OVERVIEW OF PRESENTATION

- Selected Definitions
- Protocol specifications for P1092
- Communication with Core Team
- Expedited adverse event reporting
ADVERSE EVENT

- Any untoward medical occurrence in a clinical research participant administered a study agent and which does not necessarily have a causal relationship with the study agent.

- 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 a study agent, whether or not considered related to the study agent.
All adverse events occurring in study participants must be source documented:

- Clinical description
- Severity grade
- Relationship to ARVs (each one)
- Onset and resolution dates

All must be followed to resolution or stabilization
<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Potentially life-threatening</td>
</tr>
<tr>
<td>5</td>
<td>Results in death</td>
</tr>
</tbody>
</table>

Grade adverse events per **Version 2.0** of the DAIDS Toxicity Table
<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37.4 to &lt; 38.0° C</td>
</tr>
<tr>
<td>2</td>
<td>38.0 to &lt; 38.7° C</td>
</tr>
<tr>
<td>3</td>
<td>38.7 to &lt; 39.4° C</td>
</tr>
<tr>
<td>4</td>
<td>≥ 39.4° C</td>
</tr>
<tr>
<td>Relationship Category</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Definitely related</td>
<td>The event and administration of the ARV are related in time, and a <strong>direct association</strong> can be demonstrated.</td>
</tr>
<tr>
<td>Probably related</td>
<td>The event and administration of the ARV are reasonably related in time, and the event is <strong>more likely</strong> explained by the ARV than other causes.</td>
</tr>
<tr>
<td>Possibly related</td>
<td>The event and administration of the ARV are reasonably related in time, and the event can be explained <strong>equally well</strong> by causes other than the ARV.</td>
</tr>
<tr>
<td>Probably not related</td>
<td>A potential relationship between the event and the ARV could exist (i.e., the possibility cannot be excluded), but the event is <strong>most likely</strong> explained by causes <strong>other</strong> than the ARV.</td>
</tr>
<tr>
<td>Not related</td>
<td>The toxicity is <strong>clearly explained by another cause</strong> not related to the ARV.</td>
</tr>
</tbody>
</table>
Likelihood AE is Related to Study Drug

- **0%**: Not Related
  - AE clearly explained by another cause not related to study drug

- **1-49%**: Probably Not Related
  - Potential relationship cannot be ruled out but AE most likely explained by causes other than study drug

- **50%**: Possibly Related
  - AE can be explained equally well by causes other than study drug

- **51-99%**: Probably Related
  - AE more likely explained by study drug than other causes

- **100%**: Definitely Related
  - Direct association can be demonstrated between the AE and study drug
equal weight on study drug and other causes = Possibly Related
more weight on other causes = Probably Not Related

more weight on study drug = Probably Related
What are your questions so far?
TOXICITY MANAGEMENT

- Refer to protocol Section 6
- Email questions to impaact.corep1092@fstrf.org

Management of AEs will be according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory normals will be the institutional values. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2. For all grade 3 and 4 laboratory values, sites should attempt to repeat the test within 3 days and should notify the Core Team for exceptions (longer period of time needed) up to 7 days.
Questions for P1092 Core Team: Please copy and paste this listing into the body of your email message to impaact.corep1092@fstrf.org to help ensure that all required information is included. Include the protocol number and PID in the subject line of your email.

1. Site name and number:
2. Name of person submitting query:
3. PID:
4. Reason for query (choose one):
   - Consultation on eligibility or enrollment (describe in case description)
   - Consultation on AE or toxicity management (specify grade in case description)
   - Consultation on ART regimen management (describe in case description)
   - Other (specify in case description)
5. Cohort: 1 or 2
6. Sex and age of participant:
8. Current week on study:
9. Current ARV regimen (drug names and current dose of each):
10. Case description and question or notification for Core Team:
The toxicity management guidelines specified in the protocol are:

- For adverse events for which a relationship to study drugs cannot be excluded
- Based on the severity of the events and their relationship to ARVs
Section 6.21 provides general guidelines

Sections 6.22-6.24 provide specific guidance on management of:

- Hematologic toxicity (Hgb, WBC, ANC, platelets) for participants on ZDV
- Symptomatic and asymptomatic hepatitis, including AST/ALT elevations
- Rash
GENERAL GUIDANCE

refer to protocol Section 6.21 for complete instructions

- Grade 1:
  - Continue study drugs

- Grade 2:
  - Continue study drugs
Grade 3:

- Notify Core Team within 3 business days
- Study drugs can be continued at the discretion of the site investigator for clinical events or while awaiting repeat of an abnormal laboratory test as soon as possible (at most within one week)
- If repeat test confirms Grade 3, hold all study drugs and follow abnormal values weekly

*refer to protocol Section 6.21 for complete instructions*
Grade 3 continued:

- If toxicity resolves to Grade ≤ 2 within 14 days, all study drugs can be restarted
- If Grade 3 toxicity persists for ≥14 days, or recurs to Grade ≥ 3 after re-starting study drugs, all study drugs must be permanently discontinued
- Alternatively, if the toxicity is clearly attributed to an individual study drug, that study drug may be permanently discontinued and replaced, with continuation of other drugs in the regimen

refer to protocol Section 6.21 for complete instructions
GENERAL GUIDANCE

refer to protocol Section 6.21 for complete instructions

- Grade 4, Non-Life Threatening:
  - Hold all study drugs
  - Notify Core Team within 3 business days
  - For abnormal lab tests, repeat ASAP (within 1 week)
    - If Grade 4, permanently discontinue all study drugs
    - If Grade 3, continue hold and follow lab value weekly
  - If Grade ≤2 within 14 days, restart study drug after approval from Core Team
  - If Grade ≥3 recurs, permanently discontinue all study drugs
GENERAL GUIDANCE

Grade 4, Life Threatening:

- Permanently discontinue all study drugs
- Notify Core Team within 3 business days

refer to protocol Section 6.21 for complete instructions
SPECIFIC GUIDANCE EXAMPLES

**Grade 3 hematologic toxicity**
- Notify Core Team
- Continue study drugs at discretion of site investigator/clinician
- Repeat assessment (as soon as possible, at most within 1 week)

**Grade 3 toxicity confirmed:**
- Replace ZDV with ABC (resume other study drugs if previously held)
- Otherwise hold all study drugs
- Notify Core Team and follow abnormal labs weekly until resolution to ≤ Grade 2

**Grade 3 toxicity not confirmed (or resolved to ≤ Grade 2):**
- Continue routine monitoring

**If Grade 3 toxicity persists for ≥ 14 days from date of intervention (holding drug or replacing ZDV with ABC):**
- Permanently discontinue all study drugs*

**If toxicity resolves to ≤ Grade 2 within 14 days from date of intervention (holding drug or replacing ZDV with ABC):**
- Restart study drugs (if held)
- Continue routine monitoring

**If ≥ Grade 3 toxicity recurs after reintroduction of study drugs:**
- Permanently discontinue all study drugs*

*In cases where the patient's medical condition allows.
Clinical (Symptomatic) Hepatitis
Subjects taking study drug should be monitored for the development of a clinical hepatitis syndrome. Symptoms of hepatitis include the following: fatigue, malaise, anorexia, nausea, acholic stools, bilirubinuria, jaundice, liver tenderness, or hepatomegaly. Participants with signs and symptoms suggestive of clinical hepatitis must seek medical attention immediately and have liver function tests (LFTs) and screening for hepatitis A and B performed. Management of hepatitis will be according to the grading of AST/ALT stipulated below.
Grade 1 AST/ALT

If grade 1 at entry, no additional evaluation is required; if normal at entry, follow guidance in this section:

- AST/ALT must be repeated as soon as possible (at most within one week).
- Study drugs may be continued while repeating AST/ALT as long as the participant is asymptomatic. Participants with a confirmed Grade 1 AST/ALT who are asymptomatic may continue study drugs with continued close observation.

SPECIFIC GUIDANCE EXAMPLES

refer to protocol Sections 6.22-6.24 for complete instructions
Grade 1 AST/ALT continued

- For participants with Grade 0 AST/ALT at study entry, an increase to Grade 1 even if asymptomatic may be of concern.

- Participants should be evaluated for a cause of the LFT abnormality, and should be observed for worsening LFT elevation or development of clinical hepatitis.

- Careful assessments should be undertaken for nonstudy drug-related toxicity, the lactic acidosis syndrome, and viral hepatitis as the cause of the transaminase elevation.
SPECIFIC GUIDANCE EXAMPLES

refer to protocol Sections 6.22-6.24 for complete instructions

Rash

Grade 1 or 2, on Abacavir
Study drugs may need to be held depending on rash distribution and relatedness assessment.
- If the rash is generalized and there is no specific alternative explanation for the rash:
  - Hold entire regimen,
  - Test ALT within 3 business days, and
  - Evaluate for symptoms of clinical hepatitis and hypersensitivity reaction.
If any clinical symptoms of hepatitis or ALT elevation or hypersensitivity reaction, permanently discontinue abacavir and consult with the Core Team on alternative ARV regimens.
- If the rash is not generalized or if there is a specific alternative explanation for the rash (e.g., varicella), study drugs — including abacavir — may be continued with no additional evaluation required.

Grade 3
- Hold entire regimen unless the rash is determined to be unrelated to study drug
- Notify the Core Team within 3 business days.
- If there is no specific alternative explanation for the rash (e.g., varicella), test ALT and manage per the ALT/AST guidelines in Section 6.23.
- If on abacavir, permanently discontinue abacavir. When the rash resolves, study drug may be resumed with an alternate regimen that does not include abacavir; consult with the Core Team on alternative regimens.

Grade 4
- Hold entire regimen.
- Notify and consult with the Core Team on alternative ARV regimens within 3 business days.

Note: Abacavir should never be restarted following a hypersensitivity reaction.

Grade 1 or 2, Not on Abacavir
- Continue study drugs.
- Rash may be treated symptomatically, but should be monitored closely by the site investigator.
Important Reminders

Participants who permanently discontinue all study drugs will remain in follow-up but evaluations will be performed per the Off Treatment/On Study column of the Schedule of Evaluations.

The site investigator may choose to continue these participants on non-study HAART based on local treatment standards and the best interest of the child.
What are your questions?
P1092 EXPEDITED ADVERSE EVENT REPORTING

STUDY–SPECIFIC TRAINING
15 JUNE 2015
REFERENCES AND RESOURCES

- P1092 Protocol Section 7
- DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, dated November 2014
- Manual for Expedited Reporting of Adverse Events to DAIDS
- DAERS Site User Instructional Guide for EAE Reporting
- DAERS Reference Guide for Site Reporters and Study Physicians
- Package inserts for ZDV, 3TC, LPV/r, and ABC
- DAIDS safety training resources
ADVERSE EVENT

- Any untoward medical occurrence in a clinical research participant administered a study agent and which does not necessarily have a causal relationship with the study agent.

- 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 a study agent, whether or not considered related to the study agent.
SERIOUS ADVERSE EVENT

- An adverse event 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*

*See helpful clarifications of terms in the DAIDS EAE Manual
Medical and scientific judgment should be exercised in deciding whether other AEs not listed above should be considered serious.

Important medical events 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 listed above should usually be considered serious.
An adverse event that:

- Meets protocol-specified criteria for reporting in an expedited manner to the DAIDS Regulatory Support Center (RSC) Safety Office.
Events that must be reported as EAEs for this study:

- All serious adverse events
- All malignancies and grade 3 and 4 hepatotoxicities whether or not symptomatic or related to study drug
- All other grade 3 or 4 toxicities for which a relationship to study drug cannot be ruled out

*occurring at any time while a participant is on study*
Other events that must be reported as EAEs for this study:

- Any deaths that occur within 30 days after study completion
- Any SUSARs (serious unexpected suspected adverse reactions) that study staff become aware of after study completion
The study agents for which relationship assessments are required are ZDV, 3TC, and LPV/r.

For participants who may receive ABC due to intolerance to ZDV, relationship should also be assessed for ABC.
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 initially available).
Updates also should be submitted if significant additional information becomes available after an EAE report is first submitted, e.g.,

- Updated severity grade or relationship assessment
- Information on participant status after resumption of one or more ARVs
- Newly available information on cause of death
DAERS incorporates a report printing function that should be used to print all EAE reports, including modifications and updates, for filing in participant study records.

Automated email messages confirming submission of EAE reports also should be printed and filed with the print-out of the EAE report.

*EAE reports will in include information that is also recorded on study CRFs.*

*Always cross-check across documents to avoid discrepancies.*
What are your questions?