MATRIX-001 Study-Specific Procedures (SSP) Manual
Section 7 – Clinical Considerations

TABLE OF CONTENTS

7 Introduction

This section presents information on clinical procedures performed in MATRIX-001. The Schedule of Study Visits and Evaluations in Appendix I of the protocol indicates when specific clinical and laboratory assessments are to take place. The Investigator of Record (IoR) or designee should perform symptom-directed examinations and laboratory assessments at his/her discretion at any time during any visit if s/he determines it to be clinically necessary, particularly if there are any on-going medical conditions which may require follow-up.

Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in the SSP Section 9 (Laboratory Considerations). Instructions for completing data collection forms associated with clinical procedures are provided in the SSP Section 12 (Data Collection).

7.1 Baseline Medical Conditions (Pre-existing Conditions)

The participants' baseline medical history is initially collected and documented at the screening visit on the Basic Medical and Menstrual History (MMH) Form and as needed, the Pre-existing Medical Conditions (PMC) Form. At each follow-up visit the medical history is actively reviewed and the information is updated, as necessary, on a new MMH case report form (CRF). The information ideally is directly entered into OpenClinica or alternately can be documented on standard site forms and/or narrative chart notes and then entered in OpenClinica as detailed in the site standard operating procedure (SOP) for Source Documentation. The purpose of obtaining this information is to:

- Assess and document participant eligibility for the study
- Assess and document the participant's baseline medical conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up (i.e. adverse event [AE] identification)

In order to obtain a complete, accurate, and relevant participant self-reported medical history, it will be necessary to ask the participant about significant past medical conditions as well as any current conditions. Medical history information may also be obtained from reviewing the participant's medical records, in accordance with institutional review board (IRB)/independent ethics committee (IEC) policies.

It is recommended that sites use the MATRIX-001 MMH CRF in conjunction with chart notes to guide and document medical history taking.

When collecting medical information from the participant, site clinicians should ask probing questions to obtain the most complete and accurate information possible. This is especially important regarding details about severity and frequency of baseline medical conditions. Details of all relevant conditions identified during the baseline medical history review should be recorded on the MMH CRF.

Baseline medical conditions are a subset of a participant's medical history and consist of all ongoing and/or relevant medical conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported at enrollment or before a potential participant is enrolled.

Relevant conditions include (but are not limited to): hospitalizations, surgeries, allergies, conditions requiring prescription or chronic medication (lasting for more than 2 weeks), and any condition(s) currently experienced by the participant. The clinician should record as much information as possible about the severity and frequency of any baseline medical condition in the description field on the PMC

CRF to best describe the condition at the time the participant enters the study. In addition to participant-reported conditions, the following should be recorded on the PMC CRF:

- Baseline medical Grade 1 and higher lab values
- Medically-relevant physical exam abnormalities
- Pelvic abnormal findings
- Any identified sexually transmitted infections (STI)

NOTE: Generally, it is not expected that conditions less than Grade 1 would be included on the PMC CRF, unless determined to be relevant by the site clinician.

The baseline medical history and pre-existing conditions should explore in detail any medical conditions or medications that are deemed exclusionary for this study. At the enrollment visit, a participant's history should be reviewed and updated as needed. Refer to Protocol Sections 5.2 and 5.3 for a complete listing of study inclusion and exclusion criteria.

7.1.1 Baseline Medical Conditions at Screening and Enrollment

The MMH CRF is completed based on all screening source documents including, but not limited to, the Visit Checklists, Vital Signs and Physical Exam CRF and site-specific laboratory reports.

Information documented on the MMH CRF and PMC CRF at the Screening Visit must be actively reviewed and updated, if needed, at the Enrollment Visit, especially for those conditions that were ongoing at the Screening Visit. This includes a review and update of the condition's description and severity grade. Make sure the "*Is this condition ongoing at enrollment?*" field is completed/updated for each entry prior to final eligibility confirmation. Confirmation that this assessment was reviewed should be documented in source documentation at the Enrollment visit.

If a baseline medical condition is resolved as of the date of enrollment/randomization, do not make any changes to the severity grade (similar to what is done when resolving adverse events). In this case, the response to the question, "*Is this condition ongoing at enrollment?*" must be selected "*no*." If a baseline medical condition first identified at screening is ongoing at enrollment, assess the severity at the Enrollment Visit and update the severity grade (up or down) as applicable to reflect the severity at the time of enrollment/randomization. If a change in severity occurs between screening and enrollment, then this change should be documented in the Comments section of the PMC CRF.

Recurrent Chronic Conditions: At the Enrollment Visit, current chronic conditions should be marked as "yes" for the question "Is this condition ongoing at enrollment?", even if the participant is not currently experiencing an acute event (e.g., intermittent headaches, seasonal or acute allergies). For severity grading, the highest severity experienced for the condition should be used. In the 'Description of medical history condition/event' item, note the typical severity for outbreaks/acute episodes of the condition, and whether the condition is currently being experienced by the participant, or historical. When assessing chronic conditions, it is important to note what, if any, medications a participant may take for a reported

chronic condition and whether taking this medication during study participation may result in product discontinuation. For example, if a participant suffers from chronic asthma and uses an anti-inflammatory medication or an immunomodulatory to control his/her condition, site staff are asked to use their discretion with evaluating the eligibility of this participant.

Menstruation and Bleeding Events: When collecting baseline medical history, sites should also ascertain the participant's first and last day of bleeding and a description of the participant's typical menstrual bleeding pattern. If a participant has a menstrual period between screening and enrollment, the dates of the menstrual period should be recorded/updated at enrollment when reviewing menstrual history. This can be documented in chart notes or another site- specific document.

Site staff should carefully consider any bleeding patterns; menses should not coincide with enrollment, dosing and post-dosing visits and for this reason, site staff should ensure the participant's menstrual cycle coincides with the recovery periods between cervicovaginal sampling. If needed, reschedule for when menstrual bleeding has stopped or is reduced to minor spotting keeping in mind allowed procedure windows. Expected changes in genital bleeding (changes in genital bleeding deemed to be related to the participant's contraceptive use) will not be considered an AE during follow-up. It is important to document a participant's baseline abnormal genital bleeding patterns to the extent possible to monitor for unexpected changes.

Note that any bleeding abnormalities ongoing at baseline (e.g. menorrhagia, metrorrhagia, or menometrorrhagia) should be selected as "not gradable" on the PMC CRF. This is because the DAIDS Female Genital Grading Table (FGGT) for Use in Microbicide Studies (https://rsc.niaid.nih.gov/sites/default/files/addendum-1-female-genital-grading-table-v1-nov-2007.pdf) grades these bleeding events relative to each participant's baseline bleeding pattern. In the "Description of medical condition/event" field, include text similar to what is in the FGGT row to describe the severity and frequency of the condition, and whether it is attributed to a participant's current contraceptive method. Infrequent bleeding at baseline should also be captured, using the terms "missed menses", "oligomenorrhea" or "amenorrhea" as appropriate. If infrequent bleeding is explained by contraceptive method, note this in the description field and select "not gradable". If infrequent bleeding is unexplained, assign a severity grade from 1-2 per the FGGT.

Anaphylactic Reactions: During screening, if a participant reports having a history of anaphylactic reactions (such as acute anaphylaxis after eating peanuts), even if it has happened only once before in their lifetime, it is still important for the site clinician to document these events as a pre-existing condition on the PMC CRF. Per the "acute allergic reaction" row of the DAIDS Toxicity Table, an acute anaphylactic event is considered a severity grade 4 as it is by definition a life-threatening reaction. Record the condition/event as "allergic reaction to peanuts" and note types of symptoms (e.g., "throat swelling" or "shortness of breath") indicate the severity grade 4 in the "Description of medical condition/event" field. At the Enrollment Visit, check "yes" to the question, "Is this condition ongoing at enrollment?" and mark "not gradable", as the participant was not experiencing an anaphylaxis event at the time of enrollment/randomization. An AE submission for an anaphylactic reaction is required if this same event

occurs after enrollment or during study follow-up. Any acute allergic reaction less than a grade 4 should be documented as a chronic condition.

7.1.2 Follow-up Medical History Review

An updated participant self-reported medical history is required at each scheduled visit during follow-up. A medical history review should also be performed at interim visits when a participant complains of symptoms or when the purpose of the visit is to re-assess previously-identified AEs.

One purpose of the participant-reported follow-up history is to determine whether previously- documented conditions have changed in severity or frequency. A second purpose is to determine whether new symptoms, illnesses, conditions, etc., have occurred since the medical history was last assessed. The applicable CRF, chart notes, or a site-specific tool, if desired, may serve as the source document. All newly identified participant-reported symptoms and conditions will be considered AEs and documented in the participant chart.

For purposes of this study, a "newly identified" condition is defined as one of the following:

- not present at baseline (enrollment);
- ongoing at baseline but has increased in severity or frequency during follow-up (includes ongoing baseline conditions or AEs that increase in severity or frequency during follow-up);
- ongoing at baseline, resolves during follow-up, and then re-occurs (excludes chronic condition which should be reported in accordance SSP Section 7.1.1 above)

Any symptoms reported by the participant should be further probed and evaluated. Clinicians should be sure to ask about ongoing baseline symptoms as well as any symptoms listed as "continuing" on an AE CRF.

If, during follow-up, a medical condition changes in severity or frequency from baseline, this is not updated on the MMH or PMC CRF. If the condition increases in severity or frequency from baseline, and meets requirements for AE reporting, complete an AE CRF to document the new AE (i.e., the baseline condition at an increased severity and/or frequency). The AE CRF should be selected "yes" for the question, "Was this AE a worsening of a pre-existing condition?".

If, during follow-up, a new or corrected pre-existing condition is reported, this information can be captured on new PMC CRF during follow-up, but only in instances when new information related to the participant's baseline medical history status is obtained after enrollment/randomization. If information is added to the PMC CRF after the Enrollment Visit, a chart note explaining the update is required.

Participants will be counseled to report all occurrences of unusual genital bleeding that is different from baseline reports and not attributable to contraceptive method to study staff as soon as possible after identification of the bleeding.

7.2 Concomitant Medications

The Concomitant Medications (CM) CRF is used to document all concomitant medications used by a given participant during their study participation.

Protocol section 6.6 requires site staff, beginning at screening, to document all medications taken by study participants including those used 30 days prior to the screening visit and continuing throughout the duration of the study. Medications include the following:

- Prescription and "over-the counter" medications and preparations
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Recreational drugs
  - Use of stimulants (cocaine [including crack], methamphetamine, or non-physician prescribed pharmaceutical-grade stimulants), or inhaled nitrates, or illicit injection drug use of any kind is exclusionary as outlined in eligibility but use during the study should be recorded.
- Post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP)
  - Use of PEP or PrEP is exclusionary as outlined in eligibility but use during the study should be recorded and study product discontinued per Protocol section 9.3
- Intravaginal medications/agents (tablets, creams, gels, suppositories, rings, etc.). Use of these is prohibited as outlined in protocol but use should be documented.
  - Antibacterials or antifungals, such as metronidazole, miconazole, etc.
  - Hormonal agents, such as estradiol
  - Miscellaneous, such as povodine iodine, hydroxyquinoline, copper, etc.
  - Spermicides, such as nonoxyl-9
- Contraceptive medications, if applicable
  - Injectable contraceptive (Depo, NET-EN, Cyclofem, etc.): Record each injection that the participant receives during study participation on a new log line. Enter both the start and stop dates as the date of injection. Indicate the frequency as "once". Injections of contraceptive medications used (30 days) before the Screening Visit are recorded on the CM CRF.
  - Oral contraceptive birth control pills: Record each pill pack confirmed by the participant to have been taken on a new CM CRF. Indicate the start date as the date the first pill of the pack was taken and the stop date as the date the last pill of the pack was taken. If the participant is taking birth control pills at Screening, document this pill pack on the Concomitant Medications Log, as well as any other pill packs she begins during follow-up. If a participant misses a pill, this outage does not need to be recorded on the CM CRF.
  - Implants/Intrauterine device (IUD): Record each implant/IUD on a new CM CRF. The start date should be the date of implant or insertion and the stop date should be the date the implant/IUD is removed. Indicate the frequency as "Other" and write "continuous" in the text field. For medical devices with no active medication, such as the copper IUD, indicate the dose as "1", the dose unit as "Other", and indicate "device" in the text field. For IUD

route, select "Intrauterine". For Implant route, select "Sub-dermal". If the participant has an implant/IUD in place at Screening, document this on the CM CRF, as well as any other implants or IUDs she receives during follow-up.

Use of any prohibited medications should be recorded on the CM CRF as well. Consult the PSRT if there are any questions or concerns about reported medication use. See section 7.7 for further guidance.

NOTE: Alcohol consumption should not be reported as concomitant medications on the CM CRF. Instead, excessive alcohol consumption (defined as binge drinking, heavy drinking, and any drinking by pregnant women or people younger than the local legal age limit may be considered baseline medical conditions, per site clinician judgment, in which case they should be recorded on the PMC CRF.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Site staff should ask open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring a list of all medications to study visits.

At each follow-up visit, review the participant's concomitant medications history and document this review by completing the item "Were any new concomitant medications (or changes to concomitant medications) reported at this visit?" on the Visit Summary CRF. Ask the participant if she has started taking any new medications, and record on the CM CRF any new medications she reports having started since her last medications assessment.

In addition, review all previous entries that do not have a "Stop Date" entered and ask the participant whether she is still taking the medication (and at the same dose and frequency). If the participant has stopped taking a medication, enter the last date the participant used the medication in the "Stop Date" field. If the participant is taking the same medication but at a different dose or frequency, enter the date the participant last used the medication at the original dose or frequency in the "Stop Date" field, and complete a new CM CRF entry for the new dose or frequency. Ensure that concomitant medications mentioned in previous parts of the visit are documented correctly and consistently on the CM CRF, so that study records are not discrepant.

7.3 Physical Exam

A full physical exam is required at Screening. The full physical examination will include general appearance, height, weight, vital signs, and evaluation of body systems. At Screening, during a physical exam, site staff should assess for any other medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives. Physical exams may identify additional baseline medical information that participants inadvertently do not report in their baseline medical history. In such situations, the clinician should add the information to the Basic Medical and Menstrual History Form CRF as well, since the condition was present at the time of screening.

A directed physical examination (to include assessment of general appearance, vital signs and weight at a minimum) will be done, if clinically indicated, at all other follow-up visits and interim visits. Site clinicians may use their discretion to determine what parameters or systems should be examined in response to reported symptoms or illnesses present at the time of the visit.

Vital signs and weight will be recorded at each visit after screening for all participants.

Physical exam assessments should be documented on the Vital Signs and Physical Exam CRF along with source document or in participant's chart notes.

Outlined below are the required assessments needed for a full physical exam:

- **General Appearance**

- **Weight**

Participant weight must be measured at the Screening, all follow-up visits or when clinically indicated. Weight should be measured in kilograms and can be reported up to one decimal. Scales should be calibrated per local practice standards.

- **Height**

Participant height should be measured in centimeters (rounded off to the nearest whole number) at the Screening and additionally when clinically indicated.

- **Vital Signs-** Devices are expected to be calibrated regularly per manufacturer's directions.
  Required:
  - Blood Pressure

  Collected in accordance with standard clinical site practices:
  - Heart rate
  - Respiratory rate
  - Temperature

- **Body Systems**- in accordance with standard clinical site practices
  - General appearance
  - Heart/Cardiac
  - Lung/Respiratory
  - Abdomen/Gastrointestinal

7.4 Pelvic Exam

The pelvic exam during the Screening and Enrollment visits is necessary to evaluate protocol exclusion criteria and to collect detailed information on baseline vaginal conditions. This exam scheduled during follow-up visits is necessary to assess for safety and collect required laboratory specimens. Pelvic exams are performed at each visit to assess vaginal mucosa and conduct sample collections. Only a visual exam will be performed for the peri-anal area.

Protocol Section 7.9 outlines the assessments that may be included for the vaginal exam. Detailed guidance on performing the pelvic and female genital exams, documentation of findings, and conduct of the genital specimen collections can be found in the remainder of this section.

The pelvic exam procedures should be performed in the order shown on the Visit Checklist and at designated area(s) of the genitalia as noted on the checklist. At the Dosing Visits, any genital exams and associated PK/PD specimen collection should occur prior to self-insert administration. The order of specimen collection is critical to ensure that the first specimens collected do not affect subsequent specimens. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.

Prior to the exam, prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Review documentation of prior exams and other relevant documentation from the current visit and prior visits. Explain the procedure to the participant and answer any questions s/he may have.

7.4.1 Pelvic Exam Instructions

Pelvic exams are conducted at all scheduled study visits as per protocol. Pelvic exams and pelvic samples ideally should not be collected if the participant is experiencing menstrual-like bleeding as this may interfere with visualization of the vagina and cervix and complicate interpretation of lab assays. The recovery period between cervicovaginal sampling after Visits 2, 4 and 7 should be timed to coincide with the participants' menses to minimize the chance of participants being on their menses during any of the dosing windows.

See below for special circumstances in the event a participant is experiencing menses or any vaginal bleeding at the time of an exam.

- During enrollment, if the participant is experiencing or reports vaginal bleeding beyond mild spotting, reschedule the exam and associated baseline sample collection to be completed within the 8 weeks screening window.
- During a scheduled follow-up visit, the pelvic exam and associated sample collection, and vaginal swabs, should still be completed as long as bleeding is no greater than mild spotting and the participant is comfortable. If the participant is experiencing greater than mild

bleeding, perform other protocol-specified procedures at the visit and schedule the participant to return for the pelvic sample collection as soon as possible after menses, within the visit window (as part of a split visit, if allowable). However, if it is a PK visit (i.e. V4, 6 or 7), proceed with pelvic sample collection; attempt to obtain samples in an area with less/little blood. If necessary, absorb some of the blood with a swab prior to obtain the sample(s). Note on transmittal form and in chart notes. In addition, if the participant is experiencing heavy bleeding at V6, consult the CMT regarding a temporary product hold until bleeding is minimal.

- If a participant presents for an interim visit complaining of genital symptoms, perform a pelvic exam to evaluate symptoms at that time.

General Technique:

- Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings. If not standard of care, consider having an additional person (medical assistant or nurse) present during the examination to ensure participant comfort.
- Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam.
- Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix. For most participants, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. Prior to insertion, ensure that the speculum functions properly and has no rough edges.

Position the Participant:

- Drape the participant and establish a comfortable examination position that allows for appropriate examination of the genitalia such as dorsal lithotomy with or without use of stirrups; position should allow for the perineum and vulva to be inspected. Make all necessary adjustments to equipment and room to ensure participants comfort: i.e. adjust stirrups and back elevation as needed.

Examine the External Genitalia:

- For pelvic exams, a visual exam (i.e. a naked eye examination) should be performed of the external genitalia including the perineum, and perianal area. Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness. Do not insert the speculum before examining the external genitalia.

Examine the Internal Genitalia (Cervix and Vagina):

- The speculum may be lubricated with warm water only, if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles, using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina. If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to

establish the position of the cervix. Then re-insert the speculum. Perform naked eye exam of the cervix and vagina, noting any abnormal findings.

- To complete the naked eye examination of the vagina, slowly withdraw the speculum with the blades moderately open, re-focusing as needed. Alternatively, the speculum may be rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate.
- Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed using a large saline-moistened swab (scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium. If saline is not available, a swab moistened with water will also suffice.

Perform Bimanual Exam at Screening and as needed:

- After completing all of the above-listed tissue examinations and specimen collection and removing the speculum, perform a bimanual exam for adnexal or fundal masses and/or tenderness.

7.4.1.1 Pelvic Specimen Collection

Clinicians should collect pelvic specimens following a pelvic exam with a speculum in place. Multiple samples may need to be collected at a single visit. In this scenario, samples should be collected as outlined in SSP Section 9.8.1 (Laboratory Considerations).

Pap Smear is only potentially collected at screening.

Chlamydia trachomatis (CT)/ Neisseria gonorrhea (GC)/Trichomonas (TV): Collection of vaginal swabs for NAAT for GC/CT/TV will be done at Screening, Visit 7 and at all other visits if clinically indicated, per manufacturer instructions. The clinician/assistant will use the collection swab provided in the appropriate testing kit outlined in SSP Section 9 (Laboratory Considerations).

Cervicovaginal Fluid (CVF) Collection for PD and PK: CVF should ideally be collected from the posterior fornix Ito capture Tenofovir Alafenamide (TAF)/Elvitegravir (EVG) concentration. Detailed instructions for collecting and weighing may be found in SSP Section 9 (Lab Considerations). CVF collections for PD do not need to be weighed.

CVF for Microflora/Gram Stain/pH: Vaginal fluid will be collected from the lateral vaginal wall for microflora/gram stain/pH analysis as detailed in SSP Section 9 (Lab Considerations).

Cervicovaginal Lavage (CVL) for Soluble Markers: A CVL will be collected at Visits 2-8. Detailed instructions for CVL collection may be found in SSP Section 9 (Lab Considerations).

Cervicovaginal Biopsies for IHC, PK and PD: Vaginal wall biopsies will be collected by all sites for immunohistochemistry (IHC) and PK. In addition, the EVMS site will collect cervical biopsies for anti-HIV activity. For the EVMS site, 1 or 2 biopsies for HIV may be collected or the IHC biopsies may be collected at Visit 8, if needed due to clinical concerns determined by the IoR or designee that may arise from a further biopsy being performed. Detailed instructions for collecting and weighing may be found in SSP Section 9 (Lab Considerations). IHC samples do not need to be weighed.

7.4.1.2 Documenting Pelvic Exam Findings

All findings (normal and abnormal) should be documented in the participant's chart notes or source documents. If an exam is conducted at baseline, abnormal findings will be documented on the Pelvic Exam CRF and the PMC CRF. When an exam is conducted during follow up, all abnormal findings identified will be documented on the Pelvic Exam CRF and AE CRF, as appropriate. Supplemental information may also be recorded in chart notes or on other designated source documents as needed. Per Section 5.2 of the protocol, participants must have normal vaginal mucosa to be eligible for this study.

NOTE: All pelvic exam findings consistent with the "grade 0" column of the DAIDS FGGT are considered normal.

The following also are considered normal:

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner's duct cysts
- blood vessel changes other than disruption
- skin tags
- scars
- cervical ectopy

IUD strings may be visible upon exam and are also considered a normal finding. If present, they should be documented in the chart notes or source document. Sites may determine whether they choose to consistently document the presence of IUD strings (best practice) or not. It is recommended that if a participant has an IUD, but the strings are not visible upon exam, this should be documented and followed up on.

Normal and abnormal findings will be classified according to the state of the epithelium and blood vessels associated with the finding, as follows:

Epithelium
Integrity:

- Intact
- Disrupted:
- Superficial
- Deep (complete disruption is considered deep and exposes stroma and possibly blood vessels; a bleeding area is often but not always deep)

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes "pale")

Blood Vessels
Integrity:

- Intact
- Disrupted

Pelvic exam findings should be documented using terminology corresponding to the DAIDs FGGT and the Pelvic Exam CRF, Visit Checklist or source document. For findings in which the finding term marked on the Pelvic Exam CRF, Visit Checklist or source document is more specific than the corresponding term on the FGGT, use the more specific term. All AEs should be documented per the term marked on the Pelvic Exam form. Always include the specific anatomical location of pelvic exam findings (e.g., vaginal, vulvar) in the AE term.

7.4.2 Rectal Fluid Collection Instructions

Rectal fluid samples will be collected for PK at Visits 3-8 if participant consents to the collection.

General Technique:

- Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings. If not standard of care, consider having an additional person (medical assistant or nurse) present during the collection to ensure participant comfort.

- Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam.

Position the Participant

- Position the participant in the dorsal lithotomy/stirrups or in the left lateral decubitus position (fetal position) with both legs flexed allowing a full view of the anus, peri anus and buttocks.

External anorectal examination

- A visual perianal exam should also be performed prior to sample collection. With gloved hands, the clinician should separate the participant's buttocks as far apart as is comfortable for the participant. Perform a naked eye examination of the perianal area and evaluate any abnormalities including but not limited to hemorrhoids, lesions, lumps, or rashes. Any abnormalities should be noted on the exam form.

For participants who enroll in the study, abnormal anorectal exam findings identified at the Screening and Enrollment Visits should be recorded as a baseline pre-existing medical condition and noted on the PMC CRF.

Rectal Fluid Specimen Collection: A rectal swab will be collected to capture Tenofovir Alafenamide (TAF)/Elvitegravir (EVG) concentration. Detailed instructions for collecting and weighing may be found in SSP Section 9 (Lab Considerations).

7.5 STI/RTI/UTI Evaluation, Management and Treatment

Clinical and laboratory evaluations are performed in MATRIX-001 to diagnose the following STIs and RTIs:

- Chlamydia infection
- Gonorrhea infection
- Trichomonas
- Urinary tract infection (UTI)
- Syphilis infection
- Hepatitis B
- HIV 1/HIV 2
- Herpes simplex virus (HSV)-2 (results not provided during the study)

All participants diagnosed with an active STI or reproductive tract infection (RTI) or UTI based on the presence of symptoms should be provided treatment and or referral for treatment per site standard of care and applicable site SOPs. STIs/RTIs will be treated in accordance with current local guidelines.

Potential participants presenting with an active (symptomatic or per laboratory or clinical diagnosis) infection requiring treatment at Screening or Enrollment will be excluded from study participation. Per current local guidelines, the following symptomatic infections require treatment and are exclusionary:

gonorrhea, chlamydia, syphilis, active HSV lesions, anogenital sores or ulcers, or symptomatic genital warts, chancroid, pelvic inflammatory disease (PID), other vaginitis, and trichomoniasis.

Participants who are otherwise eligible but are diagnosed with bacterial vaginosis (BV) and/or candida may be treated per local standard of care. The participant may continue the screening process and enroll 2-4 weeks post symptom resolution. Please refer to Table 1 and Section 7.7 for guidance on antibiotic/antifungal use after enrollment.

Participants who are noted to have asymptomatic BV or yeast at screening or enrollment do not require treatment; this finding can be entered as a pre-existing condition and the visit proceed as planned.

Infections should be considered "symptomatic" when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with "signs" of infection that may be observed during clinical examinations performed by study staff.

Participants' partners should be offered treatment, or referrals, as per sites' SOPs.

Urinary tract infections (UTIs)

Participants who are otherwise eligible but have symptoms consistent with a UTI at screening may be treated and enrolled if all symptoms have resolved. The following symptoms are considered indicative of a possible UTI:

- Frequent urge to urinate
- Pain and burning during urination
- Lower abdominal pain and/or uncomfortable pressure above the pubic bone

A urine culture is not required at screening.
In follow-up, suspected UTIs may be clinically managed based solely on the presence of symptoms indicative of a possible UTI. However the AE term "urinary tract infection" should be reserved for participants with a positive urine culture.

Urine dipstick will be performed per site SOP; however, sites are expected to send a urine culture for definitive diagnosis when a UTI is suspected during follow-up. The results of the urine culture do not need to be returned before presumptive treatment, but the results of the culture will influence how the AE is captured. When the participant initially reports symptoms suggestive of a urinary tract infection, capture each symptom as a separate AE. If urine culture results are positive, update the AE CRFs to reflect a single AE for grade 2 Urinary Tract Infection per UTI criteria defined in the DAIDS FGGT. If the urine culture is negative, the AE(s) will remain reported as symptoms only. Results of any urine cultures and dipsticks performed must be documented in chart notes and/or other site-specific source documents.

Note that urine dipstick testing is only performed if clinically indicated. At the screening visit, positive dipstick results do not directly impact eligibility, but abnormal protein and glucose parameters should prompt further evaluation or consideration pending IoR review. Abnormal protein and glucose uncovered

at the screening visit should be captured on the PMC CRF. In follow-up, findings of abnormal protein and glucose on the dipstick should be reported on the AE CRF as indicated. Grade the severity of the urine glucose value according to the "Proteinuria, random collection" row of the Toxicity Table. Note that findings of LE/nitrites are not gradable per the DAIDS toxicity table, and like other non-gradable labs should not be reported as a baseline conditions or AEs.
When clinically appropriate, investigators should use oral or parenteral medications when possible to avoid intravaginal or rectally administered medication use. Observed single dose treatment should be provided whenever possible, per clinician discretion.

HIV Testing

At Screening, Randomization, Visit 7, and SEV, all participants will undergo HIV testing per algorithm in Appendix II of the protocol. If confirmatory testing confirms HIV infection, the participant is not eligible for enrollment or randomization. If confirmatory testing is negative or indeterminate, the MATRIX Management Team should be consulted.

Participants who have a reactive HIV test result during follow-up visits will be temporarily held and confirmatory testing conducted. In addition, if a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed immediately. Any participant who is found to have confirmed HIV infection after enrollment, product use and study participation will be permanently discontinued. All participants with confirmed HIV infection will be counseled and referred to available resources for medical and psychosocial care and support. Resistance testing should be conducted locally. All referrals, outcomes, and follow-up plans and actions must be fully documented in participant study records. Participants will be study stopped as per Protocol section 7.4.1.

Protocol-specified examinations and laboratory tests will provide information upon which appropriate clinical care decisions can be made, including resistance testing. Study staff must refer participants to non-study HIV care providers. Study staff will provide and explain all study examination findings and test results to participants. They also will provide copies of laboratory test result reports to participants and their non-study providers (if the participant grants approval). Study investigators will be available to consult with non-study providers on optimal clinical care and treatment decisions for participants.

Syphilis testing

If syphilis is diagnosed during screening, 'syphilis seropositivity' should be recorded within the Lab Results CRF. A baseline medical history condition of syphilis seropositivity should be documented. The participant is not eligible for enrollment or randomization.

7.6 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product discontinuation (Section 9.3), guidance on product discontinuation in response to

observed AEs (Section 9.3), HIV (Section 9.4), pregnancy (Section 9.5) and early study termination (Section 9.6). All specifications of protocol sections 6 and 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use in particular. Conditions requiring permanent discontinuation are summarized below.

Prohibited Medication

Study product should be held and the PSRT consulted if a participant reports prohibited medication use between Randomization and Visit 7 as listed in Appendix III of the protocol (see Table 1). When possible, treatment options that are not prohibited by the protocol should be pursued, however clinical management of the participant should be prioritized if alternative treatment is not available.

The PSRT will work with the site to determine next steps, based on the general guidance below:

- With respect to the use of antibacterial/antifungals, should a participant report the use of these products at Visit 4, study procedures should proceed as outlined. Study product should be held for 7-10 days after completion of the medication and Visit 5 rescheduled if needed. The clinical management team should be notified.
- Should a participant report use of these products at Visit 5, the visit should be rescheduled and study product should be held for 7-10 days after completion of the medication and the clinical management team notified if this delay would place the next visit outside of the visit window.
- Should the participant report antifungal or antibacterial use at Visit 6 or between Visit 6 and Visit 7, a temporary hold should be instituted and the PSRT consulted. **Please indicate in the subject line to the safetymd alias that an urgent response is requested.** The PSRT will consider whether it would be safe to continue study product on schedule or not and notify the site. Visit 6 study procedures should proceed assuming they would not compromise participant safety.
- Should the participant report antibacterial or antifungal use at Visit 7, study procedures should proceed as outlined. The PSRT does not need to be notified. No hold will be indicated as the participant will have completed study product use but a PD will still need to be completed. Visit 8 may need to be rescheduled to after medication course is completed.

Grade 2 and higher adverse events

Per Clarification Memo #2, the protocol instruction to hold product in response to Grade 2 and higher adverse events only applies to AEs/SAEs assessed by the Investigator of Record (IoR)/ designee to clinically warrant a product hold and if a hold is instituted, requires consultation with the PSRT. The expectation is that Grade 2 and higher AEs that are deemed related to study product and AEs that are associated with the use of a prohibited medication will clinically warrant a product hold and PSRT notification.

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and product use management, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Product discontinuations must be communicated to site pharmacy staff using the MATRIX-001 Prescription form

as described in SSP Section 6 (Study Product Considerations). Product discontinuations also must be documented on this form.

Table 1: Temporary Product Hold/Permanent Discontinuation Criteria

Criteria	Permanent Discontinuation	Temporary Hold
Acquisition of HIV infection (confirmed HIV infection)*	X	
Indeterminate HIV rapid test		X
Genital STIs		X
Reported use or need of PEP*	X	
Reported use or need of PrEP	X	
Pregnancy	X	
Breastfeeding	X	
Reported use of other prohibited medications (i.e. antifungals, antivirals)		X
Grade 2 AEs assessed by the Investigator of Record (IoR)/ designee to clinically warrant a product hold,		X
Unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee	X	

** Participants who experience a known or potential HIV exposure during study participation or have a recognized risk of exposure and thus need PEP will have study product permanently discontinued and will be referred for PEP or PrEP initiation. Those who need PEP will be encouraged to start it as quickly as possible and within 72 hours of potential exposure.*

7.7 Prohibited Medications, Products and Practices

Certain medications, products and practices are contraindicated during the study participation because they may be harmful to the participant, impact product safety and drug concentration/ pharmacodynamics (PD)/biomarker safety parameters or confound adverse event determination. Participants will be counseled on avoiding using protocol specified medications and engaging in the certain practices during study participation.

These include the following: PrEP for HIV prevention, PEP for potential HIV exposure, vaginally or rectally administered products or any product containing systemic corticosteroids, antibiotics, anticonvulsants and anticoagulants. See Appendix III of the Protocol for complete list of prohibited medications. Although

prohibited, these medications should not be withheld if clinically indicated. Use of prohibited medications should be captured as protocol deviations, regardless of whether clinician or participant initiated. See Table above for guidance on permanent discontinuation versus temporary hold.

Use of aspirin (greater than 81 mg) and other non-steroidal anti-inflammatory drugs (NSAIDs), especially within 72 hours prior to and following a pharmacokinetic (PK) sample collection visit should be restricted. Should a participant report taking these medications within 72 hours prior to biopsy collection, the visit should be rescheduled within the visit window, if possible. If it is determined that rescheduling the visit within the window is not possible, the visit may proceed at IoR discretion after proper participant counseling has occurred. Rapid consultation with the Protocol Safety Review Team (PSRT) may be requested at IoR discretion to assist in determining whether biopsy collection should be delayed or proceed as scheduled. Daily consecutive use of aspirin/NSAIDS ≥4 days will need to be reported as a protocol deviation.

Participants will be asked to abstain from any vaginal and anal activity, douching, and use of all intravaginal/intrarectal objects and products starting 48 hours before enrollment sampling at Visit 2, during daily dosing, and 48 hours before through 10 days after Visit 7 following the last dose as specified in Protocol Section 6.7.2.

Participants should refrain from tampon use during study product administration phases of the trial.

Activity:	*Abstain For How Long?*

• Receptive sexual practices, including:
  ○ Penile-vaginal intercourse
  ○ Penile-anal intercourse
  ○ Receptive oral intercourse
  ○ Finger stimulation
	• Beginning 48 hrs before enrollment visit, during daily dosing phase and approximately 48 hours before and 10 days post cervicovaginal tissue collections per study requirements

• Inserting any objects into your vagina or rectum, including:
  ○ Sex toys
  ○ Female condoms
  ○ Diaphragms
  ○ Menstrual cups
  ○ Cervical caps or any other vaginal barrier method
	• Beginning 48 hrs before enrollment visit, during daily dosing phase and approximately 48 hours before and 10 days post cervicovaginal tissue collections per study requirements

• Use of vaginal products, including:
  ○ Tampons
  ○ Spermicides
  ○ Lubricants
  ○ Contraceptive vaginal rings
  ○ Douches
  ○ **Vaginal medications**
  ○ Vaginal moisturizers
	• For the duration of study participation (except for tampons, which can be used when not in study product administration phases)

• Use of oral post-exposure or pre-exposure prophylaxis (PEP or PrEP)	• For the duration of study participation, beginning 4 weeks before the enrollment visit
• Use of aspirin (greater than 81 mg)	• For 72 hours before and after a cervical biopsy collection visit
• Use of other drugs which could prolong bleeding and/or clotting or otherwise interfere with study results, including: ○ Anticoagulants (e.g., heparin, Lovenox®, warfarin, Plavix®) ○ Daily NSAIDS ○ Systemic corticosteroids (e.g., dexamethasone) ○ Endothelin Receptor Antagonists (e.g., bosentan) ○ Antibiotics ○ Anticonvulsants (e.g., carbamazepine, oxcarbazepine, phenobarbital, phenytoin) ○ Antimycobacterials (e.g., Rifbutin, Rifampin, Rifapentine) ○ Antifungals (e.g., ketoconazole) ○ Antivirals ○ St. John's Wort	• For the duration of study participation

The use of a prohibited medication should be reported as a protocol deviation. Site IoRs should use their discretion when determining whether or not to enroll participants using medications not explicitly prohibited by the protocol but that may impact study results or participant safety.

7.8 PSRT Communication

Per protocol, PSRT communication (by submitting a MATRIX-001 PSRT Query form to the safety physician) is required per protocol in the following instances.

PSRT CONSULTATION is required for:

- Co-enrollment in another study
  - At Screening to determine eligibility or during participation in MATRIX-001
  - Unless staff can prove the participant didn't receive active study product
- If IoR would like to request withdrawing a participant who is unable to comply with the study

PSRT NOTIFICATION is required for:

- Social harms judged by IoR to be serious or unexpected
- If IoR holds study product on own
  - Contact PSRT for further guidance

- If staff is unable to ascertain an outcome of pregnancy that is reported during participation

A PSRT QUERY may also be sent to the safety physician for the following reasons:

- Assistance with eligibility
- Guidance with AE reporting
- Any other safety related question

PSRT communication should go through the safety physician. Staff should complete a MATRIX-001 PSRT Query form (found on MATRIX-001 study documents page) and email to MATRIX-001 safety physician at matrix001safetyphysician@lists.matrix4prevention.org who will in turn assess and communicate directly with the PSRT team.

The clinical management team should be contacted at matrix001cmt@lists.matrix4prevention.org for the following:

- When guidance is needed in regard to modifying the timing of a study visit, PK and/or sample collection
- Deviation questions
- Any other protocol or SSP related question