

MEMOR-ANDUM

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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THROUGH: Mark Avigan, M.D., C.M., Director
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SUBJECT: 1-year Pediatric Exclusivity Postmarketing Adverse Event Review
NDA 21-500 and NDA 21-896
Drug: Emtriva® (emtricitabine) 200mg Capsules and Oral Solution
(10mg/mL)
Combination Products: Truvada® (emtricitabine/tenofovir)
Atripla® (emtricitabine/tenofovir/efavirenz)
Pediatric Exclusivity Approval Date: May 24, 2006

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1. EXECUTIVE SUMMARY

The Adverse Event Reporting System (AERS) was searched for reports of adverse events (serious and non-serious) associated with the use of emtricitabine in adult and pediatric patients (0-16 years of age). Up to the "data lock" date of June 24, 2007, AERS contains 947 reports for emtricitabine (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 3.7% of the total (35/947).

DDRE was asked to focus on the 1-year period following the granting of pediatric exclusivity, May 24, 2006 to May 25, 2007 (referred to hereafter as the *pediatric exclusivity period*). AERS was searched using a "cut-off" date of June 24, 2007 to allow time for all reports received by May 24, 2007 to be entered into the database. A total of 497 reports (crude count) were received during the pediatric exclusivity period, including both adult and pediatric reports and reports with no reported age. Twenty (crude count) of the 497 reports received during the pediatric exclusivity period reported events in patients ages 0-16 years.

After merging duplicate reports there were a total **15** unique reports received by FDA during the pediatric exclusivity period for emtricitabine. These 15 reports represent **4** pediatric reports in patients receiving emtricitabine for the treatment of HIV and an additional **11** reports in neonate following transplacental exposure to emtricitabine in combination with other antiretrovirals.

This review will focus on the **4** pediatric reports in patients receiving emtricitabine in combination with other antiretrovirals for the treatment of HIV-1 infection. The **11** reports in neonates following transplacental exposure to emtricitabine are summarized in the Appendix (Table 4) and will not be discussed further except to note that sponsors of all antiretroviral agents including emtricitabine participate in an active antiretroviral pregnancy registry¹. This registry monitors maternal-fetal outcomes of pregnant women exposed to antiretrovirals. Emtricitabine-specific serious adverse events from maternal-fetal exposures have not been noteworthy in annual reports. These cases also did not reveal any particular patterns of toxicity with regard to the use of emtricitabine, and the neonates were exposed to multiple antiretroviral agents with drug exposure occurring during various weeks of gestational development.

Per the regulatory definition for serious adverse events (CFR 314.80), which includes outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly there are four reports (hospitalizations-3 and medically significant-1) received by FDA during the pediatric exclusivity period for emtricitabine that meet this definition. All four of these serious reports (hepatotoxicity-3 and gastroenteritis-1) are labeled events. There were no deaths in pediatric patients receiving emtricitabine for the treatment of HIV-1 infection.

¹ Antiretroviral Pregnancy Registry was established in 1989 because of the potential for exposure during the first trimester of pregnancy and the potential risks of any new chemical entity, in the context of HIV status in pregnancy. All antiretroviral products for the treatment of HIV take part in the registry on approval.

This review does not reveal any new safety concerns for the use of emtricitabine in pediatric patients that were not seen in the pediatric clinical trials. The pediatric adverse event profile observed during the one-year-post exclusivity period is similar to that for adult patients. We will continue routine monitoring of adverse events with the use of emtricitabine in pediatric patients.

2. PRODUCTS, INDICATIONS, PEDIATRIC LABELING, and PEDIATRIC FILING HISTORY

2.1 Emtriva® Product Formulations

1. Emtriva® (emtricitabine) 200mg Oral Capsules approved July 2, 2003
2. Emtriva® (emtricitabine) 10mg/mL Oral Solution approved Sept. 28, 2005

2.2 Combination Products containing emtricitabine

1. Truvada® (emtricitabine/tenofovir) Tablets approved August 2, 2004
2. Atripla® (emtricitabine/tenofovir/efavirenz) Tablets approved July 12, 2006

2.3 Indication: Emtricitabine is a nucleoside analog that is indicated in combination with other antiretroviral agents for the treatment of HIV infection.

2.4 Pediatric Labeling²

CLINICAL PHARMACOLOGY

Pediatrics

The pharmacokinetics of emtricitabine at steady state were determined in 77 HIV-infected children, and the pharmacokinetic profile was characterized in four age groups (Table 1). The emtricitabine exposure achieved in children receiving a daily dose of 6mg/kg up to a maximum of 240 mg oral solution or a 200mg capsule is similar in exposures achieved in adults receiving a once-daily dose of 200mg.

The pharmacokinetics of emtricitabine were studied in 20 neonates born to HIV-positive mothers. Each mother received prenatal and intrapartum combination antiretroviral therapy. Neonates received up to 6 weeks of zidovudine prophylactically after birth. The neonates were administered two short courses of emtricitabine oral solution (each 3mg/kg QD x 4 days) during the first 3 months of life. The AUC observed in neonates who received a daily dose of 3mg/kg of emtricitabine was similar to the AUC observed in pediatric patients ≥3 months to 17 years who received a daily dose of emtricitabine as a 6mg/kg oral solution up to 240 mg or as a 200 mg capsule (Table1).

Table 1 Mean ± SD Pharmacokinetic Parameters by Age Groups for Pediatric Patients and Neonates Receiving EMTRIVA Capsules and Oral Solution

Age	HIV-exposed Neonates	HIV-Infected Pediatric Patients			
	0-3 mo (n=20) ¹	3-24 mo (n=14)	25 mo-6 yr (n=19)	7-12 yr (n=17)	13-17 yr (n=27)
Formulation					
Capsule (n)	0	0	0	10	26
Oral Solution (n)	20	14	19	7	1

² EMTRIVA (emtricitabine) Product Label, Gilead Sciences, Inc., December 2006

Dose (mg/kg) ²	3.1 (2.9-3.4)	6.1 (5.5-6.8)	6.1 (5.6-6.7)	5.6 (3.1-6.6)	4.4 (1.8-7.0)
C _{max} (µg/mL)	1.6 ± 0.6	1.9 ± 0.6	1.9 ± 0.7	2.7 ± 0.8	2.7 ± 0.9
AUC (hr·µg/mL)	11.0 ± 4.2	8.7 ± 3.2	9.0 ± 3.0	12.6 ± 3.5	12.6 ± 5.4
T _{1/2} (hr)	12.1 ± 3.1	8.9 ± 3.2	11.3 ± 6.4	8.2 ± 3.2	8.9 ± 3.3

¹Two pharmacokinetic evaluations were conducted in 20 neonates over the first 3 months of life. Median (range) age of infant on day of pharmacokinetic evaluation was 26 (5-81) days.

²Mean (range)

Pregnancy: Pregnancy Category B

Pediatric Use

The safety and efficacy of emtricitabine in patients between 3 months and 21 years of age is supported by data from three open-label non-randomized clinical studies in which emtricitabine was administered to 169 HIV-1 infected treatment-naïve and experienced (defined as virologically suppressed on a lamivudine containing regimen for which emtricitabine was substituted for lamivudine). Patients received once-daily EMTRIVA Oral Solution (6mg/kg to a maximum of 240mg/day) or EMTRIVA Capsules (a single 200 mg capsule once daily) in combination with at least two other antiretroviral agents.

Patients had a mean age of 7.9 years (range 0.3-21), 49% were male, 15% Caucasian, 61% Black and 24% Hispanic. Patients had a median baseline HIV RNA of 4.6 log₁₀ copies/mL (range 1.7-6.4) and a mean baseline CD4 cell count of 745 cells/mm³ (range 2-2650). Through 48 weeks of therapy the overall proportion of patients who achieved and sustained an HIV RNA <400 copies/mL was 86%, and < 50 copies/mL was 73%. The mean increase from baseline in CD4 cell count was 232 cells/mm³ (-945, +1512). The adverse event profile observed during these clinical trials was similar to that of adult patients, with the exception of a higher frequency of hyperpigmentation (see **ADVERSE REACTIONS**).

The pharmacokinetics of emtricitabine were studied in 20 neonates born to HIV-positive mothers. Each mother received prenatal and intrapartum combination antiretroviral therapy. Neonates received up to 6 weeks of zidovudine prophylactically after birth. The neonates were administered two short courses of emtricitabine oral solution (each 3mg/kg QD x 4 days) during the first 3 months of life. Emtricitabine exposures in neonates were similar to the exposures achieved in patients > 3 months to 17 years (see **CLINICAL PHARMACOLOGY: Pediatrics**). During the two short dosing periods on emtricitabine there were no safety issues identified in the treated neonates. All neonates were HIV-1 negative at the end of the study; the efficacy of emtricitabine in preventing or treating HIV could not be determined.

ADVERSE REACTIONS: Pediatric Patients:

Assessment of adverse reactions is based on data from 169 HIV-infected pediatric patients who received emtricitabine through Week 48. The adverse event profile in pediatric patients was generally comparable to that observed in clinical studies of EMTRIVA in adult patients.

Selected treatment-emergent adverse events, regardless of causality, reported in patients during 48 weeks of treatment were the following: infection (44%), hyperpigmentation (32%), increased cough (28%), vomiting (23%), otitis media (23%), rash (21%), rhinitis (20%), diarrhea (20%), fever (18%), pneumonia (15%), gastroenteritis (11%), abdominal pain (10%), and anemia (7%). Treatment-emergent grade 3 and 4 laboratory abnormalities were experienced by 9% of pediatric patients, including amylase >2.0 x ULN (n=4), neutrophils 750/ mm³ (n=3), ALT >5 x ULN (n=2), elevated CPK (>4 x ULN) (n=2), and one patient each with elevated bilirubin (>3.0 x ULN), elevated GGT (>10 x ULN), elevated lipase (>2.5 x ULN), decreased hemoglobin (<7 g/dL), and decreased glucose (<40 mg/dL).

DOSAGE and ADMINISTRATION

Pediatric Patients (0-3 months of age):

- **EMTRIVA Oral Solution: 3mg/kg administered once daily orally.**

Pediatric Patients (3 months through 17 years):

- **EMTRIVA Oral Solution: 6mg/kg up to a maximum of 240mg (24mL) administered once daily orally.**
- **EMTRIVA Capsules: for children weighing more than 33 kg who can swallow an intact capsule, one 200 mg capsule administered once daily orally.**

2.5 Pediatric Filing History

Emtriva® (emtricitabine) is a nucleoside analog indicated in combination with other antiretroviral agents for the treatment of the human immunodeficiency virus (HIV) infection in adult and pediatric patients (0-16 years of age). There are two available formulations (1) 200mg oral capsule and (2) 10mg/mL oral solution. Emtricitabine is also a component of two combination products, Truvada® (emtricitabine and tenofovir) tablets and Atripla® (emtricitabine, tenofovir and efavirenz) tablets.

In July 1999, a Written Request was issued for Emtriva® (emtricitabine, FTC) in which the applicant, Triangle Pharmaceuticals (now Gilead Sciences), was asked to provide (1) pharmacokinetic, safety and antiviral activity data in pediatric patients with HIV-1 infection, and (2) pharmacokinetic and safety data of emtricitabine in HIV-1 exposed neonates (born to HIV-1 infected mothers). In exchange for this information, an additional 6 months of marketing exclusivity would be granted.

In March 2005, Gilead submitted efficacy and safety data supporting use of emtricitabine (oral solution and capsules) from three open-label non-randomized clinical studies [FTC-203, FTC-202 (PACTG-1021), and FTC-211] in 169 HIV-1 infected pediatric patients >3 months of age treated for 48 weeks. These patients were HIV infected treatment-naïve and experienced (defined as virologically suppressed on a lamivudine containing regimen for which emtricitabine was substituted for lamivudine). There were no safety data in the clinical review to suggest that there is a substantial difference in either the type or frequencies of treatment-related adverse events, with the exception of hyperpigmentation, between adult and pediatric patients. Hepatotoxicity (i.e. fulminant hepatitis, acute liver failure) was not identified as a potential safety issue in these trials. However, Grade 3 and 4 laboratory abnormalities included elevated bilirubin and liver enzyme tests were observed in pediatric patients but were comparable in type and frequency observed in adult trials. Data from these trials resulted in pediatric labeling for this age group (3 months to 16 years of age), and the pediatric supplement was approved on September 25, 2005 (see Section 2.4 above).

Data from the second study requested in the Written Request was submitted in 2006 and provided data in the neonatal population (n=20). Study FTC-116 was an open-label, non-randomized study conducted in infants born to HIV-1 infected mothers. The study objectives were to evaluate emtricitabine pharmacokinetics over the first three months of life, determine how the maturing renal function affects pharmacokinetics, and assess safety and tolerability. The trial was conducted at two sites in South Africa under appropriate ethical guidelines. These data resulted in pediatric labeling for this age group (0-3 months of age), and the pediatric supplement was approved on December 22, 2006 (see Section 2.4 above).

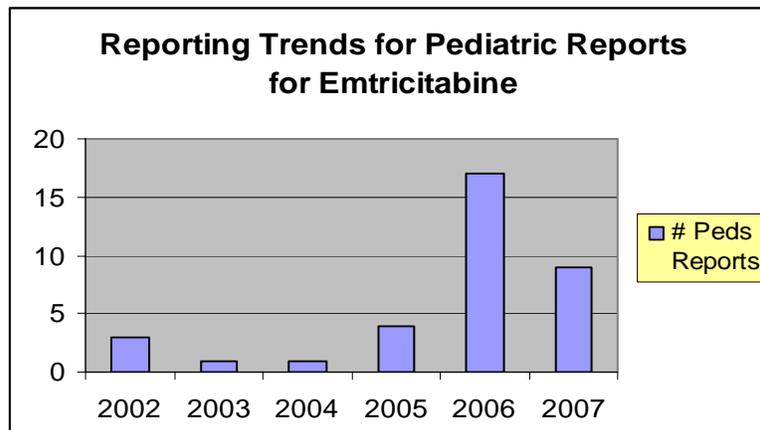
3. AERS SEARCH RESULTS: Emtriva® (emtricitabine)

3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval (Table 1)

Table 1: Crude Counts¹ of AERS Reports for Emtricitabine for All Sources from Marketing Approval through June 24, 2007 (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	774 (403)	745 (376)	92 (49)
Pediatrics (0-16 yrs.)	35 (27)	35 (27)	6 (5) ³
Age unknown (Null values)	138 (93)	119 (74)	10 (4)
Total	947 (523)	899 (477)	108 (58)

¹ May include duplicates
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.
³ After removal of duplicate reports there are a total of 4 deaths in neonates (see Section 4.2 and Table 4)

Figure 1: Reporting Trend for Pediatric Reports for Emtricitabine (From approval date through June 24, 2007)



3.2 Count of Reports: AERS Search including all sources - U.S. & foreign for Pediatric Exclusivity Period (Table 2)

Table 2: Crude counts¹ of AERS Reports for Emtricitabine for All Sources for Pediatric Exclusivity Period, May 24, 2006 through June 24, 2007 (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	400 (197)	390 (188)	45 (30)
Pediatrics (0-16 yrs)	20 (15)	20 (15)	6 (5) ³
Age unknown (Null Values)	77 (49)	68 (40)	5 (3)
Total	497 (261)	478 (243)	56 (38)

¹ May include duplicates
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.
³ After removal of duplicate reports there are a total of 4 deaths in neonates (see Section 4.2 and Table 4)

4. POSTMARKETING REVIEW OF ALL PEDIATRIC ADVERSE EVENTS RECEIVED DURING THE PEDIATRIC EXCLUSIVITY PERIOD

4.1 Case Characteristics of Pediatric Cases for Emtricitabine Received During Pediatric Exclusivity Period (n= 4)

Table 3: Characteristics of Pediatric Cases for Emtricitabine Received During the Pediatric Exclusivity Period, May 24, 2006 through June 24, 2007 (n=4)	
Gender	Male: 2 Female: 2
Age	Mean= 9.8 years Median = 11 years; (Range, 14 months to 16 years)
	0- <1 month = 0 1 month <2 yrs = 1 2-5 yrs = 0 6-11 yrs = 1 12-16 yrs = 2
Origin	US= 2 Foreign= 2 (France and South Africa)
Indications	HIV 4
Outcomes	Hospitalization-3, Medically Significant/Other-1

4.2 Fatalities

Table 2 in section 3.2 lists 6 fatalities (crude count, includes duplicate reports). After removal of duplicate reports there are a total of 4 reported deaths in neonates following transplacental exposure to emtricitabine (see Appendix, Table 4), and no reports of death in pediatric patients receiving emtricitabine for the treatment of HIV infection during the pediatric exclusivity period.

4.3 Summary of Non-Fatal Cases Received During the 1-year Post-Pediatric Exclusivity Period by Primary Adverse Event Described in Narrative (n=4)

Hepatic Events (n=3)

Patient #1: This 14-month-old HIV-infected male was enrolled in an Open-label study to evaluate safety, tolerance, antiviral activity and pharmacokinetics of emtricitabine in combination with efavirenz and didanosine in a once-daily regimen of HIV-infected antiretroviral therapy naïve or very limited antiretroviral exposed pediatric patients. His medical history included congenital toxoplasmosis and developmental delay with CT finding of encephalomalacia. In May 2006 he was hospitalized with new onset seizures. Antiretroviral therapy was held due to inability to administer. On 22 May 2006 antiretrovirals were restarted and due to pharmacy error the patient received 3 doses of emtricitabine instead of one. Hepatitis B surface antigens and hepatitis C antibody were

both negative. Three days later the patient's laboratory tests (LFTs) were slightly elevated. They continued to rise and on [redacted], AST and ALT were 439 IU/L and 518 IU/L, respectively. In comparison, the patient's LFTs were normal on [redacted]. On [redacted], AST was 359 IU/L and ALT was stable but still abnormal at 518 IU/L. On [redacted], the patient's ALT level was 397 IU/L and GGT level was 257 IU/L (normal range 5-16 IU/L). There was sub-clinical seizure activity on EEG for which the gabapentin dose was increased; otherwise, the patient was clinically stable. All antiretroviral study medications were interrupted as of 02 June 2006. On [redacted], the patient's LFTs were AST 72 IU/L, ALT 164 IU/L, and GGT 250 IU/L. The LFTs have continued to improve and the GGT level remained at grade 4 toxicity. All medications [redacted] old. The patient's GGT level continued to decline and was 164 IU/L on [redacted]. The gastroenterologist indicated that the etiology for the patient's elevated GGT and transaminases was most likely multi-factorial with suspected contributing factors being TPN, re-feeding in a malnourished child, surgery/anesthesia, HIV medications, and possible sepsis.

*Comment: Elevated ALT and GGT levels are listed in the pediatric adverse events section of the EMTRIVA label and are considered labeled. Elevated AST levels are listed under **ADVERSE REACTIONS** in adult patients. There is no information on increased LFTs or GGT levels in the **OVERDOSAGE** section of the label.*

Patient #2: A 16 year-old male with HIV and hepatitis C (HCV) co-infection since birth changed antiretroviral therapy (ART) due to multiple drug resistance from stavudine, lamivudine and lopinavir/ritonavir to emtricitabine/tenofovir (Truvada), lopinavir/ritonavir, and tipranavir. Patient experienced hepatitis and jaundice 19 days after the change in ART regimen that resolved in the days following discontinuation of antiretroviral therapy.

*Comment: Tipranavir has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities; patients co-infected with HCV have an increased risk of hepatotoxicity. Tipranavir carries a **Box Warning** for hepatotoxicity and is mostly likely the cause of the adverse reaction in this patient. A possible contributory role of emtricitabine is unknown.*

Patient#3: A 16 year-old female receiving antiretroviral therapy with emtricitabine and didanosine for one year added atazanavir and ritonavir to her HIV regimen. Six days later laboratory tests revealed elevated levels of total bilirubin and unconjugated bilirubin. The patient was asymptomatic and therapy with antiretrovirals was ongoing.

Comment: Atazanavir has been associated with asymptomatic hyperbilirubinemia in clinical trials. The increased levels of bilirubin are more temporally related to the use of atazanavir than the other antiretrovirals including emtricitabine. Elevated bilirubin levels are listed in the pediatric adverse events section of the EMTRIVA label.

GI: Gastroenteritis (n=1)

There is one report of gastroenteritis in a 6-year-old female patient from South Africa enrolled in a study involving the use of emtricitabine, stavudine and lopinavir/ritonavir for the treatment of HIV. The patient developed vomiting, right ear and eye pain, fever, generalized lymphadenopathy and epigastric tenderness approximately 1 year and 3 weeks after starting study drug. Meningitis was suspected; she was hospitalized and antiretrovirals were discontinued 3 days after onset of symptoms. Lumbar puncture, blood cultures, and gram stain and bacterial antigen tests were all negative. She later developed profuse diarrhea and was diagnosed with gastroenteritis. She recovered and study drugs were resumed 3 days later.

*Comment: Gastroenteritis is listed under **ADVERSE REACTIONS/ Pediatric Patients** in the EMTRIVA label.*

5. SUMMARY/RECOMMENDATIONS

There are four adverse events (3-hospitalization and 1-medically significant) reported in pediatric patients during the exclusivity period that meet the regulatory definition for serious (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly. All four of these serious events (3-hepatotoxicity and 1-gastroenteritis) are labeled events. There were no deaths in pediatric patients receiving emtricitabine for the treatment of HIV-1 infection.

This review does not reveal any new safety concerns for the use of emtricitabine in pediatric patients that were not seen in the pediatric clinical trials. The pediatric adverse event profile observed during the one-year-post exclusivity period is similar to that for adult patients. We will continue routine monitoring of adverse events with the use of emtricitabine in pediatric patients.

/s/ Melissa M. Truffa, R.Ph. 7-18-07
Reviewer's Signature / Date

/s/ Mark Avigan, M.D., C.M.
Division Director Signature / Date

Appendix: Table 4—All Maternal to Fetal Exposure Cases with Emtricitabine Received During the Pediatric Exclusivity Period (N=11)

	Case #	Sex/age/ Location Outcome	Antiretrovirals*	Infant's Reported Adverse Event	Comments
1.	6055485 6054817 6063491	M/newborn US Congenital Anomaly	Mother: FTC/TDF/ATV/RTV at conception and 1 st trimester LPV/RTV/ZDV/3TC/ABV 1 st trimester Dc'd 2 months later, NFV/3TC/ZDV started in 2 nd trimester At delivery: zidovudine IV	Trisomy 15 Convulsions Developmental Delay Hypotonia Apnea	Born at 37 weeks gestation by normal vaginal birth to a 30-year-old Hispanic mother. At birth diagnosed with partial Trisomy 15 and sub-clinical seizure disorder. Depending on the portion of chromosome 15 may result in autism. Unknown if seizure disorder due to partial Trisomy 15. He also had hypotonia, apnea and delayed development. He received lamivudine for 4-6 weeks. His HIV PCR was negative at discharge.
2.	6081238 6085692	F/newborn US Death	Mother: Truvada (FTC/TDF) and NVP for entire pregnancy At delivery: zidovudine IV	Pre-mature Pulmonary hypoplasia Hydrops fetalis Kyphosis, microcephaly, echogenic bowel, 2 vessel cord, oligohydranios	Born at 32 weeks + 5 days gestation by emergency C-section to 28-yr-old mother. Complication of labor included prolapsed cord and breech position. Mother positive for syphilis, HBV, HIV. Other meds: Wellbutrin, SeroQuel, cocaine, tobacco and amoxicillin. Infant was apneic, bradycardic and bruised on birth. Multiple congenital anomalies. Death several hours after birth attributed to pulmonary hypoplasia and non-viable.
3.	6146896	M/newborn US Congenital anomaly	Mother: Truvada (FTC/TDF) and NVP/Fosamprenavir/RTV for entire pregnancy	Cleft palate	Born at 37 weeks gestation with cleft palate.
4.	6002672	F/newborn US Congenital anomaly	Mother: NFV/3TC/ZDV for entire pregnancy ATV/RTV/Truvada Prior to conception	Polydactyly	Born at 34 wks of gestation to 39-yr-old mother. Polydactyly on one hand; mother with same defect.
5.	6277577	M/newborn Cote D'Ivoire Hosp	Mother: Truvada (FTC/TDF)/NVP x 2 days ZDV x 74 days prophylaxis	Infantile spasms Laryngomalacia West's syndrome	Phase 2 Open-label trial evaluating Truvada in women and infants in Africa and Asia. Gestational age not specified. Moderate cerebral sufferance at birth. Developed West's syndrome with neurological problems.
6.	6282168	M/newborn US Twin "A" Death	Mother: FosAPV/3TC/ZDV 1 st and 2 nd trimesters Truvada (FTC/TDF)/LPV/RTV 2 days prior to delivery and IV zidovudine	Premature Baby Cerebral Hemorrhage Patent Ductus Arteriosus (PDA)	Twin A born at 23 weeks of gestation to 27-yr-old mother. Born premature with PDA, germinal matrix midline shifts to right side and germinal matrix hemorrhage to left side with thrombosis. Due to critical status a decision to withdraw life support was made on day 6 of life; subsequently the baby died.

Appendix A: Table 4—All Maternal to Fetal Exposure Cases with Emtricitabine Received During the Pediatric Exclusivity Period (N=11)

	Case #	Sex/age/ Location Outcome	Antiretrovirals*	Infant's Reported Adverse Event	Comments
7.	6284438 6282165	M/newborn US Twin "B" Other	Mother: FosAPV/3TC/ZDV during pregnancy Truvada (FTC/TDF)/LPV/RTV 2 days prior to delivery and IV zidovudine	Premature Baby	Twin B born at 23 weeks of gestation to 27 yr-old mother. No birth defects started on ZDV and NVP at birth.
8.	6112810 6110936	M/newborn/ US Death	Mother: Truvada (FTC/TDF)/LPV/RTV in 3 rd trimester; 7 days before labor & delivery	Stillborn Intracranial hemorrhage Bulging Fontanelle Hypotonia	Stillborn at approximately 32 weeks of gestation to 25-yr-old mother. No respiratory effort, marked hypotonia, bulging fontanelle, large bruise on chest, massive intracranial hemorrhage and brain stem hemorrhage
9.	6338847	F/newborn Cote D'Ivoire Hosp	Mother: Truvada (FTC/TDF) and NVP on day of L&D, ZDV x 3 months before L&D	Gastrointestinal obstruction Enteritis	Phase 2 Open-label trial evaluating Truvada in women and infants in Africa and Asia. Infant started on ZDV/NVP. Developed significant abdominal distention, dehydration, malnutrition at about 1.5 months of age. X-ray suggested upper GI obstruction. Surgery consult pending.
10.	6323692	M/newborn Twin "A" Cote D'Ivoire Hosp	Mother: Truvada (FTC/TDF) and NVP on day of L&D, ZDV x 2 months before L&D	Anemia Enteritis	Phase 2 Open-label trial evaluating Truvada in women and infants in Africa and Asia. Twin pregnancy. Patient started on ZDV/NVP. At 25 days old developed febrile enteritis and decompensated anemia.
11.	6315055	M/newborn Twin "B" Cote D'Ivoire Death	Mother: (FTC/TDF) and NVP on day of L&D, ZDV x 2 months before L&D	Gastroenteritis Dehydration	Phase 2 Open-label trial evaluating Truvada in women and infants in Africa and Asia. Twin Pregnancy. This 24 day old male died from febrile gastroenteritis, dyspnea and severe malnutrition

*Antiretroviral abbreviations: ABV = abacavir, ATV = atazanavir, FTC = emtricitabine, FosAPV = fosamprenavir, 3TC= lamivudine, LPV/RTV = lopinavir/ritonavir (Kaletra), NFV = nelfinavir, NVP = nevirapine, RTV = ritonavir, ZDV = zidovudine, and TDF = tenofovir

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/s/

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