IMPAACT 2001
CLINICAL MANAGEMENT

VERSION 1.0, 10 NOVEMBER 2015
WITH LOA 1-2, CM 1-3

ADVERSE EVENT

- Any untoward medical occurrence in a clinical research participant administered an investigational product which does not necessarily have a causal relationship with the investigational product.
- An AE can therefore be any unfavorable and 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 study product.

In IMPAACT 2001, "investigational product" refers to the study drug regimen (RPT, INH, pyridoxine)

CLINICAL MANAGEMENT

- All adverse events occurring in study participants must be source documented:
  - Clinical description
  - Severity grade of each event
  - Relationship to study product (each one)
  - Onset and resolution dates
- All must be followed to resolution or stabilization

SEVERITY GRADING

Grade	Definition
1	Mild
2	Moderate
3	Severe
4	Potentially life-threatening
5	Results in death

Grade adverse events per **Version 2.0** of the DAIDS Toxicity Table

Complications during pregnancy should be graded per the Complications of Pregnancy Section of the Female Genital Grading Table for Use in Microbicide Studies, Version 1.0, November 2007

Complications of Pregnancy Section of the Female Genital Grading Table for Use in Microbicide Studies, Version 1.0, November 2007 (see page 11)

UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
COMPLICATIONS OF PREGNANCY					
First trimester bleeding	None	Spotting or bleeding less than menses with continuation of pregnancy	Bleeding like menses or heavier with continuation of pregnancy	Spontaneous abortion, or profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Spontaneous abortion with profuse bleeding and/or shock
Postabortal endometritis/salpingitis	None	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, requiring ≤ 3 days of parenteral antibiotics	Severe symptoms requiring > 3 days of IV antibiotics or development of tubo-ovarian abscess	Ruptured TOA or diffuse peritonitis or severe uterine infection for which operative intervention indicated
Postpartum hemorrhage	EBL < 500 cc for vaginal delivery or < 1000 cc after CS or reported as normal	EBL 500-1000 for vaginal delivery or 1000-1500 for CS or reported as slightly increased	EBL > 1000 for vaginal delivery or > 1500 for CS, with or without mild dizziness, no transfusion required	Hemorrhage at a level for which transfusion of 1-2 units of packed cells, but no other blood products indicated	Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated
Postpartum endometritis	None	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, treated by ≤ 3 days of parenteral antibiotics	Severe symptoms treated with > 3 days of IV antibiotics or addition of heparin	Severe infection or infection for which operative intervention is indicated
Chorioamnionitis	None	Fever (38°C – 38.4°C or 100.4°F – 100.9°F) with two or more: FHR > 160 BPM, maternal HR > 120, uterine tenderness between contractions or purulent AF or preterm labor	Same as Grade 1 plus fever 38.5°C – 40°C or 101°F – 104°F	Criteria for Grade 2 plus fetal distress or fever > 40°C or 104°F	Criteria for Grade 3 plus either fetal demise or maternal symptoms of shock

GRADATION OF RELATIONSHIP ASSESSMENT FOR AE

Relationship Category	Definition
Definitely related	The event and administration of the medication are related in time, and a **direct association** can be demonstrated.
Probably related	The event and administration of the medication are reasonably related in time, and the event is **more likely** explained by the medication than other causes.
Possibly related	The event and administration of the medication are reasonably related in time, and the event can be explained **equally well** by causes other than the medication.
Probably not related	A potential relationship between the event and the medication could exist (.e., the possibility cannot be excluded), but the event is **most likely** explained by causes **other** than the medication.
Not related	The toxicity is **clearly explained by another cause** not related to the medication.

This classification applies for AE documentation (i.e. source documentation and CRFs) and management, but does NOT apply for EAE reporting. See Section 7.3 for more information on EAE reporting.

TOXICITY MANAGEMENT

- Refer to protocol Section 8
- Email questions to Core Team: impaact.core2001@fstrf.org

Management of adverse events will be according to the best clinical practice and the judgment of the site investigator. In general, the IoR has the discretion to hold study drug regimen temporarily at any time if s/he feels that continued use would be harmful to the participant or interfere with treatment deemed clinically necessary, and the Core Team should be notified in such cases.

Unless otherwise specified, the IoR/designee should immediately consult the Core Team for further guidance on resuming study drug regimen, continuing hold temporarily, or permanent discontinuation of study drug regimen

TOXICITY MANAGEMENT GUIDELINES

- Section 8.1.12 provides general guidelines for management of AEs
- Section 8.1.1- 8.1.11 provide more specific guidance on management of:
  - Suspected TB
  - Rifamycin hypersensitivity syndrome (RHS)
  - Gastrointestinal toxicity
  - Rash
  - Fever
  - Peripheral neuropathy
  - Asymptomatic ALT or Total Bilirubin (*see LoA #2*)
  - Hepatotoxicity (symptomatic)
  - HIV-infection
  - Postpartum hemorrhage
  - New pregnancy during study follow-up

GENERAL GUIDANCE

Refer to protocol Section 8.1.12 for complete instructions

- Grades 1 and 2:
  - Continue study drug regimen
- Grades 3 and 4:
  - Hold study drug regimen (RPT, INH, pyridoxine) until AE returns to baseline levels
    - If baseline was > Grade 2, hold study drug regimen until resolution ≤ Grade 2
  - If the event does not resolve ≤ 4 weeks, permanently discontinue study drug regimen and notify the Core Team within 48 hours.

POSTPARTUM HEMORRHAGE

Refer to protocol Section 8.1.10 for complete instructions

- Postpartum hemorrhage is defined as blood loss greater than 500 mL in vaginal delivery and 1,000 mL in caesarean section within 24 hours of birth, at the discretion of the site investigator.

- As rifampin, another rifamycin product, may increase risk for postpartum hemorrhage and bleeding in the exposed neonate, mothers will have prothrombin time (PT) monitored at the following time points:

  - Baseline (all women)
  - Third trimester (at one weekly visit for women who are taking the study drug regimen *at ≥34 weeks gestational age only*)
  - During monthly visits as clinically indicated (all women)

- Infants will be monitored for PT at birth and as clinically indicated during monthly follow-up.

POSTPARTUM HEMORRHAGE

Refer to protocol Section 8.1.10 for complete instructions

- Grades 1 and 2:
  - Continue study drug regimen and follow per standard of care

POSTPARTUM HEMORRHAGE

Refer to protocol Section 8.1.10 for complete instructions

- Grades 3 and 4:
  - Hold study drug regimen (RPT, INH, pyridoxine) and assess for signs and symptoms of active bleeding and other pregnancy-related etiologies
    - *If signs of active bleeding are found*: permanently discontinue study drug regimen, administer vitamin K per standard of care, monitor bleeding and repeat PT until resolution of ≤ Grade 1.
    - *If no signs of active bleeding or other etiologies are found*: administer vitamin K per standard of care and repeat PT within 3 working days.
      - <u>If repeat PT is ≤ Grade 2</u>: resume study drug regimen and monitor PT until ≤ Grade 1.
      - <u>If repeat PT is ≥ Grade 3</u>: permanently discontinue study drug regimen. Continue to monitor PT until ≤ Grade 1.

IMPAACT 2001 EXPEDITED ADVERSE EVENT (EAE) REPORTING

VERSION 1.0, 10 NOVEMBER 2015
WITH LOA 1-2, CM 1-3

EAE REPORTING

Refer to protocol Section 7.3 for complete instructions

- Requirements, definitions, and methods for expedited reporting of adverse events are outlined in the *Version 2.0, DAIDS EAE Manual*
- The protocol specifies the following events to reported in an expedited manner:
  - EAEs for women and infants enrolled in the study
  - Serious Adverse Events (SAE) as defined in Version 2.0 of the DAIDS EAE Manual
  - All cancers and pregnancies, fetal losses, IRIS events that qualify as serious AEs, and all Grade 3 and Grade 4 toxicities
  - Selected hepatotoxic events as medically significant events:
    - All confirmed Grade 4 ALT
    - All confirmed Grade 3 ALT with Grade 2 or higher total bilirubin,
    - Symptomatic hepatitis or hypersensitivity symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) with Grade 2 or higher ALT or total bilirubin
- The agents that expedited reporting is required are rifapentine and isoniazid.
- The EAE reporting period for this study begins at enrollment and continues through the participant's final study visit (mother *or* infant study exit visit)

SERIOUS ADVERSE EVENT (SAE)

An AE (untoward medical occurrence) that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes above.

Medical and scientific judgment should be exercised in deciding whether other AEs not listed above should be considered serious.

MAPPING RELATIONSHIP CATEGORIES TO RELATIONSHIP CATEGORIES FOR EAE REPORTING

Relationship Category	Maps To	Relationship Category for EAE Reporting
Definitely related		**Related**
Probably related		**Related**
Possibly related		**Related**
Probably not related		**Not Related**
Not related		**Not Related**

EAE REPORTING PROCEDURES

- Report EAEs using the internet-based DAIDS Adverse Experience Reporting System (DAERS) or use paper-based reporting if DAERS is not available or accessible
- Refer to DAERS user and reference guides for detailed instructions
- Report within 3 reporting days of site awareness that the event meets EAE reporting criteria
- Follow all EAEs to resolution or stabilization and submit an updated EAE report to document the resolved or stable outcome of the event (if not available at time of initial report)
- Updates should also be submitted if significant additional information becomes available after an EAE report is first submitted.
- Automated email messages confirming submission of EAE reports should be printed and filed with the print-out of the EAE report

EAE reports will include information that is also recorded on study CRFs. Always cross-check across documents to avoid discrepancies.