Department of Health and Human Services
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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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Product Name:	Truvada® (emtricitabine and tenofovir disoproxil fumarate)
Pediatric Labeling Approval Date:	08-Jul-2011
Application Type/Number:	NDA 021752
Applicant/Sponsor:	Gilead Sciences, Inc.
OSE RCM #:	2015-1342

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

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

Between October 2011 and September 2016, pediatric patients 17 years and younger comprised approximately 1% of the total patients who received dispensed prescriptions for Truvada from U.S. outpatient retail pharmacies. The annual number of pediatric patients who received Truvada prescriptions from U.S. outpatient retail pharmacies increased 73% from 1,121 patients to 1,939 patients. Annually, the majority of pediatric patients were aged 12-17 years.

This review was prompted by pediatric labeling approved on 08-Jul-2011 which expanded the indication for the treatment of HIV-1 infection to pediatric patients 12 years of age and older. New pediatric labeling was approved on 10-Mar-2016 which expanded the indication from pediatric patients 12 years and older down to pediatric patients weighing at least 17 kg.

Eight adverse event cases in pediatric patients were received from 08-Jul-2011 to 29-Sep-2016, and this small number is consistent with low domestic use in pediatric patients compared to all ages. Low use may decrease the voluntary reporting of any adverse event. No significant use outside the approved indication was identified in these reports.

Of the eight pediatric adverse event cases, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and no deaths directly associated with Truvada. One death was reported due to immune reconstitution inflammatory syndrome (IRIS), which is labeled for all antiretrovirals under **Warnings and Precautions.**

There is no evidence from these data that there are new pediatric safety concerns with this drug at this time. We recommend routine pharmacovigilance monitoring.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Truvada was first approved in 2004 for the treatment of HIV-1 infection in adults in combination with other antiretroviral agents. Truvada is also approved for pre-exposure prophylaxis (PREP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

This review was prompted by pediatric labeling approved on 08-Jul-2011 which expanded the indication for the treatment of HIV-1 infection to pediatric patients 12 years of age and older.

Pediatric labeling was approved on 10-Mar-2016 which expanded the indication from pediatric patients 12 years and older down to pediatric patients weighing at least 17 kg.

Truvada is a combination of emtricitabine and tenofovir disoproxil fumarate, both nucleoside analog HIV-1 reverse transcriptase inhibitors. The individual components of Truvada have been previously presented to the Pediatric Advisory Committee (PAC):

- Emtricitabine (Emtriva®) was approved for use in adult HIV-infected patients in July 2003, and was approved for use in pediatric patients 3 months of age and older in September 2005. Emtricitabine was presented to the PAC in November 2007. The PAC recommended routine pharmacovigilance monitoring.

- Tenofovir disoproxil fumarate (Viread®) was approved for use in adult HIV-infected patients in October 2001. Tenofovir disoproxil was approved for use in HIV-infected pediatric patients 12-18 years of age in March 2010. Tenofovir disoproxil fumarate was presented to the PAC in May 2012, April 2014, and September 2014. The PAC recommended routine pharmacovigilance monitoring.

The goal of the pediatric labeling approved for Truvada on 08-Jul-2011 was to harmonize the Truvada label with recent approved changes to the emtricitabine and tenofovir disoproxil fumarate labels in pediatric patients 12 to 18 years of age.

- Formulations:

Truvada is administered orally and is supplied as tablets in four dose strengths: 200 mg/300 mg, 167 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg of emtricitabine and tenofovir disoproxil fumarate.

- Dosing:

The recommended dose in adults and pediatric patients weighing greater than or equal to 35 kg: One tablet (containing 200 mg/300 mg of emtricitabine and tenofovir disoproxil fumarate) once daily taken orally with or without food.

The recommended dose in pediatric patients weighing greater than or equal to 17 kg and able to swallow a whole tablet: one low strength tablet (100 mg/150 mg, 133 mg/200 mg, or 167 mg/250 mg based on body weight) once daily taken orally with or without food.

- Clinical Trials in Pediatric Patients

No pediatric clinical trial was conducted to evaluate the safety and efficacy of Truvada. Data from previously conducted trials with the individual drug products, emtricitabine and tenofovir disoproxil fumarate, were relied upon to support dosing recommendations for Truvada.

Adverse reactions from clinical trials in HIV-1 infected pediatric patients for the individual drug products, emtricitabine and tenofovir disoproxil fumarate are summarized below:

- Emtricitabine (Emtriva®): In addition to the adverse reactions reported in adults, anemia and hyperpigmentation were observed in 7% and 32%, respectively, of pediatric subjects (3 months to less than 18 years of age) who received treatment with emtricitabine in the larger of two open-label, uncontrolled pediatric trials (N=116).

- Tenofovir Disoproxil Fumarate (Viread®): In pediatric clinical trials (Studies 352 and 321) conducted in 184 HIV-1 infected subjects 2 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical trials of tenofovir disoproxil fumarate in adults.

  Eighty-nine pediatric subjects (2 to less than 12 years of age) received tenofovir disoproxil fumarate in Study 352 for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these 4 subjects presented with hypophosphatemia and also had decreases in total body or spine bone mineral density (BMD) Z score.

The Truvada USPI[1] includes the following information regarding bone effects of tenofovir disoproxil fumarate (DF) in pediatric and adolescent patients under **Warnings and Precautions**:

- Bone Effects of Tenofovir DF: Clinical trials evaluating tenofovir DF in pediatric and adolescent subjects were conducted. Under normal circumstances, bone mineral density (BMD) increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir DF treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected.

  The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial. If bone abnormalities are suspected then appropriate consultation should be obtained.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The Truvada USPI[1] includes the following information under **Highlights**:

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

- Do not use TRUVADA for pre-exposure prophylaxis in individuals with unknown or positive HIV-1 status. TRUVADA should be used in HIV-infected patients only in combination with other antiretroviral agents.

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

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with TRUVADA. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose and urine protein before initiating treatment with TRUVADA and periodically during treatment. Avoid administering Truvada with concurrent or recent use of nephrotoxic drugs.
- Coadministration with Other Products: Do not use with drugs containing emtricitabine, tenofovir alafenamide or tenofovir disoproxil fumarate including ATRIPLA, COMPLERA, EMTRIVA, GENVOYA, ODEFSEY, STRIBILD, VIREAD; or with drugs containing lamivudine. Do not administer in combination with HEPSERA.
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss.
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy.
- Immune reconstitution syndrome: May necessitate further evaluation and treatment.
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification.
- Comprehensive management to reduce the risk of acquiring HIV-1: Use as part of a comprehensive prevention strategy including other prevention measures; strictly adhere to dosing schedule.
- Management to reduce the risk of acquiring HIV-1 drug resistance:

  Prior to initiating TRUVADA for PrEP - if clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm negative HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection

  While using TRUVADA for PrEP - HIV-1 screening tests should be repeated at least every 3 months.

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

- In HIV-1 infected patients, the most common adverse reactions (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash.

  In HIV-1 uninfected individuals in PrEP trials, adverse reactions that were reported by more than 2% of TRUVADA subjects and more frequently than by placebo subjects were headache, abdominal pain and weight decreased.

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

- Didanosine: Tenofovir disoproxil fumarate increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted.

- HIV-1 protease inhibitors: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. When coadministered with TRUVADA, use atazanavir given with ritonavir. Coadministration of TRUVADA with atazanavir and ritonavir, darunavir and ritonavir, or lopinavir/ritonavir increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity.

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

- Nursing mothers: Women infected with HIV-1 should be instructed not to breast feed.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

This analysis was conducted using proprietary drug utilization databases available to FDA. See Appendix A for detailed descriptions of the databases used.

2.1.1 Data Sources Used

IMS Health, National Sales Perspectives™ database was used to determine the various retail and non-retail U.S. channels of distribution for Truvada for a five-year period (October 2010 through September 2016).

The IMS, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a prescription for Truvada from U.S. outpatient retail pharmacies, stratified by patient age groups (0-11, 12-17, and 18 years or older) from October 2011 through September 2016, annually.

2.2 RESULTS

2.2.1 Determining Settings of Care

Approximately 54% of U.S. sales of Truvada were distributed to retail pharmacies; 26% to mail order pharmacies; and 20% to non-retail settings.[a] Accordingly, only U.S. outpatient retail utilization patterns were examined. Mail order and non-retail pharmacy data were not included in this review.

[a] IMS Health, National Sales Perspective.™ October 2010 – September 2016. Extracted November 2016. File: NSP Truvada 2016-1342 11.2.2016.xlsx.

2.2.2 Number of Patients

Table 2.2.2. Nationally Estimated Number of Patients with Dispensed Prescriptions for Truvada®, Stratified by Patient Age*, from U.S. Outpatient Retail Pharmacies, October 2011 through September 2016, annually.

	Oct 2011-Sept2012		Oct 2012-Sept 2013		Oct 2013-Sept 2014		Oct 2014-Sept 2015		Oct 2015-Sept2016	
	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*
Total	**157,325**	***100%***	**159,590**	***100%***	**167,432**	***100%***	**191,188**	***100%***	**226,485**	***100%***
0-17 years old	1,121	*1%*	1,277	*1%*	1,411	*1%*	1,664	*1%*	1,939	*1%*
0-11 years old	131	*12%*	203	*16%*	115	*8%*	155	*9%*	131	*7%*
12-17 years old	995	*89%*	1,036	*81%*	1,304	*92%*	1,512	*91%*	1,820	*94%*
18+ years old	156,288	*99%*	158,396	*99%*	165,977	*99%*	188,722	*99%*	223,243	*99%*
Unspecified age	4	*<1%*	61	*<1%*	818	*<1%*	1,267	*1%*	2,106	*1%*

Source: IMS Health, Total Patient Tracker. October 2011 – September 2016. Extracted October 2016 and January 2017. File: TPT Truvada 2016-1342 11.2.2016 xlsx.

* Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-11 years include patients up to the day before their 12th birthday.

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

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	December 20, 2016
Time Period of Search	7/8/2011* to 9/29/16
Search Type	Quick Query Product-Manufacturer Reporting Summary
Product Name(s)	Truvada; emtricitabine\tenofovir; emtricitabine\tenofovir disoproxil; emtricitabine\tenofovir disoproxil fumarate
Search Parameters	All ages, all outcomes, worldwide

** approval date of Truvada in children ≥ 12 years of age*

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total Adult and pediatric FAERS reports* from 7/8/2011 to 9/29/2016 with Truvada

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	4020 (1312)	3601 (912)	290 (65)

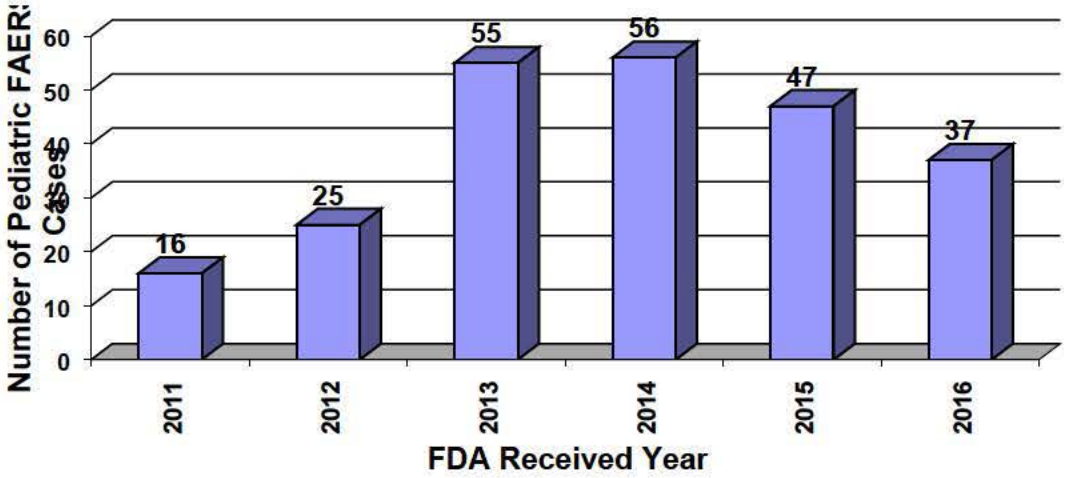
Table 3.2.1 Total Adult and pediatric FAERS reports from 7/8/2011 to 9/29/2016 with Truvada*			
Pediatrics (0 to <17 years)	240 (94)	236 (90) ‡	43 (22)

** 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

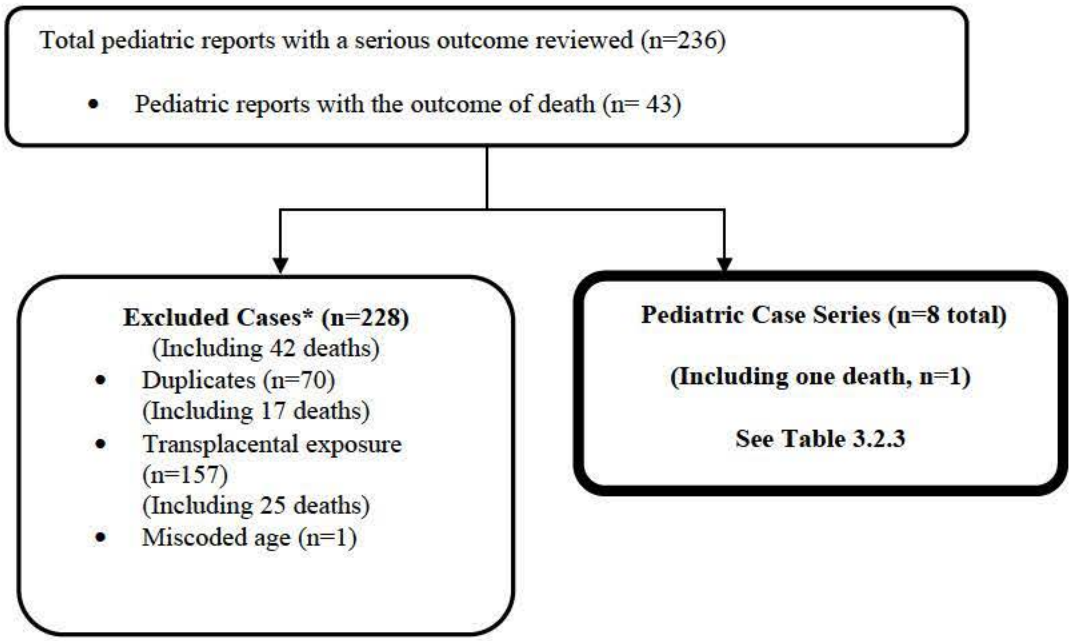
Figure 3.2.1 Serious Pediatric Reports for Truvada, by year of FDA receipt 7/8/2011 to 9/29/2016 (n=236)



3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 236 pediatric reports with a serious outcome (See Table 3.2.1). 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 Truvada



* 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 Truvada (N=8)

Age (n=8)	0 - < 1 month	0
	1 month - <2 years	0
	2- < 6 years	1
	6- <12 years	1
	12- < 17 years	6
Sex	Male	3
	Female	5
Country	United States	2
	Foreign	6

Table 3.2.3 Characteristics of Pediatric Case Series with Truvada (N=8)		
Reported Reason for Use	HIV infection	4
	Postexposure prophylaxis	1
	Accidental ingestion	1
	Unknown	2
Serious Outcomes*	Death	1
	Life-threatening	1
	Hospitalized	3
	Other serious	3

* 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=1)

One case reported death as an outcome. The death was not directly due to Truvada. The death was due to immune reconstitution inflammatory syndrome (IRIS)-associated progressive multifocal leukoencephalopathy (PML). PML is a demyelinating disease of the central nervous system that results from infection with the John Cunningham (JC) virus and occurs in people who are immunosuppressed. IRIS is an inflammatory response to indolent opportunistic infections such as the JC Virus. IRIS is labeled for all antiretrovirals medications under **Warnings and Precautions**. In cases of IRIS-associated PML the inflammation and increase in JC virus-mediated tissue destruction can be fatal. The case is summarized below:

Case reference #2, FAERS case #8646504, USA

Literature case report: Schwenk H, Ramirez-Avila L, Sheu SH, et al. Progressive multifocal leukoencephalopathy in pediatric patients: case report and literature review. Pediatr Infect Dis J 2014; 33: e99-e105.

A 15-year-old female patient, who was adopted, presented with 6-week history of fatigue, 12 kg weight loss, right hand and leg clumsiness, diplopia, dysarthria and gait instability. Although the patient's biological mother was HIV-positive, the patient's HIV status was unknown to her adoptive family. She was diagnosed with AIDS and progressive multifocal leukoencephalopathy (PML). Her CD4 count was 5 cells/mm3 and HIV viral load was 82,000 copies/mL. She began receiving combination antiretroviral therapy with nevirapine, raltegravir and emtricitabine+tenofovir disoproxil fumarate (routes, dosages and duration of treatment prior to reaction onset not stated). She soon developed worsening dysarthria, dysphagia, and aspiration of liquids. An MRI showed new and

increased bilateral medullary lesions suggestive of immune reconstitution inflammatory syndrome (IRIS). She was treated with methylprednisolone and prednisone, and was discharged following improvement of her neurologic status. One week later, she was readmitted with worsening dysarthria, urinary incontinence, inability to ambulate and new left hemiplegia. A repeat MRI demonstrated interval increase in T2-signal abnormalities of the cerebellum and brainstem, and she received further treatment with methylprednisolone. However, she experienced progressive weakness, generalised tonic-clonic seizures and inability to clear secretions. New diffuse supratentorial lesions were seen on MRI. Her condition deteriorated and she died 8 weeks after her initial presentation.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=7)

Seven non-fatal adverse event cases in pediatric patients were evaluated. DPV did not identify potential new risks, or known/labeled risks reported in unusual numbers in pediatric patients. Two cases reported unlabeled events, four reported labeled events and one reported an indication/disease related event.

No significant use outside the approved indication was identified. One case (headache, vertigo, diplopia, and abdominal pain) was in a 14-year-old patient treated for non-occupational post-exposure prophylaxis (nPEP) for sexual exposure. nPEP is not a labeled indication for any antiretroviral, however, the CDC publishes guidelines for nPEP antiretroviral regimens to prevent HIV infection. A 3-drug regimen containing Truvada (+ raltegravir or dolutegravir) is the preferred antiretroviral regimen for nPEP for adolescents and adults for sexual exposures. [2]

Another two cases were in pediatric patients less than 12 years old, which is less than the indicated age for the pediatric labeling approved on 08-Jul-2011. One case (vomiting) was an accidental ingestion of a mother's medication by her 2-year-old. The other case (drug ineffective) was in an 11-year-old patient weighing 56kg. Subsequent to the 08-Jul-2011 pediatric labeling, new pediatric labeling was approved on 10-Mar-2016 which expanded the indication from pediatric patients 12 year and older down to pediatric patients weighing at least 17 kg.

3.4.1 **Unlabeled Events: n=2**

Two cases reported unlabeled events. Causality to Truvada cannot be established due to concomitant medications which are associated with the events. Both cases are summarized below:

Unlabeled event -vertigo, diplopia (n=1): Headache, vertigo, diplopia, and abdominal pain in a 14-year-old female following 1 day of treatment with Truvada and Kaletra (lopinavir+ritonavir), for post-exposure HIV prophylaxis following a rape. The patient went to the emergency

department. Her neurological examination was normal. The clinical outcome was unknown. (Case reference #1, FAERS case # 8499989-1, France).

Reviewer comment: Headache and abdominal pain are labeled for Truvada. Vertigo and diplopia are not labeled. The events may be due to Kaletra (lopinavir+ritonavir). Headache, vertigo, visual impairment, and abdominal pain, are included in the label for Kaletra under Adverse Reactions: Clinical Trials Experience. [3]

Unlabeled event- suicidal ideation (n=1): Increase in suicidal thoughts, worsening of mood, and nausea in a 16-year-old female 3 days after beginning Kaletra and Truvada for an unknown indication. No medical history was reported. Concomitant medications included fluoxetine for 10 months (dose increased from 20 to 40mg several weeks prior to adverse events) and domperidone (dose, duration, indication not reported). Patient stopped antiretrovirals and domperidone due to nausea and patient's mood improved and thoughts reduced significantly within 1 day. (Case reference #5, FAERS case #10365788-2, Great Britain)

Reviewer comment: Nausea and depression are labeled for Truvada, suicidal ideation is not labeled. The increase in suicidal thoughts may be due to the recent dose increase in fluoxetine. Fluoxetine has a boxed warning for increased risk of suicidal thinking and behavior in children, adolescents, and young adults. [4]

3.4.2 Labeled Events: n=4

Four cases reported labeled events. Two of the four cases reported hepatic events, but causality to Truvada cannot be established due to insufficient information and concomitant medications associated with hepatotoxicity. Two other cases reported events consistent with the known risk in the labeling and no increased severity was observed. All four cases are summarized below:

Labeled event - hepatic enzyme increased, blood creatine phosphokinase increased, drug eruption (n=1): Slightly elevated serum creatine kinase levels and increased liver enzymes in a 13-year-old male patient who commenced Truvada for an unknown indication. Concomitant medications, medical history and patient's baseline laboratory results were not reported. On an unspecified date, the patient had unprotected sex and presented to the hospital with slightly elevated serum creatine kinase levels. Liver enzymes were also elevated to 7,000 (reference range and unit value unspecified). Truvada was stopped after 10 days therapy because patient's serum creatine kinase and liver enzymes continued to rise "up to 30,000" (reference range and unit value unspecified). The patient also had a "drug rash." The clinical outcome was not reported. (Case reference #3, FAERS case #10222670-2, USA)

Reviewer comment: Elevated serum creatine phosphokinase, drug rash, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT), and increased bilirubin are labeled for Truvada under section 6 - Adverse Reactions. However, causality to Truvada cannot be established due to insufficient information in the report. Liver enzymes "up to 30,000" is an unusually high level and this level may refer to the serum creatine kinase level instead of liver

enzyme levels; however, it is unclear from the case. Medical history and concomitant medications were not reported.

Labeled event – liver injury (n=1): A 12-year-old female was hospitalized for first management of tuberculosis associated with HIV infection. Two months prior laboratory results showed: Anti-HBc antibody positive, Anti-HBs antibody negative, Hepatitis B surface antigen negative, negative serology test for HCV, HBV, HEV. At baseline, before therapy initiation, liver function tests were normal except GGT at 3N. The patient began therapy with Rifater (rifampin, isoniazid, and pyrazinamide) and myambutol. Eleven days later, the patient began antiretroviral therapy with Truvada, darunavir, and ritonavir. Two days after beginning antiretroviral thearpy and 13 days after beginning tuberculosis therapy the patient experienced hepatic damage. Six days after beginning antiretroviral therapy, and 17 days after beginning tuberculosis therapy, Truvada, darunavir, ritonavir and isoniazid were discontinued. Peak values reported for liver function tests: GGT 350 IU/L, ALP 160 IU/L, ALT 262 IU/L, AST 218 IU/L, conjugated bilirubin 21 mcmol/L, total bilirubin 45 mcmol/L. The following month the patient was discharged with therapy including abacavir/lamivudine, raltegravir, and rifampicin/isoniazid/pyrazinamide. No data were available before discontinuation of rifampicin/isoniazid/pyrazinamide two months after discharge. Four months after discharge liver function tests returned normal. However, liver function tests were shown to be increased the next month (five months after discharge, six months after initial adverse events), ALT was 206 IU/L, AST 220 IU/L, GGT 183 IU/L, ALP 147 IU/L, conjugated bilirubin 8 mcmol/L and total bilirubin 14 mcmol/L. (Case reference #8, FAERS case #12627211-1, France)

Reviewer comment: Hepatitis, increased liver enzymes (most commonly AST, ALT, gamma GT), and increased bilirubin are labeled for Truvada under section 6 - Adverse Reactions. However, causality to Truvada cannot be established due to multiple concomitant medications associated with hepatotoxicity (such as darunavir, ritonavir, and antituberculosis medications). After Truvada was discontinued, liver function tests increased again 6 months later; no other information was provided.

Labeled event- accidental exposure to product, vomiting (n=1): Vomiting in a 2-year-old female who accidentally took her mother's emtricitabine/tenofovir DF 100mg. She was hospitalized and monitored. Charcoal was administered. Laboratory examinations were normal and the child was discharged. (Case reference #6, FAERS case #10738499-1, Italy)

Reviewer comment: Vomiting is labeled for Truvada under Adverse Reactions – from Clinical Trials Experience in HIV-1 Infected Subjects.The event of vomiting is consistent with the known risk in the labeling for Truvada and no increased severity was observed.

Labeled event- blood alkaline phosphatase increased, hypophosphataemia, osteopenia, osteoporosis, pain in extremity (n=1): Bilateral lower leg pain in 14-year-old male patient less than 2 months after beginning treatment with maraviroc, lopinavir+ritonavir, and Truvada for

HIV infection. He was enrolled in an open label study titled an open-label, multicenter, multiple-dose pharmacokinetic, safety and efficacy trial of maraviroc in combination with optimized background therapy for the treatment of antiretroviral experienced CCR5-tropic HIV-1 infected children 2 - <18 years of age. He was treated with ibuprofen, followed by paracetamol and diclofenac gel. Symptoms worsened and patient was hospitalized for work-up. He was diagnosed with osteopenia, low serum phosphate, and increased ALP related to Truvada. Truvada was permanently discontinued. Several weeks after discontinuation, the clinical outcome was "not resolved yet." (Case reference #7, FAERS case #10904215-3, South Africa)

Reviewer comment: The events are consistent with the known risk in the labeling for tenofovir DF-related bone and renal effects and no increased severity was observed. Under Warnings and Precautions- Bone Effects of Tenofovir DF: Bone Mineral Density, the label states in clinical trials for pediatric and adolescent subjects total body bone mineral density (BMD) was less in the tenofovir DF treated HIV-1 infected pediatric subjects as compared to the control groups. Under Warnings and Precautions- New Onset or Worsening Renal Impairment, the label states renal impairment including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported... persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy. Under Adverse Reactions – Clinical Trials in Pediatric Subjects, the label states adverse reactions consistent with proximal renal tubulopathy (hypophosphatemia and decreases in bone mineral density) were reported. Increased serum alkaline phosphatase is labeled under Adverse Reactions –from Clinical Trials Experience in HIV-1 Infected Subjects.

3.4.3 **Indication/Disease Related Events: n=1**

One case reported an indication/disease related adverse event and is summarized below:

Indication/disease related event- drug ineffective (n=1): Viral failure with a tenofovir DF-containing regimen in an 11-year- old male born in Cameroon with vertically acquired HIV infection. Therapy was changed to another regimen (also containing tenofovir DF) and the patient's viral load became undetectable (<20 copies of HIV RNA/ml). Literature report: Wagner N, Wyler-Lazareevic CA, Yerly S, Samer C, Peytavin G, Posfay-Barbe KM, Calmy A, Ambrosioni J. Dolutegravir-based antiretroviral therapy in a severely overweight child with a multidrug-resistance human immunodeficiency virus infection. A case report and review. New Microbes and New Infections. 2015;6:1-4. (Case reference #4, FAERS case # 10292565-4, Switzerland)

Reviewer comment: Therapy was changed to another tenofovir DF-containing regimen and the patient's viral load became undetectable.

4 DISCUSSION

During the time examined, pediatric patients 17 years and younger comprised approximately 1% of the total patients who received dispensed prescriptions for Truvada from U.S. outpatient retail pharmacies. The annual number of pediatric patients who received dispensed prescriptions from U.S. outpatient pharmacies increased 73%, from 1,121 patients in the year ending September 2012 to 1,939 patients in the year ending September 2016. Annually, more than 80% of total pediatric patients were aged 12-17 years.

Of note, for the estimates of pediatric patients who received Truvada, we focused our analyses on the outpatient retail pharmacy setting only, which is where the largest proportion of Truvada product sales were 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.

Eight adverse event cases in pediatric patients were received from 08-Jul-2011 (the date of pediatric labeling approval) to 29-Sep-2016, and this small number is consistent with low domestic use in pediatric patients compared to all ages. Low use may decrease the voluntary reporting of any adverse event. No significant use outside the approved indication was identified in these reports.

Of the eight pediatric adverse event cases, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and no deaths directly associated with Truvada. One death was reported due to immune reconstitution inflammatory syndrome (IRIS)-associated progressive multifocal leukoencephalopathy (PML). IRIS is labeled for all antiretrovirals under **Warnings and Precautions**.

5 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with this drug at this time.

6 RECOMMENDATIONS

Routine pharmacovigilance monitoring.

7 REFERENCES

1. Truvada® [package insert]. Foster City, CA: Gilead Sciences, Inc.; 2016
2. Centers for Disease Control and Prevention (CDC), US Public Health Service. Updates guideline for antiretroviral post exposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV-United States, 2016. Atlanta, GA: US Department of Health and Human Services, CDC;2016; available at https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf
3. Kaletra® [package insert]. North Chicago, IL: AbbVie Inc.; 2016
4. Prozac® [package insert]. Indianapolis, IN: Eli Lilly and Company; 2016

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS AND 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.

IMS Health, 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 TRUVADA (N=8)

FAERS case-version numbers and manufacturer control numbers included in pediatric case series (n=8)		
Ref #	**FAERS case-version #**	**Mfr#**
1	8499989-1 Duplicate8506247-1	FR-ABBOTT-12P-056-0922322-00 DuplicateFR-GILEAD-2012-0053468
2	8646504-2 Duplicate10185195-1 Duplicate10187187-1 Duplicate10195849-2 Duplicate10200376-1 Duplicate10210926-1 Duplicate10169889-1 Duplicate10196482-2	US-GILEAD-2012-0057203 DuplicateUS-MYLANLABS-2014S1010796 Duplicate2014AP002970 DuplicateAUR-APL-2014-05930 DuplicateUS-MICRO LABS LIMITED-ML2014-00383 Duplicate2014HINLIT0444 DuplicateUS-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2014-BI-20890GD DuplicateAUR-APL-2014-05906
3	10222670-2	US-GILEAD-2013-0078959
4	10292565-4	CH-GILEAD-2014-0106572
5	10365788-2 Duplicate10372457-1	GB-ABBVIE-14P-167-1268850-00 DuplicateGB-GILEAD-2014-0111151
6	10738499-1	IT-GILEAD-2014-0112132
7	10904215-3	ZA2015GSK004608
8	12627211-1	FR-ABBVIE-16P-056-1692766-00

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