEP is an HIV prevention method where people who do not have HIV take a medication to reduce their risk of becoming infected. Study staff can provide you with additional information about PrEP if you are interested in learning more, and where to access PrEP.

[*SITES TO INCLUDE/AMEND THE FOLLOWING, IF APPLICABLE*: You may be able to join other studies here or in the community. There may be other places where you can go for HIV counseling and testing and family planning. We will tell you about those studies and those places if you wish.]

**COSTS TO YOU**

[*SITES TO COMPLETE ACCORDING TO SITE CAPACITY*] There is no cost to you or your partner for study visits, study products, physical/clinical exams, laboratory tests or other procedures. We can give you treatments for STIs (other than HIV) at no cost while you are in the study, or we can refer you for available treatment.

**REIMBURSEMENT**

[*SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT:*] You will receive [*SITES TO INSERT AMOUNT $XX*] for your time, inconvenience, and travel to and from the clinic for each scheduled study visit. You may receive [*SITES TO INSERT AMOUNT $XX*] for any extra study visits requested by the study doctor/study team. If you are chosen to take part in the in-depth interview, you will receive [*SITES TO INSERT AMOUNT $XX*].

**CONFIDENTIALITY**

We will make every effort to keep your information private and confidential. But we cannot guarantee it.

Study visits will take place in private. We will keep the information about your study visits in a secure place that only certain people can access for the purposes of this study. We will only enter your information into computers protected by passwords and will not include information that could identify you or your partner. Your identity on these records will be indicated by a number rather than by your name, and the information linking these numbers with your name will be kept separate from the research records. You can choose not to answer questions at any time. If you are selected to do the in-depth interview, you can choose not to answer questions at any time.

We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names. We will store the original records, including the audio recordings, for at least two years after either the study insert is approved for use or research on the insert is stopped. These records will be stored in a secure, locked location.

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff must take steps to keep you and others safe. This means that we have to share any information with the authorities (hospital, police, or social services) that tells us you or your partner may be in danger. For example, if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you.

The study staff may use your personal information to verify that you and your partner are not in any other research studies. This study will not use your name or identify you personally in any publication.

[*SITES TO INSERT INFORMATION ABOUT SYSTEMS CURRENTLY IN PLACE TO ENSURE PARTICIPANTS ARE NOT PART OF OTHER CONFLICTING STUDIES, INCLUDING BIOMETRIC IDENTIFICATION SYSTEMS; SEE EXAMPLE BELOW FOR SOUTH AFRICA SITE:*

In clinical studies where drugs, vaccines or medical devices (study products) are being assessed, it is important that you are enrolled in only one clinical study at a time. Using more than one study product at the same time may lead to drug interactions and side effects. It may affect your health and the outcome of the study.

The Biometric Co-Enrollment Prevention System (BCEPS) is a web-based system developed by the South African Medical Research Council's IT (Information Technology) department, for the prevention of co-enrolment (being enrolled in more than one study at a time). It is a secure system that is used to ensure your safety, as well as study data integrity.

Authorized study staff will enter your South African Identification number (SA ID) or SA/foreign Passport Number into the system to check if you are enrolled in any study within any of the organizations using BCEPS in South Africa. During screening for a study at a CAPRISA clinic/site, your SA ID number or SA/foreign Passport Number and fingerprints are captured onto the system. At every visit thereafter, your SA ID number or SA/foreign Passport Number and fingerprints will be checked.]

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US OHRP, USAID and/or USAID contractors, the local government or medicines regulatory agency, and other local, national, or international regulatory authorities
- [*SITES TO INSERT APPLICABLE LOCAL AND NATIONAL AUTHORITIES*]
- CONRAD representatives
- MATRIX representatives
- Study monitors
- Site IRBs/IECs
- Study staff

[*US SITE TO INCLUDE/AMEND THE FOLLOWING:* Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form, you provide your authorization for the use and disclosure of information protected by the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. This includes things learned from the procedures described in this consent form. Study staff may also collect other information including your name, address, date of birth, and information from your medical records.]

[*NON-US SITES TO INCLUDE/AMEND THE FOLLOWING:* As part of your participation in this research study, your personal information may be sent to the United States for analysis or storage. This includes things learned from the procedures described in this consent form. Study staff may also collect other information including your name, address, date of birth, and information from your medical records. There are laws in the U.S. to protect your personal information when in that country.]

[*SOUTH AFRICA SITE TO INCLUDE/AMEND THE FOLLOWING:* The Protection of Personal Information Act (POPIA) ensures that all South African institutions collect, process, store, and share your personal information in a responsible manner and that they will be held accountable should they abuse or compromise your personal information.]

People outside the study team may need to see or receive your information for this study, such as those listed above. We cannot do this study without your authorization to use and give out your information to them. You do not have to give us this authorization. If you do not, then you may not join this study.

The use and disclosure of your information has no time limit. You may cancel your authorization to use and disclose your information at any time by notifying the Principal Investigator of this study in writing. If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

**RESEARCH-RELATED INJURY**

[*SITES TO SPECIFY INSTITUTIONAL POLICY:* It is unlikely that you will be injured by being in this study. If you are injured or get sick from being in this study, please tell study staff immediately.

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. If you become ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you for ongoing treatment for the injury, if needed. Clinical trial insurance is provided by CONRAD and will be responsible for compensating you for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research center or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because you used other medicine during the study that you did not tell us about.

- Any injury that happens because you did not follow instructions given by the study doctor or nurse.
- Any injury that happens because of negligence on your part.]

[*SITES TO SPECIFY ANY ADDITIONAL POLICY RELATED TO EMERGENCY MEDICAL ATTENTION*]

[*US SITE TO INCLUDE/AMEND THE FOLLOWING:* To pay these medical expenses, the sponsor will need to know some information about you, like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.]

You are not giving up any legal rights by signing this form.

**CLINICALTRIALS.GOV**
A description of this research study will be available on https://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

[*SOUTH AFRICA SITE TO INCLUDE LANGUAGE RELATED TO SOUTH AFRICAN NATIONAL CLINICAL TRIALS REGISTER*]

**YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER**
[*SITES TO SPECIFY INSTITUTIONAL POLICY:*] Being in this study is completely voluntary. You or your partner may choose not to join this study or leave this study at any time. If you or your partner choose not to join or to leave the study, you can still join other studies and you can still access non-study services you would normally get at this or another clinic. If you want the results of the study after it is over, let the study staff members know.

**PROBLEMS OR QUESTIONS**
If you or your partner ever have any questions about the study, or if you have a research-related injury, you should contact [*SITES TO INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF*] at [*SITES TO INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS*].

If you or your partner have questions about your rights as a research participant, you should contact [*SITES TO INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE*] at [*SITES TO INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER*].

*[SITES TO OMIT THE FOLLOWING IF A SEPARATE CONSENT IS REQUIRED FOR IDI]*

**CONSENT TO PARTICIPATE IN AN IN-DEPTH INTERVIEW**

We would like to ask your and your partner's permission to participate in an in-depth interview (IDI) at the end of the study to gather more feedback about the vaginal insert. If you agree and are selected to participate in the IDI, trained study staff will ask you questions about your experiences with your partner using the product, about product design, packaging and delivery, and other topics related to product use during sex. The IDI may be conducted at the study site, over a secure digital platform, or an agreed upon location. If both you and your partner agree and are selected to participate in the interview, you will be given the option of completing the interview individually or as a couple.

The IDI is anticipated to last approximately 60-90 minutes. Study staff will take notes and record the interview. You can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names to identify them. These materials will be stored in a secure, locked location for at least two years after either the study insert is approved for use or research on the insert is stopped.

Please read the following statement carefully and initial and date one option. We will reconfirm the decision you and your partner make today at later study visits should you change your mind about participating in the IDI.

**You can still enroll in this study if you or your partner decide not to participate in the IDI. You can withdraw your consent to participate in the IDI at any time.**

| | | |
|---|---|---|
| _____ Initials | _____ Date | I DO agree to participate in an in-depth interview. I understand the interview will be recorded and notes will be taken. |
| _____ Initials | _____ Date | I DO NOT agree to participate in an in-depth interview. |

*[SITES TO OMIT THE FOLLOWING IF NOT APPLICABLE]*

**CONSENT FOR OFF-SITE VISITS**

If the site determines that an off-site visit is appropriate and with your permission, members of the research team at this clinic may be able to schedule off-site visits with you and your partner at your home or at another location as part of the study. Some of the scheduled study visits and some of the study procedures may take place at your home or other location(s) outside of the research clinic. For example, if your partner needs to receive vaginal inserts or to have a urine or blood sample collected but is unable to come into the clinic. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the time it will take) and the procedures in place to maintain your information in a confidential manner. However, it is important that you know that off-site visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

We will only conduct visits outside of the clinic if you give us permission to do so. Please read the following statement carefully and initial and date one option. Choosing not to have study visit procedures outside of the study clinic will not affect your participation in this study. Even if you agree today, you can withdraw your consent for off-site visits at any time by providing your request in writing to the person in charge of this study. In addition, before each off-site visit, we will confirm with you that you still agree and remember today's discussion.

| | | |
|---|---|---|
| _____<br>Initials | _____<br>Date | I DO agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary. |
| _____<br>Initials | _____<br>Date | I DO NOT agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary. |

**SIGNATURE PAGE**

*[SITES TO INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/IEC:]*
All of the above has been explained to me and all of my current questions have been answered. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form or their representatives.

Any questions I have about my rights as a research participant will be answered by *[SITES TO INSERT LOCAL IRB/IEC INFORMATION].*

I voluntarily agree to be in this research study. A copy of this permission form will be given to me.

_____
Participant's Name (Print)

_____ _____
Participant's Signature Date

_____
Study Staff's Name Conducting
Consent Discussion (Print)

_____ _____
Study Staff Conducting Date
Consent Discussion (Signature)

_____
Witness Name (Print), if required

_____ _____
Witness Signature, if required Date

## APPENDIX VIII: SAMPLE INFORMED CONSENT FORM (CLINICAL RESEARCH SITE STAFF)

## SAMPLE INFORMED CONSENT FORM

**MATRIX-004**
**Phase I Evaluation of the Impact of Vaginal Coitus on the Pharmacokinetics of Tenofovir Alafenamide and Elvitegravir Vaginal Insert**

**USAID**

**Version 1.0**
**18 October 2024**

**PRINCIPAL INVESTIGATOR:** *[SITES TO INSERT]*
**INSTITUTION:** *[SITES TO INSERT]*
**AFTER HOURS CONTACT DETAILS:** *[SITES TO INSERT]*
**STUDY SITE CONTACT DETAILS:** *[SITES TO INSERT]*
**SHORT TITLE:** Impact of Coitus on TAF/EVG Vaginal Insert

**INFORMED CONSENT**
[*SITES TO INSERT APPROPRIATE GREETING*] The MATRIX-004 study is funded by the US Agency for International Development (USAID) and conducted by CONRAD as part of the MATRIX (Microbicide R&D to Advance HIV Prevention Technologies through Responsive Innovation and eXcellence) Collaborative. You are being invited to take part in an In-depth Interview (IDI) because you were a researcher involved with the administration of vaginal inserts containing tenofovir alafenamide (TAF) and elvitegravir (EVG) in this research study.

**YOUR PARTICIPATION IS VOLUNTARY**
This is a one-time IDI with an impartial interviewer who will guide you through a detailed discussion about your experience as a staff member at this clinical trial site, as you have been interacting with participants who have used this fast-dissolving insert in this study, and perhaps also previously in an earlier study which also used a fast-dissolving insert (MATRIX-001). We believe your insights as a clinical staff member who worked on this/these studies and from interacting with these clinical trial participants, are valuable. Your perspective will help us understand considerations related to providing this HIV prevention product in a clinical setting.

You may decide not to take part in the IDI or withdraw your interview transcripts at any time. Deciding not to to take part in the IDI or withdrawing your interview transcripts will not affect your relationship with your employer or the clinic where this study is happening.

**WHAT WILL I BE ASKED TO DO IF I DECIDE TO TAKE PART IN THE INTERVIEW?**
You will have to free up to 2 hours at a convenient time during the workday to sit with an interviewer. If you agree to participate, you will be invited to take part in an IDI in a private room in the research clinic or another private location, if it is more convenient. We will ask you to complete a form with your basic demographic information, and then have an open discussion where we'll ask you what you think about the fast-dissolving insert, about the potential interest

or not in using this product among people in your community, and what issues might come up for health care providers if these products were to be made available. The interviewer will take notes and will audio-record the interview. No incentives or reimbursement will be provided for your time.

**CONFIDENTIALITY**
We will make every effort to keep your information private and confidential. But we cannot guarantee it.

The study visit will take place in private. Your interview records will be kept in a secure location and will be de-identified. Your transcript will identify you by your professional designation only (e.g., Clinician 1 or Nurse 2). Your name will not appear on any of the interview records. We will store the original records, including the audio recordings, for at least three years after completion of the study. These records will be stored in a secure, locked location.

The results of this study may be published. This study will not use your name or identify you personally in any publication. We may share information from the study with other researchers. We will not share your name or information that can identify you.

You are not giving up any legal rights by signing this form.

**PROBLEMS OR QUESTIONS**
If you have any questions or problems at any time during your participation in the IDI, you should contact [*INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF*] at [*INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS*].

If you have questions about your rights as a research participant, you should contact [*INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE*] at [*INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER*].

**SIGNATURE PAGE**

*[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/IEC:]*
All of the above has been explained to me and all of my current questions have been answered. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form or their representatives.

Any questions I have about my rights as a research participant will be answered by *[INSERT LOCAL IRB/IEC INFORMATION].*

I voluntarily agree to be in this research study. A copy of this permission form will be given to me.

_____
Participant's Name (Print)

_____ _____
Participant's Signature Date

_____
Study Staff's Name Conducting
Consent Discussion (Print)

_____ _____
Study Staff Conducting Date
Consent Discussion (Signature)

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