MTN-026 Clinical Management Overview

Overview of Topics

- Physical and Genital Exams
- Medical and Menstrual History
- STI Management
- Concomitant Medications
- Prohibited Medications and Practices

Physical Examination: Timing and Documentation

- When:
  - Required at Screening and Enrollment and, as indicated, at other times throughout study
- Documentation:
  - Physical Exam CRF is recommended source document
  - Transcribe medically-relevant abnormal findings at Screening or Enrollment onto Baseline Medical History CRF
  - During follow-up, transcribe abnormalities onto AE CRF as needed
- Cross-reference with Con Meds Log

Physical Examination Components

- Temperature
- Blood pressure
- Pulse
- Respirations
- Weight
- General Appearance
- Height
- Abdomen
- Lymph nodes
- HEENT
- Neck
- Oral Mucosa
- Heart
- Lungs
- Extremities
- Neurological
- Skin

Pelvic Examination

- Required at:
  - Screening, Enrollment, Visits 4, 5, or 6, Visit 13 and Visits 14, 15 or 16
  - If indicated at Visits 3 and 7-12
- Pay careful attention to differences in specimen collection at different visits
- Pay careful attention to the order of specimen collection
- Menses – attempt to avoid pelvic during menses.
- How can you prevent/anticipate this?

Pelvic Exam Terminology

- Use terms from the Pelvic Exam CRF or FGGT
- Use routine QC/QA opportunities to help ensure consistency of terminology across staff and exams
- Common Pelvic Finding Terms:
  - Erythema, Edema, Petechiae, Ecchymosis, Peeling, Ulceration, Abrasion and Laceration

Pelvic Exam and Bleeding

- Genital bleeding
  - Menses should not occur for visit 2 (enrollment through visit 6)
  - Avoid pelvic exams during bleeding as this may interfere with visualization of the vagina, cervix and complicate interpretation of lab assays
  - Okay if there is mild spotting, per clinical discretion

Pelvic Exam Technique

- Naked eye examination – external genitalia
  - Palpate for inguinal lymphadenopathy
  - Do NOT insert the speculum before examining the external genitalia
- Cervix and vagina – internal genitalia
  - Warm water speculum lubrication only
  - If cervix is poorly visualized, withdraw speculum conduct internal exam to establish position of the cervix and then re-insert the speculum

Pelvic Exam Technique

- Remove visual obstruction (mucus, etc.)
  - Gentle dabbing saline-moistened swab
  - Avoid local trauma/bleeding
- Bimanual exam – at screening and when clinically indicated

Pap

- If clinically indicated for women ≥ 21 years old that do not have documentation of a satisfactory Pap within the past 3 years prior to Enrollment
- Abnormal Pap results obtained at screening should be recorded within Baseline Medical History Log CRF
  - Follow "Pap" row of the Female Genital Toxicity Table
  - Atypical Glandular Cells (AGC) and AGC-favor neoplastic are not specifically mentioned in the Pap row of the FGGT but should be assigned severity grades 1 and 2, respectively

Pap

- If abnormal cytology is uncovered at screening is followed by biopsy in follow up, report an AE for the histologic diagnosis ONLY IF the biopsy result is a higher grade than the baseline Pap
- Ignore STI associated notations of findings on Pap
  - Hyphal elements, findings consistent with BV

Cervical Biopsies

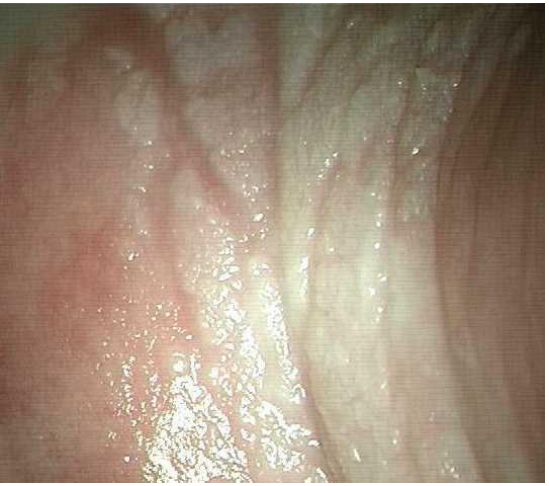
- Last sample collected
- No anesthetic used/required
- Inform participant of a small amount of expected bleeding from the vagina 1-2 days following the procedure
- No insertion of anything into the vagina or engaging in vaginal sex for 72 hours PRIOR to and 7 days FOLLOWING the collection of these samples
- No NSAIDs or aspirin for 72 hours prior to biopsy collection

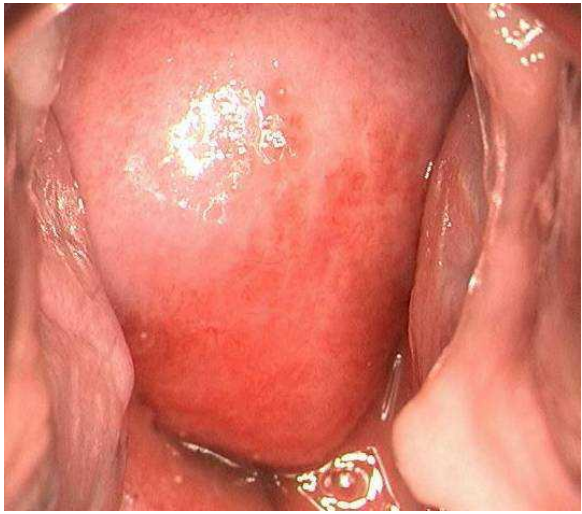
Pelvic Exam Findings

- NORMAL
  - Gland openings
  - Nabothian cysts
  - Mucus retention cysts
  - Gartner's duct cysts
  - Blood vessel changes other than disruption
  - Skin tags
  - Scars
  - Cervical ectopy
  - IUCD strings
  - Some (scant) bleeding from speculum insertion/removal or biopsy

Pelvic Exam Findings

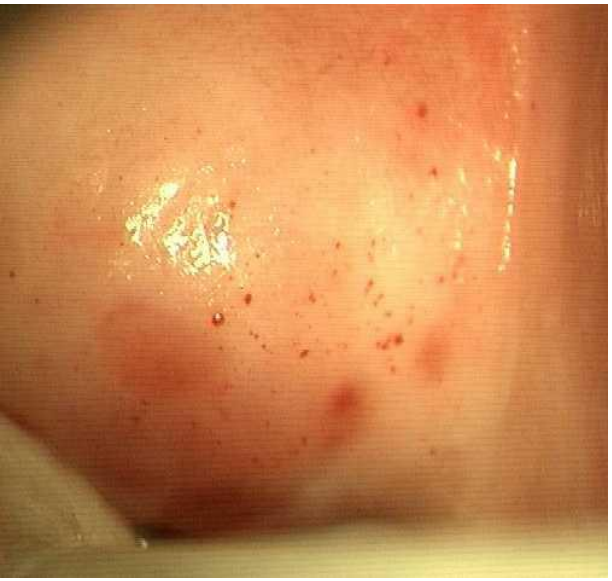
- Epithelium
  - Superficial epithelial disruption (does not penetrate subepithelial tissue) OR localized erythema/edema
  - Deep epithelial disruption penetrates into and exposes the subeptheial tissue, including, sometimes vessels

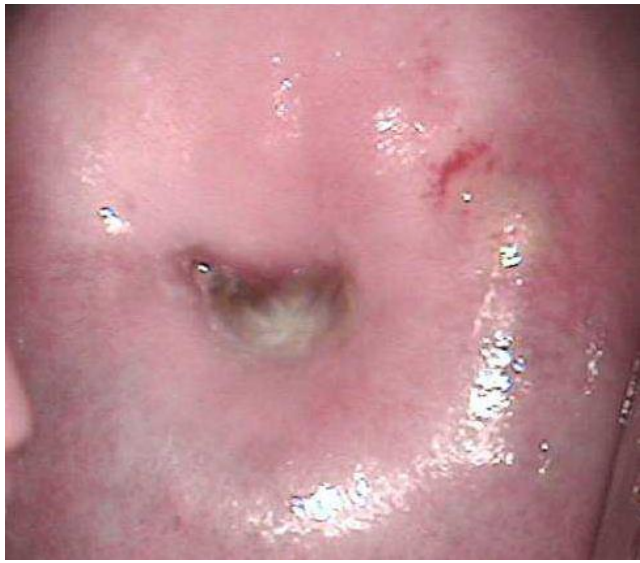




Pelvic Exam Findings

- Blood vessels
  - Petechia
  - Ecchymosis





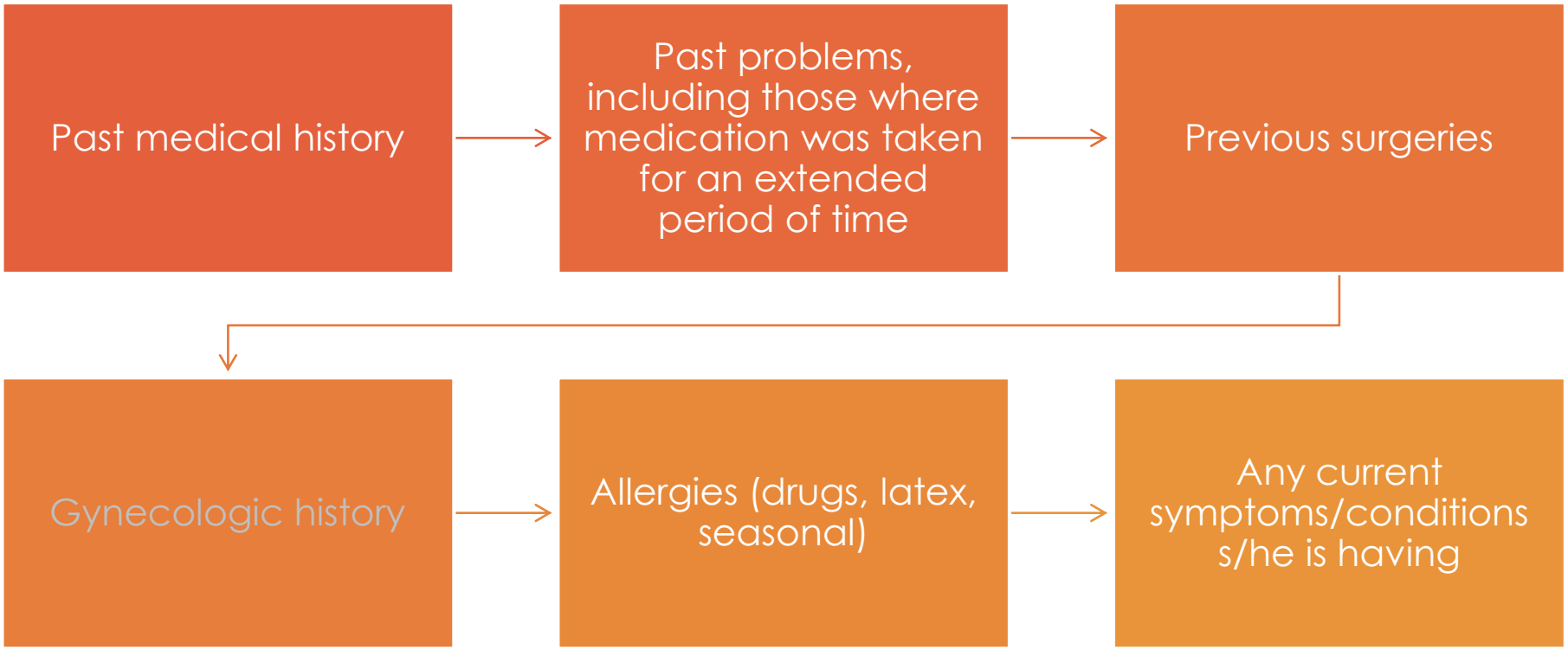
Anorectal Exams

- Anal exam for hemorrhoids, lesions, lumps, rash, ulcers
- If perianal ulcers or vesicles are observed then pursue HSV 1/2 swabbing after visual examination and PRIOR to digital exam
- Digital rectal exam – PRIOR to anoscope/sigmoidoscope
- Rectal specimen collection – sparing lubrication of anoscope
- A reminder of NO use of NSAIDs, aspirin PRIOR to rectal sample collections (PK, PD, mucosal safety biopsies)
- Not allowed: non-study based enemas/douches or laxatives

Anorectal Biopsies

- Endoscopy – sampling occurs 15 cm from the anal verge
- Vitals signs obtained and documented following tissue collection
- Small amount of bleeding from the rectum is normal (noticeable when wiping after a bowel movement) for 2-3 days after the procedure
- Excessive bleeding (of fever, severe abdominal or anorectal pain, anal discharge) is not expected and is reportable and ought to prompt ER evaluation

Baseline Medical History



Baseline Medical History Guide

Baseline Medical History Questions

Part I: General Medical History

Ask participant the following questions. If response is **YES**, indicate the associated body system number from Part II where the description can be found and describe in Part II. If response is **NO,** the remainder of this form should still be completed.

		No	Yes → (associated body system)	Comments
1	Does the participant have any health problems?	☐	☐ → _____	
2	Has the participant ever been hospitalized for any reason other than giving birth?	☐	☐ → _____	
3	Has the participant ever had surgery, including a hysterectomy?	☐	☐ → _____	
4	In the past year, has the participant been to the emergency room?	☐	☐ → _____	
5	Has the participant had any medical or health problems in the past year?	☐	☐ → _____	

Baseline Medical History

Relevant items should be recorded on **Baseline Medical History CRF**

- Such as: hospitalizations; surgeries; allergies; conditions requiring prescription or chronic medication (lasting for more than 2 weeks); and any current conditions

Baseline Bleeding

- Baseline Menstrual History
  - Collected at Screening
  - Documented on Screening Menstrual History CRF
  - Moving away from strict ranges for menses
  - Moving towards FGGT definitions of bleeding abnormalities
  - Changes in bleeding patterns will be assessed during follow-up

UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ABNORMAL UTERINE BLEEDING UNRELATED TO PREGNANCY					
Menorrhagia [2] (prolonged and/or heavy menstrual bleeding)	Participant report of normal bleeding relative to her baseline	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Metrorrhagia [2] (intermenstrual or frequent bleeding)	None or any expected nonmenstrual bleeding	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Unexplained infrequent bleeding (excludes expected absence of menses due to hormonal contraception or pregnancy/postpartum)	Participant report of normal or expected bleeding frequency	No menses for 1-3 months (missed menses)	No menses for > 3 months (oligomenorrhea/ amenorrhea)	NA	NA
Postcoital bleeding	None	Occasional (< 25% of coital acts) OR Increase from usual with no or minimal interference with usual social functioning (including sexual functioning)	Frequent (25-75% of coital acts) OR Increase from usual with moderate interference with usual social functioning (including sexual)	Consistent (> 75% of coital acts) OR Incapacitating or severe interference with usual social functioning (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock

Baseline Medical Conditions

- Comprehensive Snap-Shot at Enrollment
  - Information obtained from history taking
  - Abnormal screening labs
  - Abnormal physical exam findings
  - Abnormal pelvic and rectal exam findings
  - Documented on Baseline Medical History CRF

Follow-up Medical History

- Medical history must be updated at all follow-up visits
  - Are previously reports conditions ongoing?
  - Are there new or worsening symptoms?
- Site clinicians can use their expertise to elicit complete and accurate information
  - How are you?
  - At your last visit, you reported X. Has this resolved?
  - Any current symptoms?
  - Any issues since your last visit?
  - Have you taken any medications since your last visit?

Follow-up Medical History Bleeding

- Consider asking:
  - Any gynecological problems since your last visit?

Follow-up Medical History Documentation

- Review MUST be documented
  - Chart notes, or
  - Site specific tool
- All newly-identified symptoms and conditions will be documented on the AE Log CRF
  - With exception of abnormal bleeding

Reporting GU AEs

- Vaginal discharge per FGGT
  - Participant report
  - Observed by the clinician
  - If captured both by history and on examination, only report the one with the more severe grade
- Vaginal bleeding
  - Record any genital bleeding that is different from baseline and NOT attributable to contraceptive use

STI Evaluations Performed

- Chlamydia
- Gonorrhea
- Syphilis
- HIV 1/2
- HSV 1/2 detection (as clinically indicated)
- Hepatitis B
- Hepatitis C

Female participants

- Symptomatic BV
- Symptomatic vulvovaginal candidiasis
  - In the absence of laboratory confirmed diagnosis, use the term "vulvovaginitis" if 2 or more are present:
    - Pain
    - Itching
    - Erythema
    - Edema
    - Rash
    - Tenderness
    - discharge

Female participants

- Cervicitis – when 2 ore more are present in the absence of a laboratory-confirmed STI, report as "cervicitis" and follow the DAIDS FGGT
  - Dyspareunia
  - Erythema
  - Edema
  - Tenderness
  - Discharge

UTI

- Suspected UTIs may be clinically managed based on the presence of symptoms consistent with a UTI

- Urine dipstick may be performed per site standard of care but sites are expected to send a urine culture for definitive diagnosis/capture
- Capture abnormalities from the dipstick (protein, glucose) in the Baseline Medical History Log CRF per DAIDS toxicity table

HIV testing

- If at screening and/or enrollment a participant has signs/symptoms suggestive of acute HIV, the participant is NOT eligible for enrollment

- Participants who fail screening due to concern for acute HIV should have repeat testing no sooner than two months following the prior negative HIV test. If the HIV antibody test is negative and the participant no longer has symptoms suggestive of acute viral infection, then the participant may undergo a second screening attempt for the study

HIV Reporting

- HIV is NOT included in the DAIDS Toxicity Table and is NOT considered an AE for data collection/reporting
- NO reporting of "HIV" or "HIV infection"
- You MAY report "seroconversion illness" if a participant seroconverts and develops one or more signs of symptoms of acute HIV

Concomitant Medications

- Concomitant Medications Log CRF
  - Prescription and OTC medications/preparations
  - Vaccinations
  - Vitamins and other nutritional supplements
  - Herbal, naturopathic, traditional preparations

Permanent Product Discontinuation

- Prohibited mediation use
- Unable or unwilling to comply with study procedures or otherwise might be at undue risk to safety and well being by continuing product use, according to site IoR/designee
- Anorectal STIs
- Acquisition of HIV (reactive rapid test)
- Pregnancy
- Breastfeeding
- Grade 3 AE RELATED to study product
- Grade 4 AE (regardless of relationship)

Prohibited Practices

- Exclusion criteria
  - PEP in the past six mos
  - PrEP in the past six mos (or anticipated use during trial)
  - Systemic immunomodulatory medications in the past 6 mos (or anticipated use during trial)
  - RAI without a condom and/or penile-vaginal intercourse with a known HIV positive partner in the past 6 mos
  - Injection drug use
  - Anogenital STI in the past 3 mos

Prohibited Practices

Abstaining from inserting any non-study products into the rectum or vagina for 72 hours prior to clinic visits and during the study product use periods

- Male participants:
  - Abstain (72 hours post bx) from receptive anal intercourse, receptive oral anogenital stimulation, rectal stimulation via fingers, rectal insertion of sex toys
- Female participants:
  - Abstain (7 days post bx) RAI, penile-vaginal intercourse, receptive oral anogenital stimulation, vaginal or rectal stimulation via fingers, and vaginal or rectal insertion of sex toys.

Prohibited Practices

- Prohibited medications
  - Heparin
  - Low molecular weight heparin (Lovenox)
  - Warfarin
  - Clopidogrel
  - Hormone-replacement therapy in tablet, injectable or gel form
  - CYP3A inducers/inhibitors