

## Case Study: All About AEs

The subject was a 26 year old, HIV infected, female, enrolled in the study on 19 Dec 2013, who died on 14 Apr 2014 and the cause of death was probable severe bacterial pneumonia.

On 19 Dec 2013, the subject was randomized to Arm 1B of the study and started on the study agents efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 milligrams (mg) orally every evening, bleomycin 20 units intravenously one cycle every three weeks and vincristine 2 mg intravenously one cycle every three weeks.

Prior to study enrollment, the subject was treated for suspected bacterial pneumonia and also had a history of oral thrush. Three weeks prior to enrollment, the subject was started on pulmonary tuberculosis (TB) treatment based on symptoms and X-ray findings. The subject's condition improved after receiving treatment.

While on the study, the subject completed all six cycles of the study treatment without experiencing any toxicity. On study weeks 6 and 9, the subject had study-defined partial response based on resolution of tumor associated edema and oral lesions respectively.

On 9 Apr 2014, at week 15 study visit, the subject complained of new onset of cough (grade 2) associated with exacerbation of shortness of breath over the previous few days. She did not report experiencing fever. A chest X-ray did not show progression of pulmonary Kaposi's sarcoma. The subject had objective improvement in the cutaneous Kaposi's sarcoma.

On 9 Apr 2014, during the study visit, a clinical diagnosis of viral lower respiratory tract infection (LRTI) or bacterial pneumonia was made. The subject was treated with azithromycin. Oxygen saturation on room air was 96-99%. The subject also received the sixth cycle of bleomycin and vincristine.

On 10 Apr 2014, the subject was admitted to a local hospital for cough, chest pain, and fever of one day duration. She was administered intravenous ceftriaxone. On 11 Apr 2014, the subject was discharged home on azithromycin.

On 12 Apr 2014, the subject collapsed at home. She was rushed to the local hospital. The subject's mother reported that the subject collapsed with severe shortness of breath but had no convulsions or fever. The mother reported one episode of hemoptysis on 11 Apr 2014.

On 12 Apr 2014, upon admission, the subject's vital signs were: blood pressure 104/44 mm Hg, respiratory rate of 60 breaths per minute and pulse rate of 160 beats per minute. The subject was dyspneic and hypoxic with oxygen saturation at 27% at room air which later improved to 57% on oxygen. Chest examination revealed wide spread crackles. There was facial edema, cutaneous and oral lesions that were attributed to Kaposi's sarcoma. The impression was decompensation with disseminated pulmonary Kaposi's sarcoma and reactivation of TB.

*This case study was developed from an actual EAE submission. All subject identifiers have been removed to maintain confidentiality.*

On 12 Apr 2014, the subject's clinically significant laboratory results were as follows: hemoglobin 6.6 g/dL, white blood count  $14.2 \times 10^3/\text{uL}$ , red blood count  $2.70 \times 10^6/\text{uL}$ , platelets  $116 \times 10^3/\text{uL}$ , absolute neutrophil count  $12.85 \times 10^3/\text{uL}$ , sodium 138 mmo/L, potassium 4.1 mmol/L, carbon dioxide 16.9 mmol/L, glucose 215 mg/dL, calcium 1.85 mmol/L, albumin 2.4 g/dL, and alanine aminotransferase 5 IU/L. The blood test for malaria parasite was negative. Samples were obtained for blood and sputum culture. The subject was started on ceftriaxone 2 grams once daily, levofloxacin 500 mg once daily, hydrocortisone 100 milligrams thrice daily, and dexamethasone 8 mg. One unit of blood was transfused.

On 13 Apr 2014, the subject's condition worsened. Oxygen saturation went down to 36% despite oxygen therapy. Her respiratory rate was 64 breaths per minute and pulse rate was 144 beats per minute. The medications prescribed earlier were continued without change.

On 14 Apr 2014, at 0200 hours, the subject complained of feeling very hot. However, her body temperature was 36.4 degrees Celsius. At 0515 hours, the subject had gasping respirations with a respiratory rate of 162 breaths per minute. Her blood pressure was 87/52 mm Hg, temperature 33.9 degrees Celsius and oxygen saturation 46% on oxygen therapy. The subject was later pronounced dead.

The site Principal Investigator has assessed the event of death due to probable severe bacterial pneumonia as not related to the study agents efavirenz/emtricitabine/tenofovir disoproxil fumarate, bleomycin and vincristine.

Past Medical History: HIV infection, Kaposi's sarcoma, oral thrush, suspected bacterial pneumonia, and pulmonary TB three weeks prior enrollment.

Obstetric and Gynecological History: No significant hx.

Social History: No history of smoking and alcohol or recreational drug use.