

Case Review: All About AEs

DAIDS Regulatory Support Center (RSC) Safety Office

Site Specific Training

Webinar

November 18, 2014



National Institute of
Allergy and
Infectious Diseases



Regulatory
Support
Center

Objectives

- To review a case and be able to identify symptoms and symptom clusters
 - To decide on AE terms, the Primary AE, how many Primary AEs
 - To identify clinically significant events associated with the Primary AE
- To decide which AEs meet reporting criteria to DAIDS in an expedited timeframe

Objectives

- To determine if available information is adequate (e.g., identifiers, study product information, AE information [such as AE outcome, treatment provided], supporting information or documents)
- Construct a comprehensive narrative
 - Use Quick Reference Card Adverse Event Checklist to make sure all relevant information is provided
- To perform an assessment of the case

**5 MINUTES TO READ
THE CASE HANDOUT**

Questions

- Identify the symptoms
- Cluster the symptoms
- Decide on AE terms
- Decide on the Primary AE and its clinically associated events
- How many Primary AEs?
- How many Primary AEs are reportable to DAIDS?
- What relevant info is missing from the narrative?
 - Use the checklist

Case Review

- **19 Dec 2013:** 26 year old HIV infected female enrolled
- **19 Dec 2013:** Started on the study products efavirenz/emtricitabine/tenofovir disoproxil fumarate, bleomycin, and vincristine
- **9 Apr 2014:** week 15 study visit
 - Complaints of new onset of cough (grade 2) and exacerbation of shortness of breath
 - Clinical diagnosis of viral lower respiratory tract infection (LRTI) or bacterial pneumonia. Oxygen saturation 96-99%. CXR with no progressive signs of pulmonary Kaposi's sarcoma.
 - Azithromycin prescribed and sixth cycle of bleomycin and vincristine received

Case Review

- **10 Apr 2014:** Admitted to hospital for cough, chest pain, and fever. Administered IV ceftriaxone.
- **11 Apr 2014:** Discharged on azithromycin. One episode of hemoptysis at home.
- **12 Apr 2014:** Collapsed from severe shortness of breath (no convulsions or fever). Rushed to hospital.

Case Review

■ 12 Apr 2014: Hospital work-up

- Vital signs at admission: BP 104/44 mm Hg, RR 60 bpm, PR 160 bpm.
- PE: facial edema, cutaneous and oral lesions, dyspnea, and hypoxia (oxygen saturation 27% at room air, improved to 57% on oxygen). Chest examination: widespread crackles.
- Labs: Hgb 6.6 g/dL, WBC $14.2 \times 10^3/\mu\text{L}$, RBC $2.70 \times 10^6/\mu\text{L}$, Plt $116 \times 10^3/\mu\text{L}$, ANC $12.85 \times 10^3/\mu\text{L}$, Na 138 mmol/L, K 4.1 mmol/L, CO_2 16.9 mmol/L, Glu 215 mg/dL, Ca 1.85 mmol/L, albumin 2.4 g/dL, ALT 5 IU/L, and MP negative.

Case Review

- **12 Apr 2014:** Hospital Admission
 - Impression: decompensation with disseminated pulmonary Kaposi's sarcoma and reactivation of TB.
 - Tx: Ceftriaxone, levofloxacin, hydrocortisone, and dexamethasone. Transfused one unit of whole blood.
- **13 Apr 2014:** Condition worsens. Oxygen saturation decreases to 36%, RR 64 bpm, PR 144 bpm. Medications continued without change.

Case Review

- **14 Apr 2014:** Complaint of feeling very hot. Body temperature 36.4°C. At 0515 hours, gasping with RR 162 bpm, BP 87/52 mm Hg, body temperature 33.9°C and oxygen saturation 46%. The subject was later pronounced dead.
- **PI Assessment:** Death due to probable severe bacterial pneumonia NR to efavirenz/emtricitabine disoproxil fumarate, bleomycin, and vincristine.

Case Review

- **PMH:** HIV infection, Kaposi's sarcoma, oral thrush, suspected bacterial pneumonia. Pulmonary TB treatment 3 weeks prior enrollment
- **Obst & Gyn Hx:** No significant history
- **Social Hx:** No history of smoking, alcohol or recreational drug use.

Case Review

Symptoms	Symptom Cluster	AE Term
Cough, shortness of breath	Cough, shortness of breath	Upper respiratory tract infection
Cough, shortness of breath, CXR: No significant findings	Cough, shortness of breath	Viral lower respiratory tract infection
Cough, chest pain, fever	Cough, chest pain, fever	Bacterial pneumonia
Shortness of breath, hemoptysis	Shortness of breath, hemoptysis	TB, Chronic lung infection, Probable lung tumor
Collapsing	Collapsing, cough, shortness of breath, chest pain, fever, hemoptysis	TB, Pneumonia, Viral syndrome

Case Review

Symptoms	Symptom Cluster	AE Term
Dyspnea, hypoxia, widespread crackles in lungs, facial edema, cutaneous and oral lesions, RR 60 bpm, PR 160 bpm	<ol style="list-style-type: none"> Dyspnea, hypoxia, widespread crackles in lungs, RR 60 bpm Facial edema, cutaneous and oral lesions 	<ol style="list-style-type: none"> TB, Pneumonia Kaposi's Sarcoma, Autoimmune disorder, Acute renal disorder
Labs: Hgb 6.6 g/dL, WBC 14.2 x10 ³ /uL, RBC 2.70x10 ⁶ /uL, Plt 116x10 ³ /uL, ANC 12.85x10 ³ /uL	Anemia, thrombocytopenia	Anemia, thrombocytopenia
Labs: Na 138 mmol/L, K 4.1 mmol/L, CO ₂ 16.9 mmol/L, Glu 215 mg/dL, Ca 1.85 mmol/L, albumin 2.4 g/dL		Metabolic disorder

Case Review

Primary AE	SAE	Reportable to DAIDS
Upper respiratory tract infection	No	No (Did not meet reporting criteria)
Bacterial pneumonia	Yes	Yes (Hospitalization)
TB	No	No (Did not meet reporting criteria)
Anemia, thrombocytopenia	Yes	Yes (Hospitalization for transfusion)
Acute renal disorder/Metabolic disorder	No	Insufficient information

Missing Information: Narrative- 1

- Signs/Symptoms
- Predisposing factors
- Diagnostic workup
- Treatment for AE, include outcome
- Hospitalization
- Concomitant medications
- PMH
- Supporting information

Missing Information: Narrative- 2

- Provide information on reported Primary AE
- Describe:
 - clinical course
 - therapeutic measures
 - outcome
 - relevant past medical history
 - concomitant medication(s)
 - alternative etiologies
 - any contributing factors
 - all other relevant information

Missing Information: Narrative- 3

- **Signs and Symptoms:** Provide information on baseline, current course, severity, frequency, duration, other characteristics
- **Primary AE:** Provide details from PE. Missing obvious information (e.g., vitals, HEENT, abdominal exam, hematologic manifestations)? If abnormal, any repeat tests, tx, resolution?
- **Lab Tests:** Any relevant labs? Include units, normal ranges. If abnormal, provide baseline and progression, hospital course, resolution.
- **Diagnostic Tests:** Provide indication and results as appropriate. Repeat tests if abnormal?

Missing Information: Narrative- 4

- **Treatment:** Details of treatment (e.g. antibiotics, steroids, oxygen, blood transfusion) including date started, completion, components, frequency, quantity of medications.
- **Hospital Course:** Details of AE on admission and subsequent AEs. Distinguish between ongoing evolution of admission AE vs new AE.
- **Concomitant Meds:** Details of medications taken at the time of the onset of AE (not same as treatment medications), include indications for use.
- **Past Medical History:** Provide all relevant information including previous workup, tx, resolution (e.g. HIV infection, Kaposi's sarcoma, oral thrush, TB, suspected bacterial pneumonia).

Missing Information: Narrative- 5

- **Family History:** Provide any relevant history
- **Social History:** Provide any other relevant history
- **Other Supporting Information:** Discharge summary, notes from previous doctors, death certificate/autopsy report if indicated
- **Resolution of AE:** Final status of AE (and all other abnormal results), Study product(s) status, Study participation status

Teaching Points

- **Provide relevant information with adequate details to allow for assessment of the case by sponsor clinician and reviewing authority**
 - Distinguish symptom, sign, condition, and diagnosis
 - Formulate course of event?
 - Confirm site assessment?
- **Without additional queries**
 - If information unavailable to site, express what information is pending or being sought and will be provided as soon as available

Teaching Points

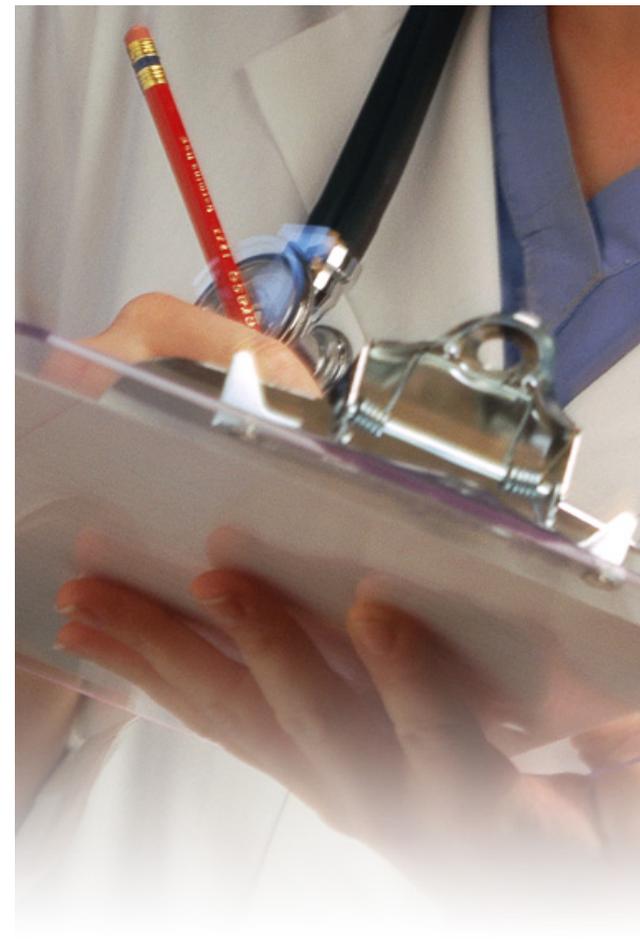
- **Continue to follow case until resolution or stable**
- **Additional information received at site reviewed for:**
 - Impact on initial assessment
 - Clinical association with the Primary AE in initial submission....or is it another Primary AE?
 - If another Primary AE, does it meet reporting criteria?

Teaching Points

- **Evolving case:** difficult to have entire picture; only responsible for reporting when aware; Follow case and provide updates
- **Difficult to distinguish between being part of the Primary AE or additional Primary AE**
- **Use best judgment as a medically qualified person**
- **It is recognized that:**
 - At the time of event awareness: limited knowledge
 - With aggregate data (if available): knowledge changes
 - At study end: data analysis may reveal further knowledge

Levels of Review

- **AEs are assessed for:**
 - Seriousness
 - Relationship
 - Expectedness
 - Severity
- **Site Level:** Study physician listed on the 1572/IoR (Investigator of Record) Agreement is responsible for the assessment of AEs
 - Study provisions for safety monitoring e.g. PSRT
- **Sponsor Level:** DAIDS MOs provide secondary review; consult with SPT as necessary



Site vs. Sponsor Assessment

Site Assessment

- Site advantage: has access to subject; may elicit further info, perform PE, obtain tests, labs, records
- Information from self-report (may lack validation)
- Know subject best
- Judgment stands
- Open to dialog with sponsor

Sponsor Assessment

- Information limited to what was submitted from site
- May initiate queries to site: incur time and delay
- Constraint: Must adhere to reporting timelines to FDA
- MO level: Serious? Unexpected? Related?
- Open to dialog with Site PI, DAIDS, MO