PELVIC EXAMS AND EVALUATIONS

MTN 005
Study Specific Training
TIMING OF PELVIC EXAM

- Every scheduled visit
- When clinically indicated
- Before the study product is resumed if the study product was held in response to a vaginal complaint or finding

Resources
- WHO/CONRAD Manual
- MTN-005 SSP Manual ⇒ checklists
HELPFUL HINTS

- Pay careful attention to
  - Which evaluations are required at all exams,
  - Which are required at some but not all exams,
  - And which are required only when clinically indicated
PERFORMING THE PELVIC EXAM

- Two person procedure: clinician and assistant
- Ensure required supplies and paperwork are easily accessible in the exam room
- Review specimen collection requirements for each visit in preparation for each exam
- Pay careful attention to the required sequence of swab collection and required handling of each swab
PELVIC SWAB COLLECTION

Location, Location, Location (and order)
- Trichomonas (swab from kit)- lateral wall
- BV and Yeast (prn)- lateral wall
- Vaginal floral assessment- lateral wall
- pH (prn)- lateral wall
- Gram stain- lateral wall
- GC/CT- cervical canal
- Innate factors- cervical canal
- Pap smear (prn)- ecto and endo cervix
- Herpes- at site of lesion
PELVIC EXAM TERMINOLOGY

- To document findings, use terms from the FGGT and the pelvic exam case report forms
  - When the term from the case report form is more specific than the term from the FGGT, use the term from the case report form
  - Use routine QC/QA opportunities to help ensure consistency of terminology across staff and exams
PAP SMEAR MANAGEMENT

- See SSP Section 10.8
- Perform at Screening as needed
  - A pap performed in 12 months prior to screen can be used to confirm eligibility

Eligibility Considerations
- Grade 2 (HSIL) is exclusionary
- Grade 1 (LSIL or ASCUS) may be ok!
  - Ppts may be enrolled after complete evaluation (colposcopy) provided treatment (LEEP or Cryo) is not indicated
  - Colposcopy is ok
  - Biopsy is ok if healing is documented prior to enrollment
  - The need for a pap smear in 6 months is not considered “treatment”
- Grade 0 is acceptable
PELVIC EXAM CHECKLIST
SUMMARY OF EVENTS

- Palpate lymph nodes
- Naked eye exam of external genitalia
- Insert speculum
- Naked eye of cervix and vagina
- Collect specimens
- Remove speculum
COLPOSCOPY
COLPOSCOPY IN MTN 005

- Background
- Performing Colposcopy
- Documenting Colposcopy
EVALUATING SAFETY

How to evaluate the safety of candidate microbicides?

- **Systemic safety**
  - Adverse events
  - Lab values
  - Physical exam

- **Local safety**
  - Adverse events
  - Flora changes,
  - Naked eye pelvic exam
  - Colposcopy
HISTORY

- Colposcopy has been the standard technique for safety assessment of vaginal products
- Goal: detection of epithelial changes
  - *May* increase the likelihood of acquisition of HIV or other STI
- Generally accepted reference is the WHO/CONRAD Manual
THE HYPOTHESIS:
EPITHELIAL CHANGES INCREASE RISK OF INFECTION

- **Mechanical disruption** of epithelium and/or underlying blood vessels
  - Portals of entry for pathogens
  - Increase in availability of target cells
- **Inflammation**
  - Could loosen tight junctions between cells
  - Release enzymes that destroy tissue
  - Attract target cells for HIV
  - Increase viral load in genital secretions by activation of latent virus in mucosal immune cells
- Colposcopy allows for close inspection of the epithelium
...BUT WHAT DO EPITHELIAL CHANGES REALLY MEAN?

- Epithelial changes could...

  - Lead to an increased risk of STI, including HIV, or
  - Cause discomfort without increasing the risk of infection, or
  - Be of no clinical significance!
THE JURY IS OUT!
LIMITATIONS OF COLPOSCOPY

- Many requirements
  - Reliable electricity
  - Expensive equipment
  - Specific training

- Variation between observers

- Decision of what to record is very often subjective

- Yields large number of observations
  - Not well established which are most important when evaluating product safety
COLPOSCOPY IN PERSPECTIVE

- Screening tool for products in early phases

- More research needed to better understand which findings indicate risk
Performing Colposcopy
In MTN 005
TIMING OF COLPOSCOPY

- Enrollment
- 12 week Visit
- 16 week/Study Termination Visit
- As clinically indicated
  - Follow up to abnormal colpo findings
  - Closer look at naked eye finding
SUPPLIES

- Speculum
  - Plastic or metal
  - Inspected to ensure that it is free of rough edges that could cause epithelial injury

- Swabs
  - Moistened with saline
  - Only large swabs moistened with saline may be applied to the epithelium

- Lavage materials: pipette or syringe, saline
  - To rinse the cervix
PARTICIPANT POSITIONING

- Soft table
- Lithotomy position with leg supports so that the perineum and vulva can be inspected
- At all times, ensure physical & emotional comfort/privacy
EXTERNAL GENITALIA

- Examine the external genitalia with the naked eye
  - Record findings
- Then examine the external genitalia with colposcope
  - Usually 4-10X magnification
  - Record findings
- All findings recorded on Pelvic Exam Diagrams (Non-DF CRF)
LAVAGE

- Gently lavage cervix and vaginal walls if needed
- Use normal saline
- Don’t touch tissue with syringe
- Aspirate against posterior blade of speculum
COLPOSCOPIC EXAM: CERVIX

- Magnification usually 4-10x

- Record findings
  - All findings on Pelvic Exam Diagrams CRF
  - Abnormal findings on Pelvic Exam CRF, item 7a
  - No AE Log CRF!

- Use photography/video as indicated
COLPOSCOPIC EXAM: FORNICES

- Magnification usually 4-10x
  - Anterior
  - Right lateral
  - Left lateral
  - Posterior
- Often requires significant manipulation
- Record findings per previous slide
COLPOSCOPIC EXAM: VAGINA

- Move colposcope to bring lateral walls into focus
- Slowly withdraw speculum (relax blades as necessary for comfort and refocusing)
- View anterior and posterior walls as you withdraw
- Will need to move colposcope back as withdraw speculum
- Record findings per earlier slide
Describing Colposcopic Findings in MTN 005
WELL-DEFINED TERMS

- Makes communication between investigators easier
- Can be used to double-check what is recorded regarding intactness of the epithelium and blood vessels
- CONRAD/WHO Manual Table 1 (page 8) is your new best friend
# Table 1. Terminology for Colposcopic Findings

The results of the colposcopic examination should be documented using the terms in Table 1 and by recording the status of the epithelium and blood vessels for each numbered finding.

<table>
<thead>
<tr>
<th>Term</th>
<th>Status of epithelium*</th>
<th>Status of blood vessels</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>Intact</td>
<td>Intact</td>
<td>Distinguished by color (erythema being redder than normal, edema either normal or paler than normal, and grossly white findings being white). Grossly white findings are sharply demarcated whereas edema and erythema may be sharp or diffuse.</td>
</tr>
<tr>
<td>Edema</td>
<td>Intact</td>
<td>Intact</td>
<td></td>
</tr>
<tr>
<td>Grossly white finding</td>
<td>Intact</td>
<td>Intact</td>
<td></td>
</tr>
</tbody>
</table>
| Petechiae             | Intact                | Disrupted               | ≤ 3mm
| Ecchymosis            | Intact                | Disrupted               | > 3mm
| Peeling               | Disrupted, superficial | Intact                  | Fragment of disrupted epithelium may remain attached to the area from which it has peeled off. Generally has well demarcated outline. Underlying epithelium looks normal. |
| Ulcer                 | Disrupted, superficial or deep | Intact or disrupted | May include sloughing at base. Generally round or oval with sharply demarcated outline. Superficial ulcers are more accurately called erosions. |
| Abrasion              | Disrupted, superficial or deep | Intact or disrupted | Distinguished from other findings in this class by diffuse or poorly demarcated outline |
| Laceration            | Disrupted, superficial or deep | Intact or disrupted | Sharply demarcated linear finding. Includes fissures. Lacerations appear to be the result of trauma. Fissures appear to be linear “pulling apart” or wearing away of tissue. |

*Superficial epithelial disruption does not penetrate into the subepithelial tissue. Deep epithelial disruption penetrates into and exposes the subepithelial tissue and possibly blood vessels. If bleeding from the finding is present, the disruption should be recorded as deep.
EPITHELIAL DISRUPTION

- Peeling (superficial epithelial disruption)
  - Does not penetrate into the subepithelial tissue
- Deep epithelial disruption
  - Penetrates into and exposes subepithelial tissue and possibly vessels
  - If bleeding from finding is present, disruption should be recorded as deep even if it appears that only a minimal amount of tissue has been lost
- Assessment of disruption depth is subjective, even with magnification of colposcopy
NORMAL CERVIX

- Mucosa
  - Typically uniformly pink
  - Epithelium intact
  - Vessels intact
- Normal variants are not lesions
  - Ectropion
  - Gland openings
  - Scarring from cone biopsies
ERYTHEMA

- Reddened areas
  - Margins may or may not be clearly defined
  - Epithelium intact
  - Vessels intact
EDEMA

- Epithelium
  - Intact
  - Swollen
- Vessels
  - Intact
- Color
  - Normal or pale white
PETECHIAE

- Punctate red areas
- Individual or group
- Epithelium intact
- Vessels disrupted
- **Diameter ≤3mm**
- Color of finding is red or purple
PETECHIAE OF CERVIX

Gland

Os
ECCHYMOSIS

- Epithelium intact
- Vessels disrupted
- **Size >3mm**
- Color is red or purple
PEELING

- Epithelium disrupted but *superficially*
- Vessels intact
- Fragment may remain attached to area of peeling
- Generally well-demarcated
- Underlying epithelium appears normal
PEELING OF VAGINA
PEELING OF CERVIX

Cervical Os
ULCERATION

- Disrupted epithelium
  - Superficial or deep
- Vessels intact or disrupted
- May include sloughing
- Sharply demarcated outline
ABRASION

- Epithelium disrupted
  - Superficial or deep
- Vessels intact or disrupted
- Diffuse or poorly demarcated outline
LACERATION

- A “cut” or “fissure”
- Epithelium disrupted
  - Superficial or deep
- Vessels intact or disrupted
- Appears to be linear “pulling apart” or wearing away of tissue
## BASELINE LESIONS

Lesions at baseline colposcopy in Pittsburgh (n=569)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Erythema</td>
<td>90</td>
<td>15.8%</td>
</tr>
<tr>
<td>Petechiae</td>
<td>107</td>
<td>18.8%</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>23</td>
<td>4.0%</td>
</tr>
<tr>
<td>Peeling</td>
<td>12</td>
<td>2.1%</td>
</tr>
<tr>
<td>Ulceration</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Abrasion</td>
<td>10</td>
<td>1.8%</td>
</tr>
<tr>
<td>Laceration</td>
<td>4</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Total # of women with a lesion = 137 (34.6%)

NORMAL FINDINGS

- Ectopy
NORMAL FINDINGS

- Nabothian cysts
NORMAL FINDINGS

- Cervical polyp
Documenting Colposcopic Findings
In MTN 005
DOCUMENTING COLPOSCOPIC FINDINGS

- If uncertain if the lesion is “abnormal,” compare to the manual

- Document all colposcopic findings (normal and abnormal) on Pelvic Exam Diagrams CRF

- Document abnormal colpo findings on Pelvic Exam CRF, item 7-7a (not on AE Log CRF)

- Further documentation of colposcopic (and naked eye findings) on the pelvic exam diagram is encouraged: e.g., location, extent, detailed description

- Saved colposcopy images facilitate comparison.
If a lesion is present on naked eye exam AND colposcopy, document in both places on the Pelvic Exam CRF (item 1a and 7a).

Only document colposcopic findings in the colposcopic findings section (item 7a).

- Participant report is documented elsewhere
- Only report the finding as seen on colposcopy in the colposcopy section
  - For example, if an abnormality is characterized as erythema on naked eye exam, but abrasion on colpo, mark “erythema” in the non-colpo findings section and “abrasion” in the colpo findings section.
COLPOSOPIC FINDINGS AT FOLLOW-UP

- Treat each colposcopy as a separate event

- Report all colposcopic findings at follow-up on the appropriate form, even if present at baseline
WHEN IS A COLPOSCOPIC FINDING AN ADVERSE EVENT?

- Abnormal findings observed by colpo (and not naked eye exam) are not adverse events (Section 8.3.1)
- Adverse events are clinical findings on naked eye exam, patient reports, and laboratory changes
- Colposcopic findings can coexist with adverse events, but only abnormal findings observed via naked-eye are reported as AEs
  - Vaginal erythema in a participant with vaginal candidiasis
  - Vulvar edema in a participant with an HSV outbreak
  - Cervical ecchymosis in a participant with dysuria
SCENARIO 1

- Participant enrolls in MTN 005
  - On baseline colposcopic exam, no lesions are noted
- At 12 Week Clinic Visit
  - The participant is without complaint
  - The physical exam, including pelvic, is normal
  - On colposcopic exam, this is what is visualized
SCENARIO 1
SCENARIO 1

- How would you describe this?
- Is this an abnormal colposcopic finding?
- How might you decide?
- Do you need to report an adverse event?
- If so,
  - What is it?
  - What severity?
  - What association?
SCENARIO 2

- Participant enrolls in MTN 005
  - On baseline colposcopic exam, no lesions are noted
- At 12 Week Clinic Visit
  - The participant complains of vaginal itch
  - On pelvic exam, thick white discharge and global erythema is noted.
  - The patient’s wet mount is positive for yeast. Other tests are negative.
  - On colposcopic exam, this is what is visualized
SCENARIO 2
SCENARIO 2

- How would you describe this?
- Is this an abnormal colposcopic finding?
- How might you decide?
- Do you need to report an adverse event?
  - If so,
    - What is the AE?
    - What severity?
    - What association
- What is your follow-up plan?
SCENARIO 3

- Participant enrolls in MTN 005
  - On baseline colposcopic exam, the following is noted
- No abnormal finding noted on naked eye pelvic exam
SCENARIO 3

- How would you describe this?
- Is this an abnormal colposcopic finding?
- How might you decide?
- Do you need to report an adverse event?
- If so,
  - What is it?
  - What severity?
  - What association
- Does this affect her eligibility?
SCENARIO 3

- At 12 Week Clinic Visit
  - The participant complains of vulvar erythema
  - Pelvic exam is normal, without lesions. You do not see the erythema.
  - On colposcopic exam, the vulva is normal.
  - This is the image of the cervix.
SCENARIO 3
SCENARIO 3

- How would you describe this?
- Is this an abnormal colposcopic finding?
- How might you decide?
- Do you need to report an adverse event?
- If so,
  - What is it?
  - What severity?
  - What association
WHAT IF...

- I can’t get a good view of the cervix?
- I’m having trouble finishing the colposcopy because the participant can’t tolerate the exam very well?
- I see a lesion, but I’m not quite sure what to call it?
- I see a lesion that seems to be getting worse?
MANAGING CLINICAL EVENTS
GENERAL GUIDELINE

- Findings observed on colposcopy only do NOT impact product use
EPITHELIAL DISRUPTION

- Superficial findings do NOT impact product use
  - Includes abrasion and peeling
  - Require reevaluation in 48-72 hours
  - If worsens, hold and consult PSRT

- Deep epithelial findings DO impact product use
  - Includes ulceration
  - Remove ring
  - Reevaluate in 48-72 hours
    - If improved, reinsert ring
    - If no improvement reevaluate in 48-72 hours
      - If improved, reinsert ring
      - If no improvement, consult PSRT
ERYTHEMA AND EDEMA

- Depends on extend of finding and symptoms
  - <50% and asymptomatic
    - Continue product and reevaluate at next visit
  - <50% and symptomatic
    - Continue product and reevaluate in 48-72 hours
      - If worsens, hold product and consult PSRT
  - >50% regardless of symptoms
    - Hold product
    - Reevaluate in 48-72 hours
      - If resolved, resume product
      - If unresolved, reevaluate 48-72 hours
        - If resolved, resume product
        - If unresolved, consult PSRT
OTHER EVENTS

- **Continue study product for:**
  - Vaginitis
  - Gonorrhea or chlamydia without evidence of cervicitis
  - Unexpected genital bleeding
  - Petechiae
  - Ecchymosis

- **Remove study ring for:**
  - Cervicitis
    - Evaluate for GC/CT
    - Reevaluate in 48-72 hours
  - Pregnancy
  - HIV seroconversion
QUESTIONS?