**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

# Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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|---|---|
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| **Product Name:** | Sustiva® (efavirenz) |
| **Pediatric Labeling Approval Date:** | 02-May-2013 |
| **Application Type/Number:** | NDA 020972 (capsule), NDA 021360 (tablet) |
| **Applicant/Sponsor:** | Bristol Myers Squibb |
| **OSE RCM #:** | 2016-352 |

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## EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for efavirenz in pediatric patients.

Efavirenz (Sustiva®) was first approved in 1998 and is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients at least 3 months old and weighing at least 3.5 kg. Efavirenz is an HIV-1 specific, non-nucleoside reverse transcriptase inhibitor (NNRTI). Other efavirenz-containing products include Atripla®, a fixed dose combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate, approved in 2006.

In order to capture pediatric use of efavirenz and to provide context for the adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS) database for efavirenz, drug utilization patterns were assessed. From March 2013 through February 2016, a nationally estimated number of 25,079 patients received a dispensed prescription for Sustiva from U.S. outpatient retail pharmacies, of which the pediatric population aged 0-16 years accounted for 1.3% (328 patients). An estimated 145,501 patients received a dispensed prescription for Atripla, of which the pediatric population aged 0-16 years accounted for less than 1% (405 patients). Although there appears to be some off-label use of Atripla in pediatric patients younger than one year old, the use was very low and may be due to error. Furthermore, this use cannot be validated due to the lack of access to patient medical records.

Twenty-seven adverse event cases, including nine deaths, in pediatric patients received from 02-May-2013 (date of pediatric labeling) to 29-Feb-2016 were evaluated. Only three of the 27 cases were domestic, and this small number is consistent with low domestic use.

Of the 27 reports reviewed, there were no new major safety signals, no increased severity or frequency of any labeled adverse events, and no deaths solely attributed to efavirenz. All deaths appear to be related to the efficacy of combination antiretroviral therapy (cART), or disease progression despite cART. One case of catatonia, an unlabeled event, appears causally related to efavirenz. Causality to efavirenz is suggested by a temporal relationship to a dose increase of efavirenz, rapid abatement of symptoms following efavirenz discontinuation, and pharmacologic properties of efavirenz. Efavirenz treatment can result in a number of psychiatric and other nervous system adverse reactions. Catatonia is a distinctive syndrome requiring specific treatment with intravenous benzodiazepines and is potentially lethal if not properly treated in a timely manner. The already existing description of psychiatric and nervous system adverse events in the efavirenz label does not adequately describe catatonia.

DPV II recommends adding catatonia to the label in the existing description of psychiatric and nervous system adverse events under **Warnings and Precautions.**

# 1 INTRODUCTION

## 1.1 PEDIATRIC REGULATORY HISTORY

This review was prompted by pediatric labeling on 02-May-2013 that expanded the indication to patients at least 3 months old and weighing at least 3.5 kg.

- Formulations:

Efavirenz is administered orally and is supplied as 50mg and 200mg capsules, and as 600mg film-coated tablets.

For pediatric patients at least 3 months old and weighing at least 3.5 kg who cannot swallow capsules or tablets, the capsule contents may be administered with a small amount (1 to 2 teaspoons) of food.

- Approved Indications for Use:

Efavirenz in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and in pediatric patients at least 3 months old and weighing at least 3.5 kg.

- Pivotal Clinical Trials in Pediatric Patients:

The safety, pharmacokinetic profile, and virologic and immunologic responses of efavirenz were evaluated in antiretroviral-naive and -experienced HIV-1 infected pediatric patients 3 months to 21 years of age in three open-label clinical trials (see below).

Use of efavirenz in patients younger than 3 months of age or less than 3.5 kg body weight is not recommended because the safety, pharmacokinetics, and antiviral activity of efavirenz have not been evaluated in this age group and there is a risk of developing HIV resistance if efavirenz is underdosed.

> Study AI266-922 - an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz in combination with didanosine and antiretroviral-naive and -experienced pediatric patients. Thirty-seven patients 3 months to 6 years of age (median 0.7 years) were treated with efavirenz. The median time on study therapy was 60 weeks; 27% of patients discontinued before Week 48.
>
> Study PACTG 1021 - an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz in combination with didanosine and emtricitabine in pediatric patients who were antiretroviral therapy naive. Forty-three patients 3 months to 21 years of age (median 9.6 years) were dosed with efavirenz. The median time on study therapy was 181 weeks; 16% of patients discontinued before Week 48.

Study PACTG 382 -an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz in combination with nelfinavir and a nucleoside reverse transcriptase inhibitor (NRTI) in antiretroviral-naive and NRTI-experienced pediatric patients. One hundred two patients 3 months to 16 years of age (median 5.7 years) were treated with efavirenz. Eighty-seven percent of patients had received prior antiretroviral therapy. The median time on study therapy was 118 weeks; 25% of patients discontinued before Week 48.

Assessment of adverse reactions was based on the above three clinical trials in 182 HIV-1 infected pediatric patients (3 months to 21 years of age) who received efavirenz in combination with other antiretroviral agents for a median of 123 weeks. The adverse reactions observed in the three trials were similar to those observed in clinical trials in adults except that rash was more common in pediatric patients (32% for all grades regardless of causality) and more often of higher grade (i.e., more severe). Two (1.1%) pediatric patients experienced Grade 3 rash (confluent rash with fever, generalized rash), and four (2.2%) pediatric patients had Grade 4 rash (all erythema multiforme). Five pediatric patients (2.7%) discontinued from the study because of rash.

### 1.2 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS

No recent DPV reviews have been completed that included pediatric cases and are currently pending regulatory action.

### 1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

The United States Package Insert (USPI) [1] includes the following information under **Highlights**:

**----------CONTRAINDICATIONS----------**

- Efavirenz is contraindicated in patients with previously demonstrated hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.

**----------WARNINGS AND PRECAUTIONS----------**

- Do not use as a single agent or add on as a sole agent to a failing regimen. Consider potential for cross-resistance when choosing other agents.
- Not recommended with ATRIPLA, which contains efavirenz, emtricitabine, and tenofovir disoproxil fumarate, unless needed for dose adjustment when coadministered with rifampin.

- Serious psychiatric symptoms: Immediate medical evaluation is recommended for serious psychiatric symptoms such as severe depression or suicidal ideation.
- Nervous system symptoms (NSS): NSS are frequent and usually begin 1-2 days after initiating therapy and resolve in 2-4 weeks. Dosing at bedtime may improve tolerability. NSS are not predictive of onset of psychiatric symptoms.
- Embryo-Fetal Toxicity: Avoid administration in the first trimester of pregnancy as fetal harm may occur.
- Hepatotoxicity: Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B or C coinfection, marked transaminase elevations, or who are taking medications associated with liver toxicity. Among reported cases of hepatic failure, a few occurred in patients with no pre-existing hepatic disease.
- Rash: Rash usually begins within 1-2 weeks after initiating therapy and resolves within 4 weeks. Discontinue if severe rash develops.
- Convulsions: Use caution in patients with a history of seizures.
- Lipids: Total cholesterol and triglyceride elevations. Monitor before therapy and periodically thereafter.
- Immune reconstitution syndrome: May necessitate further evaluation and treatment.
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy.

----------**ADVERSE REACTIONS**----------

- Most common adverse reactions (>5%, moderate-severe) are impaired concentration, abnormal dreams, rash, dizziness, nausea, headache, fatigue, insomnia, and vomiting.

----------**DRUG INTERACTIONS**----------

- Coadministration of efavirenz can alter the concentrations of other drugs and other drugs may alter the concentrations of efavirenz. The potential for drug-drug interactions should be considered before and during therapy.

----------**USE IN SPECIFIC POPULATIONS**----------

- Lactation: Breastfeeding not recommended.
- Females and Males of Reproductive Potential: Pregnancy testing and contraception are recommended.
- Hepatic impairment: SUSTIVA is not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment.
- Pediatric patients: The incidence of rash was higher than in adults.

# 2 DRUG UTILIZATION DATA

## 2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to the FDA to conduct this analysis. ***Appendix A*** includes detailed descriptions of the databases.

### *2.1.1 Determining Settings of Care*

The IMS Health, IMS National Sales Perspectives™ database was used to determine the various settings of care where efavirenz (Sustiva®) and efavirenz in combination with emtricitabine and tenofovir (Atripla®) are distributed by the manufacturers. Sales data from March 2013 through February 2016 showed that approximately 52% of efavirenz bottles (as Sustiva OR Atripla) were sold to U.S. outpatient retail pharmacies, followed by 25% to mail order/specialty pharmacy settings, and 23% to non-retail settings.[2] As a result, outpatient retail pharmacy utilization patterns were examined. Based on these results, we examined the drug utilization data for only the U.S. outpatient retail settings.

### *2.1.2 Data Sources Used*

The IMS Health, Total Patient Tracker™ database was used to obtain the nationally estimated number of unique patients who received dispensed prescriptions for Sustiva or Atripla from U.S. outpatient retail pharmacies, stratified by patient age groups (0-11 months, 1-16, and 17 years and older) from March 1, 2013 through February 29, 2016, aggregated.

### 2.2 DRUG UTILIZATION DATA RESULTS

**Table 2.2. Nationally estimated number of unique patients with dispensed prescriptions for Sustiva® (efavirenz) or Atripla® (efavirenz/emtricitabine/tenofovir), stratified by patient age*, from U.S. outpatient retail pharmacies, March 2013 - February 2016, aggregated.**

| | March 1, 2013 - February 29, 2016 | |
|---|---|---|
| | Patient Count† N | *Share* % |
| **Atripla® Total Patients** | **145,501** | ***100%*** |
| 0-16 years | 405 | *<1%* |
| 0-11 months | 17‡ | *4%* |
| 1-16 years | 390 | *96%* |
| 17+ years | 145,079 | *99.7%* |
| Unknown age | 864 | *<1%* |
| **Sustiva® Total Patients** | **25,079** | ***100%*** |
| 0-16 years | 328 | *1.3%* |
| 0-11 months | 0 | *0%* |
| 1-16 years | 328 | *100%* |
| 17+ years | 24,733 | *98.6%* |
| Unknown age | 217 | *0.9%* |

Source: IMS Health, Total Patient Tracker. Mar 2013 – Feb 2016. Extracted Apr 2016. File TPT 2016-352 efavirenz Sustiva Atripla by age Mar2013-Feb2016.xlsx.

* Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months old).

† Unique patient counts may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in the individual categories.

‡ Although there appears to be some off-label use of Atripla in pediatric patients younger than one year old, the patient count is very low and may be due to error. This use cannot be validated due to the lack of access to patient medical records.

## 3 POSTMARKET ADVERSE EVENT REPORTS

### 3.1 METHODS AND MATERIALS

#### 3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See ***Appendix B*** for a description of the FAERS database.

| ***Table 3.1.1 FAERS Search Strategy*** | |
|---|---|
| Date of Search | 29-Feb-2016 |
| Time Period of Search | 02-May-2013* - 29-Feb-2016 |
| Search Type | Quick Query and<br>Product-Manufacturer Reporting Summary |

| | |
|---|---|
| Product Name(s) | (search included all efavirenz-containing products)<br>Sustiva, Atripla, Atripla Access, Efavirenz |
| Search Parameters | All ages, all outcomes, worldwide |

*[*] Approval date of pediatric labeling*

## 3.2 RESULTS

### 3.2.1 Total number of FAERS reports by Age

Table 3.2.1 below includes the number of adult and pediatric FAERS reports received since the date of pediatric labeling. These numbers include duplicate reports and transplacental exposures and have not been assessed for causality.

***Table 3.2.1 Total Adult and Pediatric FAERS reports* 02-May-2013 to 29-Feb-2016 with Efavirenz***

| | All reports (US) | Serious[†] (US) | Death (US) |
|---|---|---|---|
| **Adults (≥ 17 years)** | 1881 (813) | 1508 (462) | 215 (36) |
| **Pediatrics (0 - <17 years)** | 145 (35) | **143[‡] (34)** | 26[§] (7) |

** May include duplicates and transplacental exposures, and have not been assessed for causality*

*† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.*

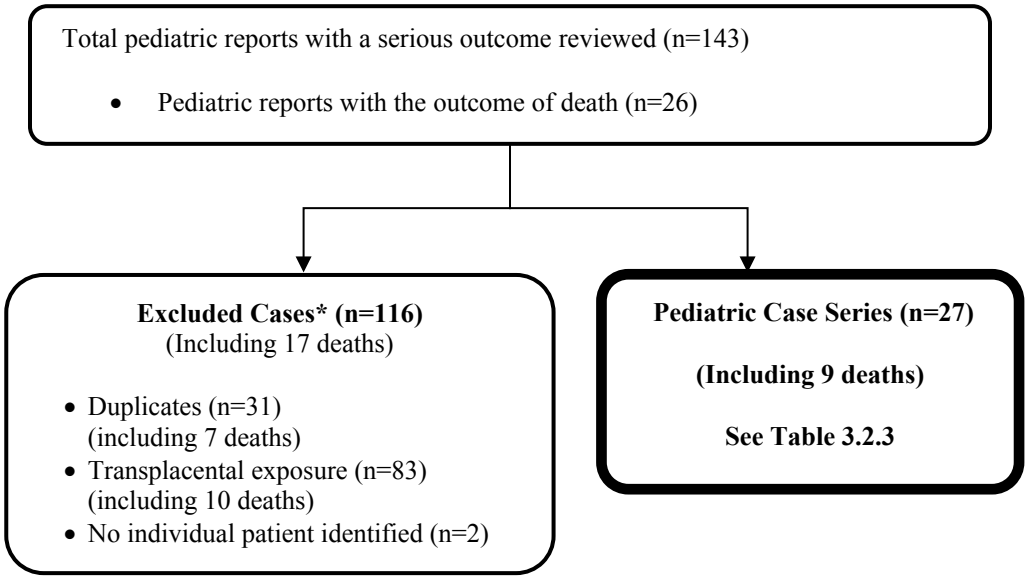
*[‡] See Figure 3.2.2*

*[§] Two additional reports of pediatric deaths were identified among reports not reporting an age.*

### 3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 143 pediatric reports with a serious outcome (See Table 3.2.1). After excluding transplacental exposure cases and two cases that did not identify an individual patient, and combining duplicate reports, 27 cases of direct exposure remained. See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

***Figure 3.2.2 Selection of Serious Pediatric Cases with Efavirenz***




* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

### 3.2.3 Characteristics of Pediatric Case Series

***Appendix C*** lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

***Table 3.2.3 Characteristics of Pediatric Case Series with Efavirenz (27=number in case series)***

| | | |
|---|---|---|
| Age (n=27) | 0 - < 1 month | 0 |
| | 1 month - <2 years | 1 |
| | 2- < 6 years | 2 |
| | 6- <12 years | 10 |
| | 12- < 17 years | 14 |
| Sex | Male | 10 |
| | Female | 16 |
| | Unknown | 1 |
| Country | United States | 3 |
| | Foreign | 24 |
| Reported Reason for Use | HIV infection | 25 |
| | Unknown | 2 |
| Serious Outcome* | Death | 9 |
| | Life-threatening | 1 |
| | Hospitalized | 8 |
| | Disability | 0 |

| | | |
|---|---|---|
| | Congenital anomaly | 0 |
| | Required Intervention | 0 |
| | Other serious | 9 |

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

### 3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=9)

A total of nine cases reported death as an outcome. No deaths were solely attributed to efavirenz, but could have been related to the efficacy of the combination antiretroviral therapy (cART), or disease progression despite cART.

Three deaths occurred in the setting of immune reconstitution inflammatory syndrome (IRIS), which is labeled for all antiretrovirals under **Warnings and Precautions**. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jiroveci pneumonia, or tuberculosis), which may necessitate further evaluation and treatment. IRIS that involves worsening of some malignancies, such as Kaposi's sarcoma, may also occur.

Six deaths occurred due to underlying HIV infection/immunosuppression (antiretroviral drug resistance-1, HIV-related opportunistic infection-3, unspecified infection-2).

All nine fatal pediatric adverse event cases are summarized in ***Appendix D***.

### 3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=18)

In addition to the nine fatal pediatric adverse event cases, we evaluated eighteen non-fatal pediatric serious adverse event cases. Of these 18 cases, 3 reported unlabeled adverse events, 11 reported labeled adverse events (such as rash), and 4 reported events due to underlying HIV infection/immunosuppression.

**Unlabeled Events (n=3):**
No new major safety signals were identified. Three unlabeled adverse events were evaluated.

**Catatonia (n=1)**
One case of catatonia, an unlabeled event, was reported in a 16-year-old male. A causal contribution by efavirenz is suggested by a temporal relationship to an efavirenz dose increase

with abatement of symptoms following efavirenz discontinuation. The case is summarized below:

Literature case report: Lingeswaran A. Antiretroviral treatment induced catatonia in 16-year-old boy. J Pediatri Neurosci 2014; 9:283-285.

A 16-year-old male with a history of HIV infection, birth asphyxia with no developmental delay, pulmonary tuberculosis (diagnosed at age 14 years), and no past psychiatric history, began treatment with zidovudine, abacavir, and efavirenz. Two years later the daily dosage of zidovudine, abacavir, and efavirenz were increased. Dosing was reported to be zidovudine 250mg 2 times a day, abacavir 300mg one in the morning and two at night and 300mg efavirenz at night, but it is not clear if this was before or after the recent dose increase. His weight was not reported and dosing was reported to be in the therapeutic range. Two months later the patient presented with mutism, grimacing, excitement, echopraxia, and withdrawal symptoms in addition to poor sleep and was hospitalized. Zidovudine, abacavir, and efavirenz were stopped and the patient was treated with risperidone 1mg twice daily. Within five days, all catatonic symptoms resolved. He was restarted on antiretroviral therapy at a reduced dosage with no evidence of any psychiatric symptomatology at six weeks (FAERS case #10783942-2, duplicate 11457592-1, duplicate11415550-1, duplicate 11403790-1, India).

**Adult cases of catatonia (n=3)**

To provide context for this adverse event a FAERS search was conducted on 11-Jul-2016 using the MedDRA Preferred Term *catatonia*. Three other cases since approval in females aged 29 to 47 years were identified. Two of the three reported elevated efavirenz levels and one of these reported the events abated after efavirenz was stopped and reappeared when efavirenz was restarted (positive rechallenge). The cases are described below:

Literature case report: Sabato S, Wesselingh S, Fuller A, Ray J, Mijch, A. Efavirenz-induced catatonia. AIDS 2002;16:1841-2.

A 47-year-old female with a history of HIV infection since 1988 secondary to injection drug use, hepatitis C, benzodiazepine dependence, depression, chronic low-grade suicidal ideation, passive aggressive personality disorder, and multiple benzodiazepine overdoses, began treatment with efavirenz (200mg in the morning and 400mg at night), lamivudine and stavudine. Her weight was not reported. Since beginning efavirenz, she required frequent hospitalizations due to inability to cope and neuropsychiatric symptoms, which culminated in an admission for catatonia, psychosis, and extreme psychomotor retardation three years after beginning efavirenz. At presentation, her CD4 cell count was 550 cells/ul and her HIV plasma viral load was 1400 copies/ml. Concomitant medications included moclobemide, domperidone, and oxazepam. Serum and radiological investigations failed to demonstrate an etiology, except for a plasma efavirenz concentration of 25375 ug/ml. There was no evidence of HIV encephalopathy. Cerebrospinal fluid efavirenz concentration was 134 ug/ml. Efavirenz was withheld, and antipsychotic medication was administered. The patient's condition varied from extreme paranoid psychosis to manic acute brain syndrome. She was able to obey simple commands but was slow to comply cognitively and physically. After 3 weeks she recovered, was alert, orientated, and appropriate. A retroactive assay of stored plasma showed an increasing plasma

efavirenz concentration over time, peaking 4 weeks before presentation, when she was already experiencing symptoms and signs of an acute brain syndrome (FAERS case #3850189-1, Australia).

A 33-year-old female with a history of HIV infection began treated with efavirenz (3 dosage forms daily). Her weight was not reported. Concomitant medications included lamivudine and zidovudine (duration not reported). Four days later, she presented with catatonia, speech defect, marked psychic and physical asthenia. Efavirenz was discontinued and she was admitted to prevent any suicide attempt. She recovered (FAERS case #4084470-1, France).

Literature case report: Ramirez-Duque N, Lopez-Cortes LF. Neuropsychiatric adverse effects associated with efavirenz. Enferm Infec Microbiol Clin 2006; 24:64-7.

A 29-year-old female (patient #3 of 3) with a history of HIV infection, stage C3 (CD4 cell count 182 cells/mL, HIV RNA 812,831 copies/mL), drug abuse, and disseminated tuberculosis began tuberculostatic treatment with rifampicin 600mg daily, isoniazid 300mg daily, and pyrazinamide 1.5g daily. Her weight was 41kg. Concomitant medications included trimethoprim+sulfamethoxazole. Approximately one month later, she began daily therapy with efavirenz 800mg, zidovudine 30mg, and lamivudine 300mg. One month after starting treatment, her trough concentration of efavirenz was 1.5mg/mL. Two months after starting treatment, she was hospitalized with catatonia, bradypsychic status, and confusion, accompanied by vomiting with no other symptoms. One week prior to admission, the patient had started oral metoclopramide 10mg every 8 hours. Antiretroviral medication and metoclopramide were stopped. A brain MRI showed no pathological findings. Her CD4 cell count was 374 cells/mL and HIV viral load was < 50 copies/mL. The symptoms resolved after a few days and were attributed to metoclopramide. One month later, the same antiretroviral regimen was reinitiated. Two months later, the patient presented in the clinic with dysarthria, bradypsychic status, inability to tandem walk, dysmetria. Plasma concentration of efavirenz was >100mg/mL 3 hours after dosing and 24 mg/mL after 24 hours. The onset of the neurological symptoms coincided with the discontinuation of tuberculosis treatment. Antiviral treatment was discontinued and symptoms disappeared in a few days (FAERS case 5981977-1, Spain).

**Hypersensitivity: rash with liver involvement (n=1)**

Rash and hepatotoxicity are labeled for efavirenz as separate adverse events under **Warnings and Precautions**. Hypersensitivity, which generally involves skin reactions in conjunction with systemic symptoms or organ dysfunction, is not labeled. One case of hypersensitivity, with both rash and liver involvement, was reported in a 9-year-old female with HIV infection 15 days after beginning raltegravir, abacavir, lamivudine, and efavirenz. All antiretrovirals and trimethoprim+sulfamethoxazole were discontinued and the adverse events improved. Causality to efavirenz is unlikely as efavirenz and lamivudine were restarted and the patient was discharged. Raltegravir, abacavir and trimethoprim+sulfamethoxazole, which are labeled for serious hypersensitivity reactions, were not restarted (FAERS case #10861281-2, duplicate 10873994-1).

**Fanconi syndrome acquired (n=1)**
One case of Fanconi syndrome (renal proximal tubulopathy with phosphate wasting) was reported in an 8-year-old female with HIV infection approximately 17 months after beginning efavirenz, lamivudine, and tenofovir disoproxil fumarate therapy. The events were not due to efavirenz. Fanconi syndrome is a known side effect of tenofovir disoproxil fumarate and is included in the tenofovir disoproxil fumarate label under Warnings and Precautions. Tenofovir disoproxil fumarate was discontinued and replaced by abacavir. Two months later renal function had improved (FAERS case #9605094-2).

**Labeled Events (n=11):**
No known/labeled risks were reported in unusual numbers in pediatric patients. The 11 cases reporting labeled adverse events are summarized in ***Appendix E***.

**Non-fatal disease-related events (n=4):**
Four non-fatal cases, in addition to the six fatal cases summarized in Appendix D, reported events that were not directly due to efavirenz but were due to underlying HIV infection/immunosuppression. The non-fatal disease-related events are summarized in ***Appendix E***.

## 4 DISCUSSION

Analysis of drug utilization data showed that pediatric patients aged 0-16 years old accounted for 1.3% of total patients who received a dispensed prescription for Sustiva and less than 1% of patients who received Atripla from U.S. outpatient retail pharmacies from March 2013 through February 2016. For both medications, the vast majority of use in pediatric patients was among children 1-16 years old. However, there was a small fraction of use among infants younger than one year old. Although there appears to be some off-label use of Atripla in these young patients, this use cannot be validated due to the lack of access to patient medical records. Of note, we focused our analyses on the outpatient retail pharmacy setting only where the largest proportion of efavirenz-containing product sales was distributed. However, because HIV medications may be dispensed from HIV clinics and other settings not captured in this analysis, it is important to note that these estimates may not be representative of all treatment for HIV in the U.S. and should be interpreted with caution.

Twenty-seven adverse event cases, including nine deaths, in pediatric patients received from 02-May-2013 (date of pediatric labeling) to 29-Feb-2016 were evaluated. Only three of the 27 cases were domestic, and this small number is consistent with low domestic use.

Of the 27 reports reviewed in pediatric patients, there were no new major safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with efavirenz. Twenty-six of the 27 reports reported adverse events that were either consistent with the labeling for efavirenz, were due to other co-suspect medication or were due to underlying HIV infection/immunosuppression.

Although no new major safety signals were identified, one pediatric case of catatonia, an unlabeled event, appears to be causally related to efavirenz. Causality to efavirenz is suggested by a temporal relationship to a dose increase of efavirenz, rapid abatement of symptoms following efavirenz discontinuation, and pharmacologic properties of efavirenz. Efavirenz treatment can result in a number of psychiatric and other nervous system adverse reactions. We do not believe catatonia is a unique adverse event in children. Three additional catatonia cases for all ages, with positive dechallenge and one with a positive rechallenge, were identified in the FAERS database since approval. Elevated efavirenz plasma levels, possibly due to decreased metabolism of efavirenz, were reported in two of these cases (25,735 ug/mL, and >100mg/mL, respectively), and may have contributed to the adverse events.

Catatonia is defined by the presence of three or more of 12 psychomotor features that may involve decreased motor activity (such as stupor), decreased engagement during interview or physical examination (such as mutism), or excessive and peculiar motor activity (such as agitation, echopraxia). Catatonia symptoms may be present in psychiatric conditions (such as depression, bipolar disorder, schizophrenia, or other psychotic disorders) or with medical conditions including drug-induced and toxic states. In some cases a patient may wax and wane between decreased and excessive motor activity. The seemingly opposing and variable manifestations contribute to a decreased recognition of catatonia. [3] If properly diagnosed, patients can respond immediately to intravenous benzodiazepines.

A causal relationship between efavirenz and catatonia is biologically plausible. Efavirenz is extensively labeled for serious psychiatric and nervous system symptoms under **Warnings and Precautions**. Psychiatric symptoms reported in patients receiving efavirenz in controlled trials include severe depression, suicide ideation and attempts, aggressive behavior, paranoid reactions, and manic reactions. Delusions and psychosis-like behavior have also been reported. Fifty-three percent of patients receiving efavirenz in controlled trials reported CNS symptoms including dizziness, insomnia, impaired concentration, somnolence, abnormal dreams, and hallucinations. Stupor, which is a feature of catatonia involving decreased motor activity, was reported to occur in clinical trials in efavirenz-treated patients under **Adverse Reactions – Clinical Trials Experience**.

Catatonia requires specific treatment with intravenous benzodiazepines and is a medical emergency, and potentially lethal if not properly treated in a timely manner. Catatonia is a

distinctive syndrome that is often misinterpreted as another medical condition. Although psychiatric and nervous system adverse events are extensively labeled for efavirenz under **Warnings and Precautions**, terms such as "psychosis-like behavior", "manic reactions", and "severe depression" do not adequately describe catatonia.

## 5 CONCLUSION

Of the 27 reports reviewed in pediatric patients, there were no new major safety signals, no increased severity or frequency of any labeled adverse events, and no deaths solely attributed to efavirenz.

One pediatric case of catatonia, an unlabeled event, appears causally related to efavirenz. Causality to efavirenz is suggested by a temporal relationship to a dose increase of efavirenz, rapid abatement of symptoms following efavirenz discontinuation, and pharmacologic properties of efavirenz. The existing description of psychiatric and nervous system adverse events in the efavirenz label does not adequately describe catatonia.

## 6 RECOMMENDATIONS

DPV II recommends adding catatonia to the label in the existing description of psychiatric and nervous system adverse events under **Warnings and Precautions.**

## 7 REFERENCES


1. Sustiva [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; revised March 2016.
2. IMS Health, IMS National Sales Perspectives™. Mar 2013 – Feb 2016. Extracted Mar 2016. File: NSP 2016-352 Sustiva Atripla eaches by channel Mar2013-Feb2016.xlsx.
3. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.
4. Shapiro, AM. Clinical Review. NDA supplement 20-972 S43 /21-360 S31; DARRTS 08-Apr-2013.

# 8 APPENDICES

## 8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

**IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Findings from the drug utilization analysis should be interpreted in the context of the known limitations of the databases used. Based on sales data from March 2013 through February 2016, efavirenz was primarily distributed to U.S. outpatient retail pharmacies. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

**IMS, Total Patient Tracker (TPT)**

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

## 8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

**FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

## 8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH EFAVIRENZ (N=27)

| FAERS case-version numbers and manufacturer control numbers included in pediatric case series (n=27) | | |
|---|---|---|
| **Ref #** | **FAERS case-version #** | **Mfr#** |
| 1 | 9722638-1 | B0898397A |
| 2 | 9368913-2<br>duplicate 9349255-1 | AUR-APL-2013-05030<br>duplicate IN-BRISTOL-MYERS SQUIBB COMPANY-18979351 |
| 3 | 9351941-1 | ZA-VIIV HEALTHCARE LIMITED-B0899930A |
| 4 | 9605094-2 | IT-GILEAD-2013-0084756 |
| 5 | 9723402-1<br>duplicate 11170562-1<br>duplicate 11153105-1<br>duplicate 10651845-1<br>duplicate 10624899-2<br>duplicate 9731730-1 | US-BRISTOL-MYERS SQUIBB COMPANY-19867423<br>duplicate GB2015GSK073606<br>duplicate GB-GLAXOSMITHKLINE-GB2015GSK073606<br>duplicate 2014HINLIT1043<br>duplicate GB-AUROBINDO-AUR-APL-2014-12710<br>duplicate US-BRISTOL-MYERS SQUIBB COMPANY-19864081 |
| 6 | 9892310-3<br>duplicate 10207459-3 | US-009507513-1402USA004802<br>duplicate US-BRISTOL-MYERS SQUIBB COMPANY-20225124 |
| 7 | 10073787-2 | ZA-ABBVIE-13A-143-1070047-00 |
| 8 | 10150329-1 | DE-BRISTOL-MYERS SQUIBB COMPANY-20674081 |
| 9 | 10210570-1 | 2014HINLIT0455 |
| 10 | 10273158-1<br>duplicate10862522-1<br>duplicate10803696-1<br>duplicate10287058-1 | 2014AP003487<br>duplicateUS2015GSK018734<br>duplicateUS-GLAXOSMITHKLINE-US2015GSK018734<br>duplicate2014AP003487 |
| 11 | 10305812-1 | MW-GILEAD-2014-0108679 |
| 12 | 10546059-2 | US-BMSGILMSD-2014-0119794 |
| 13 | 10620286-1 | IE-BMSGILMSD-2014-0124924 |
| 14 | 10660054-2<br>duplicate10671033-1 | FR-GLAXOSMITHKLINE-FR2014GSK018422<br>duplicate FR2014GSK018422 |
| 15 | 10783942-2<br>duplicate11457592-1<br>duplicate11415550-1<br>duplicate11403790-1 | IN-AUROBINDO-AUR-APL-2015-01044<br>duplicate 2015HINLIT0706<br>duplicate IN-VIIV HEALTHCARE LIMITED-IN2015GSK121403<br>duplicate IN-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-055093 |
| 16 | 10849060-1<br>duplicate 10880695-1<br>duplicate 10853519-1 | IN-AUROBINDO-AUR-APL-2015-01366<br>duplicate 2015HINLIT0172<br>duplicate IN-RANBAXY-2015R1-93256 |
| 17 | 10853561-1<br>duplicate 10852881-2<br>duplicate10880691-1 | IN-RANBAXY-2015R1-93273<br>duplicate IN-AUROBINDO-AUR-APL-2015-01369<br>duplicate 2015HINLIT0175 |
| 18 | 10861281-1<br>duplicate 10873994-1 | US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-002624<br>duplicate ZA-009507513-1412ZAF004514 |
| 19 | 10891605-1<br>duplicate 10911991-1 | IN-GLAXOSMITHKLINE-IN2015GSK029621<br>duplicate IN2015GSK029621 |
| 20 | 10978477-2<br>duplicate 11055572-1 | KE-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-019001<br>duplicate US-009507513-1503GBR013971 |
| 21 | 11082121-1<br>duplicate 11092389-1 | GB-GLAXOSMITHKLINE-GB2015GSK059254<br>duplicate GB2015GSK059254 |
| 22 | 11082112-1<br>duplicate 11092387-1 | GB-GLAXOSMITHKLINE-GB2015GSK058611<br>duplicate GB2015GSK058611 |
| 23 | 11235228-3<br>duplicate11256110-2 | KZ-GLAXOSMITHKLINE-KZ2015GSK091882<br>duplicate KZ-VIIV HEALTHCARE LIMITED-KZ2015GSK091882 |

| FAERS case-version numbers and manufacturer control numbers included in pediatric case series (n=27) | | |
|---|---|---|
| **Ref #** | **FAERS case-version #** | **Mfr#** |
| | duplicate11247552-1 | duplicate KZ2015GSK091882 |
| 24 | 11593294-1 | US-CIPLA LTD.-2015US07723 |
| 25 | 11593397-1 | US-CIPLA LTD.-2015US07720 |
| 26 | 11688153-1 | ZA-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-075673 |
| 27 | 11688232-1 | ZA-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-074364 |

## 8.4 APPENDIX D. CASE SUMMARIES FOR FATAL PEDIATRIC ADVERSE EVENTS (N=9)

**Fatal immune reconstitution inflammatory syndrome (n=3):**

Literature case report: Gkentzi D, Tebruegge M, Tudor-Williams G, et al. Incidence, Spectrum and Outcome of Immune Reconstitution Syndrome in HIV-infected Children after Initiation of Antiretroviral Therapy. Pediatr Infect Dis J 2014; 33(9): 953-8.

A 14-year-old male with HIV infection and pulmonary mycobacterium-avium-intracellulare complex (MAI) enrolled in a study for HIV-1 infected, antiretroviral treatment naive children at a large center providing care for HIV-infected children in the United Kingdom. His baseline CD4 count was 5 cells/uL (1%) and HIV viral load was 59,128 copies/mL. Seven weeks after starting lamivudine, abacavir, efavirenz and zidovudine, the patient presented with pyrexia, abdominal pain and intermittent diarrhea. He had been diagnosed with pulmonary MAI infection 4 months earlier, treated with rifabutin, ciprofloxacin and azithromycin. Abdominal ultrasound revealed hepatomegaly and mesenteric lymphadenopathy. An abdominal lymph node biopsy showed granulomatous changes and acid-fast bacilli. MAI was subsequently grown in tissue cultures. Immunohistology revealed high numbers of CD4+ and CD8+ lymphocytes, consistent with immune reconstitution inflammatory syndrome (IRIS). Amikacin and ethambutol were added to the antimycobacterial regimen in conjunction with broad-spectrum antibiotics and prednisolone. The action taken with lamivudine, abacavir, and efavirenz was unknown. Zidovudine was discontinued. After initial improvement, the patient developed marked respiratory symptoms with pulmonary infiltrates and pleural effusions. Despite specific therapy, and later discontinuation of antiretrovirals, the patient died 2 months later (FAERS case #11082121-1, duplicate 11092389-1, Great Britain).

Literature case report: Gkentzi D, et al (see above reference)

An 8-year-old female with HIV infection and pulmonary tuberculosis enrolled in a study for HIV-1 infected, antiretroviral treatment naive children at a large center providing care for HIV-infected children in the United Kingdom. Her baseline CD4 count was 1 cell/uL (3%) and HIV viral load was 76,019 copies/mL. Seven weeks after starting lamivudine, abacavir, and efavirenz, the patient presented with respiratory symptoms and generalized lymphadenopathy. She was on quadruple therapy for pulmonary tuberculosis diagnosed 5 months earlier. She deteriorated rapidly and required ventilation. A chest radiograph showed diffuse pulmonary changes. A bronchoalveolar lavage revealed acid-fast bacilli without evidence of other coinfections. Abdominal ultrasound demonstrated hepatosplenomegaly and marked intraabdominal lymphadenopathy. Bone marrow and liver biopsies showed acid-fast bacilli. The subject was treated with rifampicin, isoniazid, pyrazinamide, ethambutol, ciprofloxacin and methylprednisolone. The action taken with lamivudine, abacavir, and efavirenz was unknown. Mycobacterium tuberculosis and Mycobacterium avium intracellulare (MAI), both resistant to rifampicin and isoniazid, were isolated in tissue cultures. Despite broad-spectrum antibiotic, antifungal, additional antimycobacterial agents and treatment with methylprednisolone, she died from multiorgan failure eight weeks after admission (FAERS case #11082112-1, duplicate 11092387-1, Great Britain).

Literature case report: Reddy-Holdcraft S, Mehta P, Agrawal A. Paclitaxel for relapsed or recurrent HIV-associated pediatric Kaposi's sarcoma. AIDS 2014; 28(5):800-2.

A 12-year-old male with HIV infection started tuberculosis therapy. Approximately 6 weeks later, he started antiretroviral therapy with stavudine, lamivudine and efavirenz. Two weeks later, he presented with lesions consistent with Kaposi's sarcoma, and pericardial effusion. Tuberculosis and Kaposi's sarcoma-associated immune reconstitution inflammatory syndrome (IRIS) were diagnostic considerations. Bleomycin, vincristine, and doxorubicin therapy was started for Kaposi's sarcoma. He developed peripheral neuropathy, likely due to combination of vincristine and stavudine. Stavudine was switched to abacavir. His Kaposi's sarcoma disease progressed and he was changed to paclitaxel for salvage. After the second paclitaxel cycle, he again showed signs of progression and passed away from respiratory symptoms (FAERS case #10210570-1, Botswana).

**Fatal disease-related events (n=6):**

**Antiretroviral drug resistance (n=1):**

Literature case report: Shah I, Parikh S. HIV Genotype Resistance Testing in Antiretroviral (ART) Exposed Indian Children – A need of the hour. Indian J Pediatr 2013; 80(4):340-2.

A 10-year-old male with HIV infection was treated since approximately 5 years of age with antiretroviral therapy that included zidovudine and nevirapine, followed by stavudine, lamivudine and efavirenz. At approximately 7 years of age, he was switched to didanosine, abacavir and lopinavir+ritonavir therapy. Approximately two years later, his HIV viral load was 1,800,000 copies per ml and CD4 cell count was 61 cells/mm3 (11.47%). He presented with wasting (weight 15kg), facial molluscum contagiousum and oral thrush. His antiretroviral therapy was changed to abacavir, lamivudine , and lopinavir+ritonavir. Six months later, his HIV viral load was 73,200 copies per ml and abdomen ultrasonography showed mesenteric lymph nodes with mesenteric thickening. He was started on four anti-tuberculous therapy drugs (rifabutin based) and antiretroviral therapy continued. Four months later, his HIV viral load was undetectable but CD4 cell count was 10 cells/mm3. Genotype resistance testing showed resistance to multiple antiretrovirals, including efavirenz. The patient subsequently succumbed to his illness (FAERS case #9368913-2, duplicate 9349255-1, India).

**HIV-related opportunistic infection (n=3):**

Three deaths were reported due to tuberculosis.

Study patient: Study CO-US-164-0423 entitled "REduction of Early MortALITY in HIV-infected Adults and Children Starting Antiretroviral Therapy: a Randomised Controlled Trial (REALITY)."

A 16-year-old female subject (race unspecified), with HIV infection, was hospitalized pending exploratory laparotomy for left adnexal/ ovarian mass that was seen on a pelvic scan that was

thought to possibly be lymphadenopathy or a tumor. Her baseline CD4 cell count was 4 cells/uL. A pregnancy test was negative. While hospitalized, study treatment with tenofovir disoproxil fumarate, emtricitabine, efavirenz and raltegravir was commenced. Eighteen days later the patient developed vomiting, shortness of breath and hypotension with a blood pressure of 84/39, heart rate of 116 and oxygen saturation of 95%. She had normocytic anemia and ascites. The patient scored a 14/15 on the coma scale and was noted as having a tender epigastrium and bilateral pleural effusion. The patient was diagnosed with disseminated tuberculosis and abdominal sepsis. The patient received treatment with unspecified tuberculosis medications, ceftriaxone, metronidazole, and fluids. Nineteen days after starting study treatment, the patient died due to presumptive disseminated tuberculosis and abdominal sepsis (FAERS case #10305812-1, Malawi).

Literature case report: Isaakidis P, Paryani R, Khan S, et al. Poor Outcomes in a Cohort of HIV-infected Adolescents Undergoing Treatment for Multidrug-Resistant Tuberculosis in Mumbai, India. PLOS One 2013;8 (7):e68869.

A 14-year-old male (patient 1 of 11) with HIV and pulmonary and extrapulmonary tuberculosis began treatment with stavudine, lamivudine and efavirenz. At the time of multidrug resistant tuberculosis diagnosis, his CD4 cell count was 243 cells/ul. Five months after beginning antiretroviral treatment, he began second line TB regimen of amoxicillin/clavulanic acid, capreomycin, levofloxacin, ethionamide, and cycloserine. The patient experienced convulsions 5 weeks later, gastrointestinal intolerance 9 weeks later, and peripheral neuropathy 56 weeks later. He defaulted after 17 months of treatment and then died 1 month after default due to convulsions and brain tuberculoma (FAERS case #10849060-1, duplicate 10880695-1, duplicate 10853519-1, India).

Literature case report: Isaakidis P, et al (see above reference)

A 16-year old female (patient 6 of 11) with HIV and pulmonary and extrapulmonary tuberculosis began treatment with stavudine, lamivudine, and efavirenz. At the time of multidrug resistant tuberculosis diagnosis, her CD4 cell count was 92 cells/ul. Six months after beginning antiretroviral treatment, she began second line TB regimen of amoxicillin/clavulanic acid, capreomycin, moxifloxacin, isoniazid, ethionamide, para-aminosalicylic acid, and pyrazinamide. The patient experienced gastrointestinal intolerance one week later and psychosis 2 weeks later. Sixteen days after starting second line TB the patient died due to brain tuberculoma (FAERS case #10853561-1, duplicate 10852881-2, duplicate 10880691-1, India).

**Unspecified infection – from pivotal clinical trial AI266-922 (n=2):**
Two deaths due to unspecified infections were reported from pivotal clinical trial AI266-922. The deaths were not considered directly due to efavirenz by investigators or the medical officer reviewer.

Study patient: Subject AI266922-5-20 in Group 3, narrative obtained from medical officer review. [4]

A 2-year-old white female died on Day 288 from heart failure due to complications from pneumonia. One week prior to her death, her viral load (HIV RNA) was < 50 copies/mL, her

CD4 cell count was 743 cells/mm3, and her CD4 percent was 23% (FAERS case #11593294-1, Foreign).

Study patient: Subject AI266922-27-51 in Group 1, narrative obtained from medical officer review. [4]

A 3-month-old black South African female died on Day 23 due to a bacterial infection. She had a history of bacterial sepsis and esophageal candidiasis prior to initiation of study therapy, and there was no evidence of immune reconstitution inflammatory syndrome. She died unexpectedly at home. Her parents did not seek medical attention and no treatment was reported (FAERS case #11593397-1, South Africa).

## 8.5 APPENDIX E. CASE SUMMARIES FOR NON-FATAL LABELED (N=11) AND DISEASE-RELATED PEDIATRIC SERIOUS ADVERSE EVENTS (N=4)

**Labeled Events (n=11):**

**Rash (n=2)**

Rash is labeled in the **Warnings and Precautions** section. Both reviewed cases were consistent with the labeling. In one case, a 16-year-old female with HIV infection developed a grade 3-4 rash an unspecified time after beginning efavirenz, emtricitabine, and tenofovir disoproxil fumarate therapy. No other information such as concomitant medications, action taken regarding antiretroviral medication, or outcome was reported (FAERS case #10546059-2). In the second case, a 9-year-old female with HIV infection, who was HLAB5701 negative, developed a maculopapular eruption and fatigue nine days after beginning abacavir, lamivudine, and efavirenz. No digestive or respiratory symptoms were reported. Abacavir, lamivudine, and efavirenz were discontinued and the rash resolved within 3 days (FAERS case #10660054-2, duplicate 10671033-1).

**Hepatotoxicity (n=1)**

Hepatotoxicity is labeled in the **Warnings and Precautions** section. One case reported a 9-year-old male with HIV infection experienced toxic hepatitis within 3 weeks of beginning abacavir, lamivudine, and efavirenz therapy and was switched to abacavir, lamivudine and lopinavir+ritonavir. Causality to efavirenz is unlikely, as the events did not abate after discontinuation of efavirenz (FAERS case #11235228-3, duplicate 11256110-2, duplicate 11247552-1).

**Suicidality (n=1)**

Psychiatric events, including depression and suicidality, are labeled in the **Warnings and Precautions** section. One case reported a 14-year-old (gender not reported) took an overdose of 36 Atripla (emtricitabine+tenofovir disoproxil fumarate + efavirenz) tablets. The case did not provide enough information for assessment (FAERS case #10620286-1)

**Peripheral neuropathy (n=1)**

Neuropathy is labeled under **Adverse Reactions-Postmarketing Experience**. One case of peripheral neuropathy (burning sensation on soles of feet) was reported in a 10-year-old female with a history of HIV infection, pulmonary tuberculosis, and chronic suppurative otitis media. The patient had been treated with 3 years of stavudine, lamivudine, and efavirenz therapy and 2 years of linezolid, terizidone, isoniazid, pyrazinamide, capreomycin, ofloxacin, amoxicillin/clavulanic acid, clarithromycin and aminosalicylic acid therapy. The peripheral neuropathy appears more likely due to stavudine, linezolid, or terizidone use as the events abated

following stavudine discontinuation and linezolid and terizidone dose reduction (FAERS case #10073787-2).

**Ataxia (n=2)**

Ataxia is labeled under **Adverse Reactions-Postmarketing Experience**. Two cases of ataxia were reported in patients with elevated efavirenz plasma levels. The elevated plasma levels were thought to be due to a polymorphism of the CYP2B6 metabolizing enzyme of the cytochrome P450 system. Efavirenz is a substrate of this enzyme. In one case, a 6-year old female with HIV infection presented with confusion, vomiting and difficulty walking within one year of beginning efavirenz, lamivudine and abacavir therapy (FAERS case #11688232-1). In the second case, a 13-year-old female with HIV infection presented with an acute onset of ataxic gait 18 months after beginning efavirenz, abacavir and lamivudine therapy (FAERS cases #11688153-1). Both patients recovered following efavirenz discontinuation.

**Non-fatal immune reconstitution inflammatory syndrome (n=3)**

Three non-fatal cases of immune reconstitution inflammatory syndrome (IRIS) , which is labeled for antiretrovirals under **Warnings and Precautions**, were reported. Three other cases that were fatal are summarized in Appendix D. In one non-fatal case, a 14-year-old male with HIV infection and disseminated tuberculosis developed IRIS-related acute kidney injury and systemic inflammation two weeks after beginning efavirenz, emtricitabine and tenofovir disoproxil fumarate therapy. He was treated with prednisone and switched to an unspecified regimen without tenofovir disoproxil fumarate, which is associated with nephrotoxicity, and recovered (FAERS case #10273158-1, duplicate 10862522-1, duplicate 10803696-1, duplicate 10287058-1). In the second non-fatal case, a 12-year-old female with a history of HIV infection and cerebellar abscess due to mycobacterium tuberculosis was treated with rifampicin, isoniazid, pyrazinamide and ethionamide. Two months later, she began first-line antiretroviral therapy with abacavir, lamivudine and efavirenz. She was admitted six months later with a CD4 count of 7 cells/mm3 due to treatment non-compliance. After a dramatic decrease in HIV viral load, she was discharged. She was readmitted the following month with a diagnosis of intramedullary conus tuberculosis. Tuberculosis treatment was recommenced with steroid therapy and she recovered (FAERS case #9351941-1). In the third non-fatal case, a 10–year-old female with HIV infection and recent history of chicken pox presented with right-sided hemiplegia four weeks after starting efavirenz, abacavir, and lamivudine therapy. She was diagnosed with cerebral infarction due to varicella zoster virus (VZV)-related central nervous system (CNS) IRIS and was treated with acyclovir followed by valaciclovir. Fifteen months later, some improvement of vascular abnormalities was noted and her neurology had improved (FAERS case #9723402-1, duplicate 11170562-1, duplicate 11153105-1, duplicate 10651845-1, duplicate 10624899-2, duplicate 9731730-1).

**Pancreatitis (n=1)**

Pancreatitis is labeled under **Adverse Reactions - Clinical Trials Experience**. The label states a causal relationship has not been established. In one case, a 16-year-old male with HIV

infection had been treated for 20 months with stavudine, lamivudine and efavirenz. He was hospitalized with antiretroviral-associated pancreatitis with treatment failure presenting as occult infection, prolonged fever, failure to thrive and persistent mucocutaneous candidiasis. Following a switch to efavirenz and lopinavir+ ritonavir therapy he presented with septic shock and splenic micro-abscesses and recovered after treatment with antibiotics, tuberculosis therapy, and a new antiretroviral regimen with raltegravir, darunavir, tenofovir disoproxil fumarate, emtricitabine and ritonavir. The events appear more likely due to concomitant stavudine, lamivudine, or lopinavir+ritonavir, which are labeled for pancreatitis under Warnings and Precautions (FAERS case #9722638-1).

**Non-fatal disease-related events (n=4):**

Four non-fatal cases, in addition to the fatal cases summarized in Appendix D, reported events that were not directly due to efavirenz but were due to underlying HIV infection/immunosuppression:

- Tuberculosis adenitis-related gastroenteritis and jaundice in a 12-year-old male with HIV infection and lymph node tuberculosis following one month of efavirenz and raltegravir therapy and two months of tuberculosis therapy. Antiretroviral and tuberculosis therapy were continued. The patient responded well to gastroenteritis treatment and was discharged (FAERS case #10978477-2, duplicate 11055572-1).

- Mycobacterium encephalopathy in a 10-year-old female with a history of HIV infection and mycobacterium infection following several years of efavirenz therapy. Efavirenz therapy was continued. The events were ongoing (FAERS case #10150329-1).

- Subacute sclerosing panencephalitits caused by altered measles virus in a 14-year-old male with history of HIV infection (WHO clinical stage IV) diagnosed at age 7 years. The events began an unknown amount of time after beginning lamivudine, zidovudine and efavirenz therapy. Antiretroviral therapy was continued. He was treated with antiepileptic medications and was stable seven months later without any worsening of symptoms (FAERS case #10891605-1).

- Drug resistance to indinavir in a 2-year-old female. The patient had possible resistance to multiple antiretrovirals including efavirenz. It was unclear if the patient had ever been treated with efavirenz therapy (FAERS case #9892310-3, duplicate 10207459-3).

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/s/

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PAULA L GISH
08/08/2016
Signing for Paula Gish and for Robert Levin, MD

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