THE ANTIRETROVIRAL PREGNANCY REGISTRY

Interim Report

1 JANUARY 1989 THROUGH 31 JANUARY 2017

(Issued: June 2017)
(Expiration: 6 months after issue)

For

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POLICY FOR PRESENTATION OF DATA

The sponsors encourage the responsible sharing of the information contained in this report with health professionals who might benefit. In an attempt to standardize dissemination and interpretation of the data, the following guidelines have been developed:

1. The data contained in this report will become out-of-date within 6 months of the report's issue date. Please contact the Antiretroviral Pregnancy Registry (+1-800-258-4263) to ensure you have obtained the most recently published report. You can also retrieve a copy of the most recently published report by visiting the website at www.APRegistry.com.
2. The data in Table 4 (pregnancy exposure in the first trimester and outcome by treatment regimen) are the most appropriate for presentation of therapy results. Presentation of results stratified by earliest trimester of exposure is imperative. Retrospectively collected data are useful for detecting patterns of defects, but are subject to biases as described in the report; **thus these data must not be compared to background rates in the general population**.
3. The Advisory Committee Consensus statement (page 10) must be included with any presentation of these data, including emphasis on the limitations of voluntary prenatal drug exposure registries such as this one.
4. When presenting data from the Registry please present Registry contact information and remind the audience that success of the Registry depends on reporting of exposures by health care professionals.
5. Please contact the Antiretroviral Pregnancy Registry staff if you have any questions, see contact information below.

Suggested Citation

Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2017. Wilmington, NC: Registry Coordinating Center; 2017. Available from URL: www.APRegistry.com.

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Note to Patients:

This report was developed to provide you and your treating doctor with information to help guide your treatment. Please discuss any concerns or questions with your doctor.

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FOREWORD

This report describes the ongoing surveillance experience of pregnancy outcomes in the Antiretroviral Pregnancy Registry for all reporting countries (previously known as the Zidovudine in Pregnancy Registry) and covers the period 1 January 1989 through 31 January 2017.

Abacavir, adefovir dipivoxil, amprenavir, atazanavir, cobicistat, darunavir, delavirdine mesylate, didanosine, dolutegravir, efavirenz, elvitegravir, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, stavudine, telbivudine, tenofovir alafenamide, tenofovir disoproxil fumarate, tipranavir, zalcitabine, and zidovudine are antiretroviral therapies being followed in this Registry. This Registry was established 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. Through this Registry, reports of patients exposed to the antiretroviral drugs followed in the Registry are received, their pregnancies followed, and the outcomes of the pregnancies obtained through voluntary reports from treating health care providers.

The Registry is intended to provide an early signal of potential risks. Registry data are provided to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. These data represent the experience of what is, as yet, a relatively small number of pregnancies.

An independent Advisory Committee reviews data and establishes a consensus regarding results of the data at that time, makes recommendations on data collected and on issues arising during the conduct of the Registry, encourages referral of exposures, and disseminates information. The Advisory Committee, including a community member, along with representatives from the Sponsor companies constitutes the Registry Steering Committee. The Steering Committee meets to discuss issues, review data, update the report, and discuss the general conduct of the Registry. Members of the Advisory Committee and Sponsor representatives to the Steering Committee are listed below. Committee members are listed alphabetically within their respective group.

Antiretroviral Pregnancy Registry Advisory Committee

Cynthia Holcroft Argani, MD Division of Maternal-Fetal Medicine Johns Hopkins Medical Center	Lynne Mofenson, MD Advisor to the Elizabeth Glaser Pediatric AIDS Foundation	Claire Thorne, PhD UCL Institute of Child Health, University College of London
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Taylor Cook Project Manager, General Medicine INC Research, LLC	

The Antiretroviral Pregnancy Registry encourages reporting of all prenatal exposures to the therapies followed in the Registry (abacavir, adefovir dipivoxil, amprenavir, atazanavir, cobicistat, darunavir, delavirdine mesylate, didanosine, dolutegravir, efavirenz, elvitegravir, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, stavudine, telbivudine, tenofovir alafenamide, tenofovir disoproxil fumarate, tipranavir, zalcitabine, and zidovudine). Patient enrollment forms and instructions can be found in Appendix G. Please direct all enrollments and inquiries to the Antiretroviral Pregnancy Registry Coordinating Center at the following:

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0800-892-1472 (Brazil)

Email: SM_APR@INCResearch.com

Website: www.APRegistry.com (for data forms and information)

ATTENTION HEALTH CARE PROVIDERS

Please visit our website at www.APRegistry.com for data forms
or contact our Registry Call Center for additional information.

The Antiretroviral Pregnancy Registry recognizes the significant participation of the following providers (listed alphabetically). We greatly appreciate the contributions of all providers and welcome providers to submit all of their cases to the Registry and be recognized.

Aaron, Erika CRNP *(Drexel College of Medicine)*

Andrews, Mary-Margaret MD *(Dartmouth-Hitchcock Medical Center)*

Badell, Martina MD *(Grady Memorial Hospital)*

Balt, Christine DNP *(Eskenazi Health)*

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Crain, Marilyn MD and Dionne-Odom, Jodie MD *(UAB Department of Pediatrics)*

Deville, Jaime MD *(UCLA Care-4-Families Clinic)*

Fearnley, Nicola MD *(Bradford Teaching Hospitals NHS Foundation Trust)*

Galang, Minerva MD *(Mercy Health-Special Immunology Services, Saint Mary's Hospital)*

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Gay, Hannah MD *(University of Mississippi Medical Center)*

Han, Guorong MD *(Second Affiliated Hospital of the Southeast University)*

Hardwicke, Robin PhD, NP-C *(The University of Texas Medical School at Houston)*

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Hayes, Erick MD *(St. Louis Children's Hospital /Washington University School of Medicine)*

Hertling, Sandra MD *(Ambulanzzentrum Infektiologie des UKE GmbH - Hamburg, Germany)*

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EXECUTIVE SUMMARY

Background

The purpose of the Antiretroviral Pregnancy Registry (Registry) is to detect any major teratogenic effects involving any of the Registry drugs* to which pregnant women are exposed (1). Registration is voluntary and confidential with information obtained from the health care provider. A Registry-assigned identifier allows for follow-up capability. Information on subjects is provided to the Registry prospectively (prior to the outcome of pregnancy being known) through their health care provider, with follow-up obtained from the health care provider after the outcome is determined. (For more details, see Appendix F: Methods beginning on page 158.) Providers are strongly urged to enroll their patients as early in pregnancy as possible to maximize the validity of the data. In addition, the Registry is very interested in assembling a group of providers who are willing to make a commitment to report all of their site's antiretroviral pregnancy exposures to the Registry, thereby assuring all cases can be considered prospective. Providers are encouraged to contact the Registry for more information about this group. The Registry is informed in its analysis by other data, for example, retrospective reports and clinical studies.

Prospective tracking of fetal drug exposure during pregnancy, particularly newer agents and new combinations of therapies remains critically important in evaluating the safety of these agents among reproductive-age women and the exposed fetus.

Each year the Registry has enrolled approximately 1300 pregnant women in the US exposed to antiretroviral drugs. This number represents approximately 15% of the 8,700 HIV positive women who give birth to live infants annually in the US (2)[γ]. Each year the Registry also enrolls approximately 200 pregnant women from other countries. Given the continued emergence of newer therapies used for treatment and prevention for which there is an ongoing need for evidence of their safety in pregnancy, sustained reporting is vital to the registry's ability to fulfill its mission of early detection of a birth defect signal, if present. Health care providers are strongly encouraged to continue reporting eligible patients to the Registry.

Data Summary

Primary Registry Analysis (Prospective Reports): In review of the data through 31 January 2017, among the prospective Registry reports, the prevalence of birth defects per 100 live births among women

*Drugs included: abacavir (ZIAGEN®, ABC), abacavir/lamivudine combination (EPZICOM®, EPZ), abacavir/lamivudine/zidovudine combination (TRIZIVIR®, TZV), abacavir/dolutegravir/lamivudine combination (TRIUMEQ®, TRI), adefovir dipivoxil (HEPSERA®, ADV), amprenavir (AGENERASE®, APV), atazanavir (REYATAZ®, ATV), atazanavir/cobicistat combination (EVOTAZ®, EVO), cobicistat (TYBOST®, COBI), darunavir (PREZISTA®, DRV), darunavir/cobicistat combination (PREZCOBIX™, PCX), delavirdine mesylate (RESCRIPTOR®, DLV), didanosine (VIDEX®, VIDEX® EC, ddI), dolutegravir (TIVICAY®, DTG), emtricitabine/ tenofovir alafenamide (DESCOVY®,DVY) efavirenz (SUSTIVA®, STOCRIN®, EFV), efavirenz/emtricitabine/ tenofovir disoproxil combination (ATRIPLA® ATR), elvitegravir (VITEKTA®, EVG), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide combination (GENVOYA®, GEN), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate combination (STRIBILD®, STB), emtricitabine (EMTRIVA®, FTC), enfuvirtide (FUZEON®, T-20), entecavir (BARACLUDE®, ETV), etravirine (INTELENCE®, ETR), fosamprenavir calcium (LEXIVA®, FOS), indinavir (CRIXIVAN®, IDV), lamivudine (EPIVIR®, 3TC), lamivudine/raltegravir combination (DUTREBIS™, DUT), lamivudine/zidovudine combination (COMBIVIR®, ZDV+3TC), lopinavir/ritonavir combination (KALETRA®, ALUVIA®, LPV/r), maraviroc (SELZENTRY®, CELSENTRI®, MVC), nelfinavir (VIRACEPT®, NFV), nevirapine (VIRAMUNE®, VIRAMUNE® XR™, NVP), raltegravir (ISENTRESS®, RAL), rilpivirine (EDURANT®, RPV), rilpivirine/emtricitabine/tenofovir alafenamide (Genvoya®,GEN) rilpivirine/emtricitabine/tenofovir disoproxil combination (COMPLERA®, CPA; EVIPLERA®, EPA), ritonavir (NORVIR®, RTV), saquinavir (FORTOVASE®, SQV-SGC), saquinavir mesylate (INVIRASE®, SQV-HGC), stavudine (ZERIT®, d4T), telbivudine (SEBIVO®, TYZEKA®, LdT), tenofovir alafenamide (VEMLIDY®, TAF), tenofovir disoproxil fumarate (VIREAD®, TDF), tenofovir disoproxil fumarate /emtricitabine (TRUVADA®, TVD), tipranavir (APTIVUS®, TPV), zalcitabine (HIVID®, ddC), and zidovudine (RETROVIR®, ZDV).

[γ] Whitmore SK, Zhang X, Taylor A, Blair JM. Estimated number of infants born to HIV-infected women in the United States and five dependent areas, 2006. J Acquir Immune Defic Syndr. 2011;57(3):218-222.

with a first trimester exposure to any of the antiretroviral therapies included in the Registry is 2.8 (95% confidence interval (CI): 2.4 - 3.2, i.e., 240 outcomes with defects of 8583 live births (Table 7). The prevalence of defects is not significantly different from the prevalence of defects among women with an initial exposure during the second and/or third trimester (2.8 per 100 live births) (prevalence ratio: 1.02, 95% CI: 0.85, 1.21).

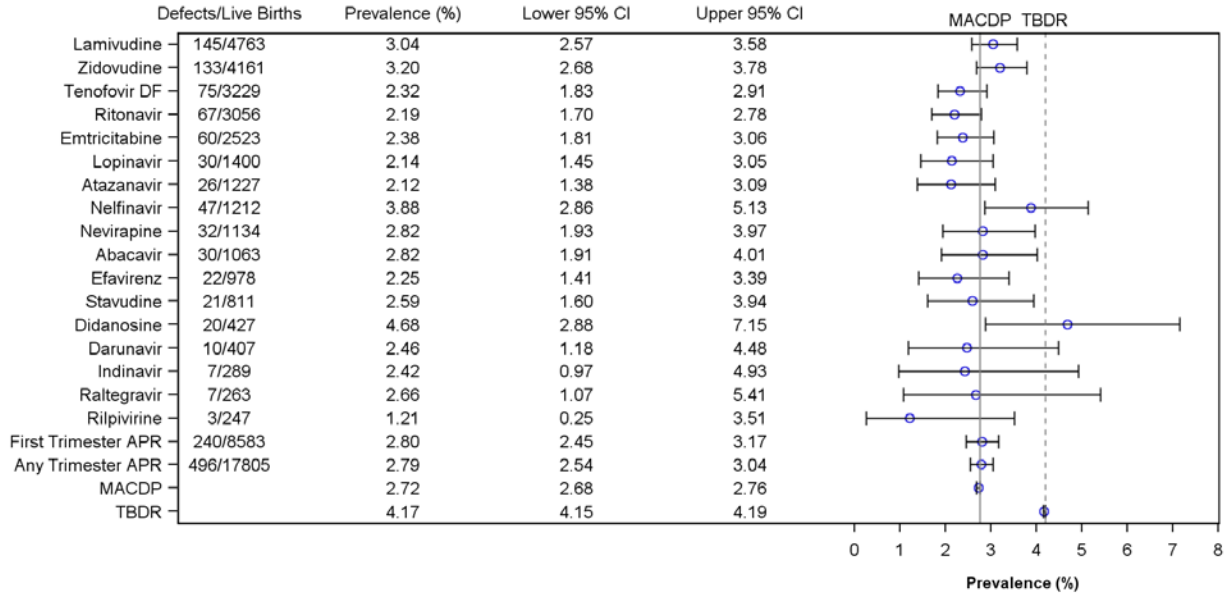
Measured against 17805 live births with exposure at any time during pregnancy, there were 496 outcomes with birth defects identified, a prevalence of 2.8 birth defects per 100 live births (95% CI: 2.5 - 3.0). This proportion is not significantly higher than those reported in the Registry's two population based comparators, the CDC's birth defects surveillance system (MACDP) (3, 4, 5, 6) (2.72 per 100 live births) and the Texas Birth Defects Registry (TBDR) (7) (4.17 per 100 live births). No increases in risk of specific defects have been detected to date when compared with observed MACDP or TBDR rates or with rates among those with earliest exposure in the second or third trimester. In analyzing individual drugs with sufficient data to warrant a separate analysis with the exception of didanosine and nelfinavir, no increases of concern in risk have been detected. For didanosine and nelfinavir, there is a modest but statistically significant increase in overall rates of defects when compared with the MACDP though not the TBDR. These defects are listed in Appendix C. No pattern of birth defects has been detected with didanosine or nelfinavir. The clinical relevance of this statistical finding is unclear. The Registry will continue to monitor didanosine and nelfinavir for any signal or pattern of birth defects.

A previously noted transient increase in rate of hypospadias cases from the addition of data from one large clinical study (WITS) has not persisted and detailed analysis does not confirm that signal. There are no additional cases of hypospadias with relevant exposure in this update.

For darunavir, didanosine, efavirenz, indinavir, raltegravir, rilpivirine, and stavudine, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date. For abacavir, atazanavir, emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, tenofovir disoproxil fumarate, and zidovudine sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date. (See table below for number of defects and prevalence per 100 live births for first trimester exposures to all drugs with sufficient data to warrant separate analysis. See Appendix A for additional data.) There are insufficient data to make similar comparisons for other drugs or specific subgroups of defects.

The Advisory Committee pays particular attention to findings from animal studies. Therefore, the Advisory Committee is closely monitoring first trimester exposures to efavirenz for anomalies including central nervous system defects. Defects have been reported in 22 among the 978 infants with first trimester exposure to efavirenz, including a single case of myelomeningocele and a single case of anophthalmia with severe oblique facial clefts and amniotic banding. During the July 2014 report period an undefined abnormality of the cerebellar vermis seen on prenatal ultrasound was reported. At birth, the infant's physical exam was normal. Upon February 2015 follow-up, it was reported that the infant was developing normally and that the parents have declined further imaging at this time. Without postnatal imaging, a central nervous system abnormality cannot be confirmed.

Figure 1: Summary of Birth Defects among First Trimester Exposures, Prospective Registry Cases Closed with Outcome through 31 January 2017



Supplemental Analyses

Retrospective Reports: Though the Registry is a prospective registry, data from retrospective reports (pregnancies with a known outcome at the time of reporting) are also reviewed to assist in the detection of any unusual patterns in birth defects. Retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population experience. Therefore, the calculation of prevalence from these reports is inappropriate. Isolated cases of neural tube defects with efavirenz exposure have been reported. No other pattern of defects (isolated or syndromic) has been found in the overall evaluation of retrospective reports and Registry cases of birth defects.

Clinical Studies: In the analysis of reports from clinical studies in pregnancy, 18 infants with defects were identified among 401 live births with first trimester exposures to an antiretroviral therapy. The prevalence of birth defects per 100 live births among women with first trimester exposures to an antiretroviral (primarily nucleoside reverse transcriptase inhibitors) is 4.5 (95% CI: 2.7 - 7.0) (Table 12). The number of defects identified with an initial exposure in the second or third trimester is 31 among 1892 live births, and the prevalence of birth defects per 100 live births is 1.6 (95% CI: 1.1 - 2.3). It is not surprising that the rate of detection of birth defects was relatively high among infants born to women enrolled in clinical studies conducted in pregnant women, as this group is often very different compared with either the CDC population-based surveillance system or the Registry. Differences include severity of disease at the time of maternal enrollment in clinical studies and rigorous infant follow-up and evaluation (e.g., echocardiography). In addition, women with first trimester exposures appeared to have more advanced disease. The higher rates of defects observed in clinical studies compared to the primary analysis are principally minor, spontaneously resolving cardiovascular defects that were detected on echocardiogram. To date, we have received 53 prospective cases of VSD, distributed across trimesters and drug exposures. Thus, the overall rate remains low and there is no apparent excess of cases among zidovudine or any drug exposure group or relevant trimester of exposure.

Reports from the Published Literature: There is a growing body of literature on the potential association between prenatal antiretroviral exposure and birth defects. The Registry attempts to identify

these studies through a systematic literature search conducted annually. The Registry has not identified a signal in any of the published studies reviewed to date.

Data Limitations

The Registry is designed to detect teratogenic effects of antiretroviral medications used in pregnancy. The occurrence of other developmental or functional defects is not systematically collected, although the Advisory Committee carefully reviews each pregnancy outcome received by the Registry. Potential limitations of registries such as this should be recognized. The limitations include, but are not limited to, underreporting (i.e., not every report of an exposure is obtained), differential reporting (i.e., there may be reasons why one report would be provided to the Registry and another would not), underascertainment of birth defects (i.e., not every birth defect is identified, e.g., reporter may not see the defect at birth), differential ascertainment of birth defects (e.g., variable use of diagnostic tests), and loss to follow-up (e.g., reports where no outcome information is obtained). Despite these limitations, such reports have been useful to supplement animal toxicology studies and clinical trial data, and to assist clinicians in weighing the risks and benefits of antiretroviral treatment during pregnancy and in counseling women with exposure during the first trimester. Moreover, accrual of additional patient experience over time will provide more definitive information regarding risks, if any, of exposure during pregnancy to the antiretroviral therapies followed in the Registry.

ADVISORY COMMITTEE CONSENSUS*

In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Given the emergence of new therapies about which data are still insufficient, health care providers are strongly encouraged to report eligible patients to the Registry at www.APRegistry.com.

PRÉCIS*

The Antiretroviral Pregnancy Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause; however, potential limitations of registries should be recognized. Providers are strongly encouraged to report eligible patients to www.APRegistry.com.

* Those wishing to cite data from this Report are encouraged to do so. However, to ensure consistency of reporting, you are required to include the consensus statement verbatim. Shorter presentations of Registry data (i.e., abstracts) may use the abbreviated précis. Editors should be reminded of this requirement and encouraged to exempt the sentence from any word count restrictions. Suggested citation: Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 1 January 2017. Wilmington, NC: Registry Coordinating Center; 2017. Available from URL: www.APRegistry.com.

SUMMARY OF CHANGES: JULY 2016 TO JANUARY 2017

Primary Prospective Analysis	***July 2016***	***January 2017***
Pregnancies Reported	20,833	21,287
Pending	317	274
Lost to follow-up	2175	2226
With follow-up data	18,341	18,787
Earliest Exposure		
1st trimester exposures	9210	9581
2nd trimester	6797	6853
3rd trimester	2331	2351
Unknown (defects only)	3	2
Outcomes		
Defects/Live births		
1st trimester	230/8227 2.8% (95% CI: 2.4% - 3.2%)	240/8583 2.8% (95% CI: 2.4% - 3.2%)
2nd/3rd trimester	252/9141 2.8% (95% CI: 2.4% - 3.1%)	254/9220 2.8% (95% CI: 2.4% - 3.1%)
Any trimester	484/17371 2.8% (95% CI: 2.5% - 3.0%)	496/17805 2.8% (95% CI: 2.5% - 3.0%)
1st to 2nd/3rdtrimester prevalence ratio	1.01 (95% CI: 0.85, 1.21)	1.02 (95% CI: 0.85, 1.21)
Defects/Live births - 1st trimester		
Lamivudine	144/4671 3.1% (2.6%, 3.6%)	145/4763 3.0% (2.6%, 3.6%)
Zidovudine	133/4144 3.2% (2.7%, 3.8%)	133/4161 3.2% (2.7%, 3.8%)
Tenofovir disoproxil fumarate	67/3007 2.2% (1.7%, 2.8%)	75/3229 2.3% (1.8%, 2.9%)
Ritonavir	65/2983 2.2% (1.7%, 2.8%)	67/3056 2.2% (1.7%, 2.8%)
Emtricitabine	54/2326 2.3% (1.7%, 3.0%)	60/2523 2.4% (1.8%, 3.1%)
Lopinavir	29/1384 2.1% (1.4%, 3.0%)	30/1400 2.1% (1.4%, 3.0%)
Atazanavir	25/1187 2.1% (1.4%, 3.1%)	26/1227 2.1% (1.4%, 3.1%)
Nelfinavir	47/1211 3.9% (2.9%, 5.1%)	47/1212 3.9% (2.9%, 5.1%)
Nevirapine	32/1124 2.8% (1.9%, 4.0%)	32/1134 2.8% (1.9%, 4.0%)
Abacavir	30/1031 2.9% (2.0%, 4.1%)	30/1063 2.8% (1.9%, 4.0%)
Efavirenz	22/934 2.4% (1.5%, 3.5%)	22/978 2.2% (1.4%, 3.4%)
Stavudine	21/811 2.6% (1.6%, 3.9%)	21/811 2.6% (1.6%, 3.9%)
Didanosine	20/426 4.7% (2.9%, 7.2%)	20/427 4.7% (2.9%, 7.2%)
Darunavir	10/385 2.6% (1.2%, 4.7%)	10/407 2.5% (1.2%, 4.5%)
Indinavir	7/289 2.4% (1.0%, 4.9%)	7/289 2.4% (1.0%, 4.9%)
Raltegravir	7/247 2.8% (1.1%, 5.8%)	7/263 2.7% (1.1%, 5.4%)
Rilpivirine	1/202 0.5% (0.0%, 2.7%)	3/247 1.2% (0.3%, 3.5%)
Clinical Studies in Pregnancy	***July 2016***	
1st trimester	16/373 4.3% (95% CI: 2.5% - 6.9%)	18/401 4.5% (95% CI: 2.7% - 7.0%)
2nd/3rd trimester	28/1822 1.5% (95% CI: 1.0% - 2.2%)	31/1892 1.6% (95% CI: 1.1% - 2.3%)
1st to 2nd/3rd trimester prevalence ratio	2.79 (95% CI: 1.53, 5.11)	2.74 (95% CI: 1.55, 4.85)

INTRODUCTION

The purpose of the Antiretroviral Pregnancy Registry (Registry) is to detect any major teratogenic effects of the following drugs to which pregnant women are exposed (1):

abacavir (ZIAGEN®, ABC), abacavir/lamivudine combination (EPZICOM®, EPZ), abacavir/lamivudine/zidovudine combination (TRIZIVIR®, TZV), abacavir/dolutegravir/lamivudine combination (TRIUMEQ®, TRI), adefovir dipivoxil (HEPSERA®, ADV)*, amprenavir (AGENERASE®, APV), atazanavir (REYATAZ®, ATV), atazanavir/cobicistat combination (EVOTAZ®, EVO), cobicistat (TYBOST®, COBI), darunavir (PREZISTA®, DRV), darunavir/cobicistat combination (PREZCOBIX™, PCX), delavirdine mesylate (RESCRIPTOR®, DLV), didanosine (VIDEX®, VIDEX® EC, DDI), dolutegravir (TIVICAY®, DTG), efavirenz (SUSTIVA®, STOCRIN®, EFV), efavirenz/emtricitabine/tenofovir disoproxil fumarate combination (ATRIPLA, ATR®), elvitegravir (VITEKTA®, EVG), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide combination (GENVOYA®, GEN), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate combination (STRIBILD®, STB), emtricitabine (EMTRIVA®, FTC), emtricitabine/tenofovir alafenamide combination (DESCOVY®, DVY), enfuvirtide (FUZEON®, T-20), entecavir (BARACLUDE®, ETV)*, etravirine (INTELENCE®, ETR), fosamprenavir calcium (LEXIVA®, FOS), indinavir (CRIXIVAN®, IDV), lamivudine (EPIVIR®, 3TC), lamivudine/raltegravir combination (DUTREBIS™, DUT), lamivudine/zidovudine combination (COMBIVIR®, ZDV+3TC), lopinavir/ritonavir combination (KALETRA®, ALUVIA®, LPV/r), maraviroc (SELZENTRY®, CENSENTRI®, MVC), nelfinavir (VIRACEPT®, NFV), nevirapine (VIRAMUNE®, VIRAMUNE® XR™, NVP), raltegravir (ISENTRESS®, RAL), rilpivirine (EDURANT®, RPV), rilpivirine/emtricitabine/tenofovir alafenamide combination (ODEFSEY®, ODE), rilpivirine/emtricitabine/tenofovir disoproxil fumarate combination (COMPLERA®, CPA; EVIPLERA®, EPA), ritonavir (NORVIR®, RTV), saquinavir (FORTOVASE®, SQV-SGC), saquinavir mesylate (INVIRASE®, SQV-HGC), stavudine (ZERIT®, d4T), telbivudine (SEBIVO®, TYZEKA®, LdT), tenofovir alafenamide (VEMLIDY®, TAF), tenofovir disoproxil fumarate (VIREAD®, TDF), tenofovir disoproxil fumarate/emtricitabine combination (TRUVADA®, TVD), tipranavir, (APTIVUS®, TPV), zalcitabine (HIVID®, ddC), and zidovudine (RETROVIR®, ZDV).

Zidovudine is indicated for use in the second and third trimesters of pregnancy to reduce the risk of maternal-fetal HIV transmission. There are also several other completed and ongoing studies in maternal-fetal transmission with other therapies. However, the safety of prenatal zidovudine or any other antiretroviral therapy exposure to the fetus has not been established.

Prospective tracking of fetal drug exposure during pregnancy, particularly newer agents and new combinations of therapies remains critically important in evaluating the safety of these agents among reproductive-age women and the exposed fetus. This study is an observational, exposure-registration and follow-up study. The study has had institutional review board (IRB) review and approval (see IRB Review, page 158). The IRB approval included a waiver from requiring patient informed consent for participation based on the Registry's process for protecting patient anonymity. Patient confidentiality is strictly upheld. The intent of the Registry is to collect data on prenatal exposures to drugs followed in the Registry, potential confounding factors (such as maternal age, disease status during pregnancy), and information related to the outcome of the pregnancy.

The Registry began as the *Zidovudine in Pregnancy Registry* in January 1989 and became the *Antiretroviral Pregnancy Registry* in January 1993. This report covers data through 31 January 2017.

* These drugs are not indicated for HIV, but are in the same class as other antiretroviral drugs in the Registry. The inclusion of these drugs allows evaluation of teratogenic risk of drugs in the same class as well as similar classes.

The Antiretroviral Pregnancy Registry is managed by INC Research, LLC under the sponsorship of AbbVie, Alvogen Inc, Amneal Pharmaceuticals LLC, Apotex Inc, Aurobindo Pharma Ltd, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Dr. Reddy's Laboratories (UK) Ltd, F.Hoffmann-La Roche, Gilead Sciences Inc, Hetero Labs Ltd, Janssen Scientific Affairs, LLC, Lupin Pharmaceuticals, Merck & Co. Inc, Mylan Laboratories, Novartis Pharmaceuticals, Prinston, Ranbaxy Inc (a Sun Pharma Company), Sandoz Inc, ScieGen Pharmaceuticals Inc, SigmaPharm Laboratories, Silarx Pharmaceuticals Inc, Strides Shasun Ltd, Sunshine Lake Pharma, Teva Pharmaceuticals, ViiV Healthcare, and West-Ward Pharmaceuticals. The scientific conduct and analysis of the Registry are overseen by an independent Advisory Committee consisting of members from the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the private sector. Members include specialists in maternal and fetal medicine, teratology, infectious disease, epidemiology, and biostatistics. The Advisory Committee reviews the Registry data, develops the Consensus Statement, provides recommendations on modifications or enhancements to the Registry, and assists in the dissemination of information and formulation of strategies to encourage enrollment in the Registry. The Advisory Committee and the Sponsor Company representatives constitute the Steering Committee, which jointly manages the general conduct of the Registry.

This Registry is intended to provide an early signal of teratogenicity associated with prenatal use of the drugs monitored through the Registry. The FDA's revised Pregnancy and Lactation Labeling Rule (PLLR), 21 CFR 201.57 Subpart B, published 04 December 2014, will eliminate the current pregnancy letter categories over the next three to five years (8). See Appendix D for information on each drug. One limitation of an exposure-registration study is that rates of drug-associated adverse events cannot be extrapolated to reflect true rates in the potential target population. Because reports of exposures are voluntary, they are subject to numerous potential selection biases. Information on possible teratogenic risk, which may be associated with perinatal HIV infection or with risk behaviors associated with maternal HIV infection, is currently insufficient. An analysis of relative risk comparing the antiretroviral drugs being monitored in the Registry to risks in the absence of drug exposure requires carefully designed epidemiologic studies, including a comparison population of pregnant women with a history of human immunodeficiency virus (HIV) disease not exposed to antiretroviral medications during pregnancy. The Registry is only one component of the overall plan for close monitoring of these medications; therefore, interpretation of information generated through this Registry must be made with caution.

This Interim Report contains analyses of voluntary, prospective reports (i.e., those reports made to the Registry prior to the outcome of pregnancy being known) of prenatal exposures to abacavir, adefovir dipivoxil, amprenavir, atazanavir, cobicistat, darunavir, delavirdine mesylate, didanosine, efavirenz, elvitegravir, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, stavudine, telbivudine, tenofovir alafenamide, tenofovir disoproxil fumarate, tipranavir, zalcitabine, and zidovudine. Prospective reports are subject to fewer biases than retrospective reports (i.e., reports made after the pregnancy outcome is known either through prenatal testing or at outcome of pregnancy). Data from retrospective reports are collected and the outcomes reviewed and evaluated; however, due to the greater potential for bias, these reports are evaluated separately. Additionally, the Registry receives information on women who are enrolled in clinical studies in pregnancy. These reports may be received sporadically through the voluntary reporting process or systematically on every case in the trial from a single source. The differences in the sources of information for the clinical study reports and, in some cases, the country where the study was conducted may make pooling these data for analysis inappropriate. However, for expediency in displaying the information in the report tables, the data are pooled. These study reports are not comparable directly to the prospective Registry reports as the inclusion/exclusion criteria, severity of disease, and length and intensity of follow-up may differ significantly.

Each year the Registry has enrolled approximately 1300 pregnant women in the US exposed to antiretroviral drugs. This number represents approximately 15% of the 8,700 HIV positive women who give birth to live infants annually in the US (2). Each year, the Registry also enrolls approximately 200 pregnant women from other countries. Given the emergence of newer therapies used for treatment and prevention for which there is an ongoing need for evidence of their safety in pregnancy, sustained reporting is vital to the registry's ability to fulfill its mission of early detection of a birth defect signal, if present. Health care providers are strongly encouraged to continue reporting eligible patients to the Registry.

Included in the primary analysis, beginning with the January 2008 Interim Report, are data from 2106 exposed pregnancies (and 2143 pregnancy outcomes) from the Women and Infants Transmission Study (WITS) (9) and, beginning with the July 2010 Interim Report, are data on 995 exposed pregnancies with outcomes from the NISDI Perinatal Study (10). Also included in the primary analysis are 72 cases from a prospective study in Botswana. The rationale for these inclusions is described on pages 19 and 27, respectively.

REGISTRY (PROSPECTIVE) CASES – PRIMARY ANALYSIS

Through 31 January 2017 there were 21287 prospective cases reported to the Registry (Table 1). There were 274 cases pending the outcome of pregnancy and 2226 lost to follow-up. Thus, there were 18787 evaluable prospective reports included in the primary analysis. Table 2 displays information on maternal characteristics including median age and clinical status indicators for cases included in the primary analysis and those lost to follow-up.

The Antiretroviral Pregnancy Registry is an international registry, and has received reports from 71 countries. Reports are predominantly from the United States and its territories (76.1%). Reports from countries outside the US comprising ≥0.1% of enrollments include: the United Kingdom (4.5%), Brazil (3.7%), Uganda (3.5%), Argentina (2.4%), South Africa (1.4%), France (1.0%), China (0.8%), Germany (0.6%), Kenya (0.6%), Botswana (0.5%), Ivory Coast (0.5%), Zimbabwe (0.5%), Canada (0.4%), Australia (0.3%), Malawi (0.3%), Thailand (0.3%), Belgium (0.2%), Denmark (0.2%), Russian Federation (0.2%), Scotland (0.2%), Spain (0.2%), Cameroon (0.1%), India (0.1%), Ireland (0.1%), Italy (0.1%), Japan (0.1%), Portugal (0.1%), Sweden (0.1%), Switzerland (0.1%), and The Netherlands (0.1%). Countries that have contributed <0.1% of enrollments include Austria, Bulgaria, Burkina Faso, Chile, Colombia, Costa Rica, Croatia, Dominican Republic, Ethiopia, Finland, Ghana, Greece, Guatemala, Haiti, Hong Kong, Hungary, Iceland, Indonesia, Israel, Korea, Lithuania, Malaysia, Mexico, New Zealand, Nigeria, Norway, Panama, Peru, Philippines, Poland, Romania, Saudi Arabia, Senegal, Singapore, Taiwan, Tanzania, Turkey, United Arab Emirates, Uruguay, and Zambia.

Antiretroviral Exposure

Of the 18787 evaluable prospective reports, 9581 were first trimester exposures to one or more of the antiretroviral drugs followed in the Registry. Table 3 displays the single and combination treatment regimens by class of antiretroviral therapy and by earliest trimester of exposure. Appendix A lists all of the single and combination therapies taken by earliest trimester of exposure. Some individuals may have received other therapies in a later trimester. Of the 18787 pregnancies reported, there were 19112 outcomes of pregnancy including 320 multiple births: 17805 live births, 571 spontaneous abortions, 225 stillbirths, and 511 induced abortions. Of the 17805 live births, 8583 had a maternal exposure to antiretroviral therapy during the first trimester. It should be noted that there were 1674 live births involving a maternal exposure to any single class of antiretroviral therapy during the first trimester. There may have been an exposure to more than one therapy within the class in the first trimester or to other therapies in other classes in other trimesters.

Table 1: Population for Analysis – Prospective Registry Cases Enrolled Through 31 January 2017

	Overall
Pregnancies Enrolled	21287
Pending Cases [1]	274 (1.3%)
Cases Lost to Follow-up [2]	2226 (10.5%)
Reports Used in Analysis	18787 (88.3%)

[1] Cases where the outcome of pregnancy is not yet known.
[2] Cases where the outcome of pregnancy has never been received despite requests or if the reporter did not know whether there was a birth defect.

Table 2: Maternal Demographics at Registration – Prospective Registry Cases Closed Through 31 January 2017

	Primary Analysis	Lost to Follow-up
Pregnancies Enrolled	18787	2226
Age (years)		
N	18556	1881
Median (Interquartile Range)	28.0 (9.0)	28.0 (8.0)
Min - Max	13 - 55	15 - 50
Missing	231	345
Indication for ARV at Start of Pregnancy		
HIV Infected [1]	17148 (91.3%)	1219 (54.8%)
HIV Uninfected [2]	313 (1.7%)	102 (4.6%)
Post-Exposure Prophylaxis (PEP)	2 (0.0%)	3 (0.1%)
Pre-Exposure Prophylaxis (PrEP)	56 (0.3%)	13 (0.6%)
Hepatitis B mono-infected	393 (2.1%)	201 (9.0%)
Unknown	446 (2.4%)	339 (15.2%)
Missing	480 (2.6%)	365 (16.4%)
Clinical Indicators		
CD4+ T-cell Categories at Start of Pregnancy		
≥ 500 cells/µL	5818 (31.0%)	476 (21.4%)
200-499 cells/µL	7613 (40.5%)	547 (24.6%)
<200 cells/µL	2748 (14.6%)	181 (8.1%)
Unknown	581 (3.1%)	213 (9.6%)
N/A	575 (3.1%)	433 (19.5%)
Missing	1452 (7.7%)	376 (16.9%)
Worst Disease Severity by History		
HIV		
A. Asymptomatic, acute (primary) HIV or PGL	13182 (70.2%)	921 (41.4%)
B. Symptomatic, not (A) or (C) conditions	1303 (6.9%)	74 (3.3%)
C. Other AIDS-indicator conditions	2221 (11.8%)	151 (6.8%)
D. CD4 < 200 cells/µL	357 (1.9%)	25 (1.1%)
Not applicable	203 (1.1%)	50 (2.2%)
Unknown	538 (2.9%)	396 (17.8%)
Missing	728 (3.9%)	523 (23.5%)
Hepatitis B		
Compensated liver disease (Pugh score < 7)	509 (2.7%)	68 (3.1%)
Compensated liver disease (Pugh score ≥ 7)	6 (0.0%)	4 (0.2%)
Unknown	9220 (49.1%)	759 (34.1%)
Not applicable	565 (3.0%)	388 (17.4%)
Missing	8487 (45.2%)	1007 (45.2%)

[1] Includes 188 patients co-infected with HIV and Hepatitis B. Includes 237 patients co-infected with HIV and Hepatitis C.
[2] Where antiretroviral drugs have been used for prophylaxis.
Note: The Registry started systematically collecting data on Hepatitis B in January 2003.
Note: The Registry began collecting data to distinguish between pre- and post-exposure prophylaxis in December 2013.

Table 3: Summary of Antiretroviral Treatment Classes [1] by Trimester of Earliest Exposure [2] – Prospective Registry Cases with Follow-up Data Closed Through 31 January 2017

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies in Primary Analysis	9581	6853	2351	18787
PI	118	21	2	142
NRTI	1513	1717	710	3940
nnRTI	45	4	2	51
NtRTI	241	12	64	317
InSTI	4	3	0	7
PI/NRTI	2499	3314	949	6762
PI/nnRTI	17	1	0	18
PI/NtRTI	14	1	0	15
PI/InSTI	50	2	0	52
NRTI/nnRTI	1228	789	318	2336
NRTI/NtRTI	465	36	21	522
NRTI/InSTI	45	18	6	69
PI/NRTI/nnRTI	262	90	34	386
PI/NRTI/NtRTI	1688	564	139	2391
PI/NRTI/EI	9	0	0	9
PI/NRTI/InSTI	25	2	8	35
PI/nnRTI/NtRTI	8	0	0	8
PI/nnRTI/InSTI	16	3	0	19
PI/NtRTI/InSTI	7	0	0	7
PI/EI/InSTI	5	0	0	5
NRTI/nnRTI/NtRTI	685	156	29	870
NRTI/NtRTI/InSTI	121	38	17	176
PI/NRTI/nnRTI/NtRTI	239	14	10	263
PI/NRTI/NtRTI/EI	12	1	0	13
PI/NRTI/NtRTI/InSTI	66	24	24	114
PI/NRTI/NtRTI/PKE	7	1	0	8
NRTI/nnRTI/NtRTI/InSTI	19	6	5	30
NRTI/NtRTI/InSTI/PKE	114	22	7	143
PI/NRTI/nnRTI/NtRTI/InSTI	7	2	2	11
PI/NRTI/NtRTI/EI/InSTI	6	0	0	6
PI/NRTI/NtRTI/InSTI/PKE	13	1	2	16
Other Combination	33	11	2	46

[1] PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, telbivudine, zalcitabine, and zidovudine.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, etravirine, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, tenofovir alafenamide, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes dolutegravir, elvitegravir, and raltegravir.
PKE=pharmacokinetic enhancer, which includes cobicistat.
[2] Exposures represent earliest trimester of exposure to an antiretroviral drug. Pregnant women may have been on other medications during the pregnancy.
Note: Treatment regimens for which no exposures were reported are excluded from the table.
Note: Treatment regimens with fewer than 5 exposures have been collapsed into the Other category.
Note: Due to unknown trimester of exposure data for 2 case(s), the specific counts may not sum to the overall total.

Pregnancy Outcomes

Of the 9745 birth outcomes with a 1st trimester exposure to an antiretroviral drug, there were 240 reports of defects (224 defects in live births, 8 in stillbirths, and 8 in induced abortions occurring ≥ 20 weeks gestation). See Table 4.

The Registry defines a defect as any major structural or chromosomal defect or two or more conditional defects occurring in an infant or fetus of at least 20 weeks gestational age. This definition differs from the public health surveillance protocols by considering reports of 2 or more conditional defects alone as a defect case, so as to cast as broad a net as possible for outcomes that may be associated with antiretroviral medication use. (See *Classification of Outcomes, page 161.*) Therefore, Table 4 excludes reports of only one conditional defect or defects identified in a fetal loss occurring earlier than 20 weeks gestation. See Appendix C for the list of defects reported to the Registry and classified by the Registry as defects. To facilitate the recognition of a potential signal, the Registry has developed an organ system classification system which removes some of the granularity in looking at individual defects by grouping similar defects or defects of similar etiology together (10). See Appendix F for further description of the system.

Of the 19112 pregnancy outcomes, 9365 were in the combined second and/or third trimester exposure group, with 254 reported birth defects (Table 4). This includes 2436 live births with a second and/or third trimester exposure in the NRTI(s) only exposure group, with 69 defect reports (data not shown in table). The live birth outcomes in the other exposure classifications were as follows: for the PI + NRTI group there were 118 defects of 4264 live births; for the NRTI + NNRTI group, 33 defects of 1104 births; for the PI + NRTI + NNRTI group, 6 defect of 126 births and in the other combination groups of 1183 live births there were 28 defects reported. See Appendix C, which lists all defect cases reported to the Registry with an exposure in any trimester. In a continued effort to provide useful information to providers, where possible, an assessment of temporal association between the exposure to antiretroviral therapy and the stage of fetal development during which the defect is apt to occur is included in Appendix C. The temporality assessments are made by a consultant medical geneticist with agreement by the Advisory Committee.

Comparator Analysis

The primary analysis of the APR's prospective cohort includes two comparisons. The overall rates of defects are compared with rates from two external comparator populations, the Metropolitan Atlanta Congenital Defects Program (MACDP) and the Texas Birth Defects Registry (TBDR). For individual drugs, an internal comparison is made between the rates of defects among first trimester exposed pregnancies and the rates among pregnancies with the same exposures beginning in the second or third trimester. Detailed descriptions of these comparisons and the comparison registries are included in the Methods section of this report (Appendix F: Methods). Briefly, the MACDP and the TBDR are active population-based surveillance systems. The MACDP covers all deliveries among residents of five counties of the metropolitan Atlanta area with approximately 50,000 annual births in a population of about 2.9 million (3, 4, and 5). The TBDR monitors all deliveries to women who are residents of the state of Texas at the time of delivery including approximately 400,000 live births annually (7). The Registry is aware of the need for further comparison populations, particularly from outside the United States; several remain under consideration.

Table 5 provides a summary of first and second/third trimester exposures to each antiretroviral drug alone or in combination and displays the proportion of birth defects reported for each of the exposures. Exposures are not mutually exclusive. For instance, the defects identified for zidovudine may be the same as some of those identified for lamivudine in the cases where both therapies were used in the first trimester.

For the overall population exposed to antiretroviral drugs in this Registry, no increases in risk of overall birth defects or specific defects have been detected to date when compared with observed rates for “early diagnoses” in population-based birth defects surveillance systems or with rates among those with earliest exposure in the second or third trimester. In analyzing individual drugs with sufficient data to warrant a separate analysis, no increases in risk have been detected with the exception of didanosine and nelfinavir. For these there is a modest but statistically significant increase in overall rates of defects when compared with the population based MACDP, but not TBDR (lower bound of the confidence interval for didanosine (2.9%) and nelfinavir (2.9%) is slightly above the higher bound (2.76%) for the comparator MACDP rate), although these rates are not increased between trimesters for these drugs. The didanosine and nelfinavir rates are also statistically significantly higher than birth defect rates for other drugs. These defects are listed in Appendix C. No pattern of birth defects has been detected with didanosine or nelfinavir. The clinical relevance of this statistical finding is uncertain. The Registry will continue to monitor didanosine and nelfinavir for any other signals or pattern of birth defects.

For darunavir, didanosine, efavirenz, indinavir, raltegravir, rilpivirine, and stavudine, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date. For abacavir, atazanavir, emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, tenofovir disoproxil fumarate, and zidovudine, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date with the exception of hypospadias following first trimester exposure to zidovudine from the addition of the WITS data.

The rates of hypospadias in first trimester exposed infants were statistically increased over those with only later exposures, the primary screening analysis of the Registry. This possible signal prompted more detailed and controlled analyses, in accordance with the Registry protocol. These analyses compared infants from women with similar first trimester exposure to other antiretrovirals without zidovudine/lamivudine; no increase was observed. Also, there is no elevation of hypospadias rates among those with the exposure under analysis in comparison with MACDP or the TBDR.

To date, four cases of micropenis with relevant first trimester exposure have been reported. The relationship between micropenis and hypospadias is unclear. An additional case of hypospadias reported in this period was without exposure to zidovudine. No changes in statistical significance of the hypospadias signal have emerged.

Thus, the Registry concludes that the data do not support a causal relationship between zidovudine/lamivudine exposure and hypospadias. The disappearance of the increase in more sophisticated analyses suggests that the increase may be related to other factors.

The Registry will continue to monitor this finding closely and provide updated reports as the situation clarifies. Reporters observing hypospadias in infants with any antiretroviral exposure are asked to report the nature and extent of the hypospadias and details of other maternal drug exposure to assist in further understanding.

Exposures in the first trimester to other antiretroviral therapies are of insufficient size to support a separate analysis. As the number of other specific therapy cases increases, evaluations of exposures to these therapies will be conducted. The Advisory Committee regularly reviews exposures to therapies alone and in combination. Comparative groups have been constructed for convenience of presentation. As an individual medication may be a larger contributor to a given group and dilute any potential signal, the Advisory Committee always reviews individual drug exposures alone and in combination with other agents.

The Advisory Committee pays particular attention to findings from animal studies. Therefore, the Advisory Committee is closely monitoring first trimester exposures to efavirenz for anomalies including central nervous system defects. Defects have been reported in 22 (2.2%, 95%CI, 1.4%, 3.4%) among the 978 infants with first trimester exposure to efavirenz. A single case of myelomeningocele has been noted previously. During the July 2008 reporting period, the Registry received a first case of anophthalmia, a defect reported in a study in monkeys. However, this case also included severe oblique facial clefts and amniotic banding, known to be associated with anophthalmia. During the July 2014 report period an undefined abnormality of the cerebellar vermis seen on prenatal ultrasound was reported. At birth, the infant's physical exam was normal. Upon February 2015 follow-up, it was reported that the infant was developing normally and that the parents have declined further imaging at this time. Without postnatal imaging, a central nervous system abnormality cannot be confirmed.

Table 6 lists the frequencies of defects reported by organ system for prospectively reported first trimester antiretroviral exposures in combination or single treatment regimen. The organ system classifications have been redefined to better categorize the defects to be consistent with the MACDP and the TBDR classifications and to increase the potential to identify a possible pattern or signal (11). Further refinements are ongoing.

Table 4: Summary of Pregnancy Outcomes [1] By Antiretroviral Treatment Regimen [2] – Prospective Registry Cases with Follow-up Data Closed Through 31 January 2017

	With Birth Defects[3] : Without Birth Defects[4]				
	Live Births	Spontaneous Losses	Still-births	Induced Abortions	Overall
Number of Outcomes [5]	468 : 17337	0 : 571	15 : 210	13 : 498	19112
Earliest Exposure [6]					
First Trimester	224 : 8359	0 : 544	8 : 114	8 : 488	9745
Second/Third Trimester	242 : 8978	0 : 27	7 : 96	5 : 10	9365
First Trimester					
PI	2 : 97	0 : 11	0 : 0	0 : 8	118
NRTI	42 : 1309	0 : 45	1 : 14	2 : 124	1537
nnRTI	0 : 37	0 : 2	0 : 0	0 : 6	45
NtRTI	3 : 181	0 : 34	0 : 0	0 : 24	242
EI	0 : 1	0 : 0	0 : 0	0 : 0	1
InSTI	0 : 2	0 : 0	0 : 0	0 : 2	4
PI/NRTI	66 : 2255	0 : 90	5 : 28	1 : 97	2542
PI/nnRTI	0 : 8	0 : 3	0 : 1	0 : 5	17
PI/NtRTI	0 : 12	0 : 0	0 : 2	0 : 1	15
PI/EI	0 : 4	0 : 0	0 : 0	0 : 0	4
PI/InSTI	2 : 38	0 : 7	0 : 0	0 : 3	50
PI/PKE	0 : 1	0 : 0	0 : 0	0 : 0	1
NRTI/nnRTI	31 : 1079	0 : 73	0 : 19	0 : 53	1255
NRTI/NtRTI	11 : 320	0 : 69	0 : 18	0 : 52	470
NRTI/EI	1 : 0	0 : 0	0 : 0	0 : 0	1
NRTI/InSTI	1 : 40	0 : 3	0 : 0	0 : 2	46
nnRTI/NtRTI	0 : 1	0 : 0	0 : 0	0 : 0	1
nnRTI/InSTI	0 : 1	0 : 0	0 : 0	0 : 0	1
NtRTI/InSTI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/NRTI/nnRTI	10 : 215	0 : 23	0 : 3	1 : 10	262
PI/NRTI/NtRTI	37 : 1533	0 : 93	0 : 14	1 : 52	1730
PI/NRTI/EI	0 : 6	0 : 2	0 : 0	0 : 1	9
PI/NRTI/InSTI	0 : 21	0 : 2	0 : 1	0 : 2	26
PI/NRTI/PKE	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/nnRTI/NtRTI	1 : 4	0 : 0	0 : 2	0 : 1	8
PI/nnRTI/EI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/nnRTI/InSTI	0 : 14	0 : 2	0 : 1	0 : 0	17
PI/NtRTI/EI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/NtRTI/InSTI	0 : 7	0 : 0	0 : 0	0 : 0	7
PI/EI/InSTI	0 : 5	0 : 0	0 : 0	0 : 0	5
NRTI/nnRTI/NtRTI	11 : 609	0 : 47	1 : 8	1 : 19	696
NRTI/NtRTI/EI	0 : 2	0 : 0	0 : 0	0 : 0	2
NRTI/NtRTI/InSTI	4 : 104	0 : 8	1 : 0	1 : 5	123
NRTI/EI/InSTI	0 : 1	0 : 0	0 : 0	0 : 0	1
nnRTI/EI/InSTI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/NRTI/nnRTI/NtRTI	0 : 216	0 : 15	0 : 1	1 : 8	241
PI/NRTI/nnRTI/InSTI	0 : 2	0 : 0	0 : 0	0 : 0	2
PI/NRTI/NtRTI/EI	0 : 11	0 : 0	0 : 0	0 : 1	12
PI/NRTI/NtRTI/InSTI	0 : 52	0 : 8	0 : 0	0 : 6	66
PI/NRTI/NtRTI/PKE	0 : 7	0 : 0	0 : 0	0 : 0	7
PI/NRTI/EI/InSTI	0 : 1	0 : 0	0 : 0	0 : 1	2
PI/nnRTI/NtRTI/EI	0 : 1	0 : 1	0 : 0	0 : 0	2
PI/nnRTI/InSTI/PKE	0 : 0	0 : 1	0 : 0	0 : 0	1
NRTI/nnRTI/NtRTI/EI	0 : 1	0 : 0	0 : 0	0 : 0	1
NRTI/nnRTI/NtRTI/InSTI	0 : 19	0 : 1	0 : 0	0 : 0	20
NRTI/NtRTI/EI/InSTI	0 : 3	0 : 0	0 : 0	0 : 0	3
NRTI/NtRTI/InSTI/PKE	2 : 106	0 : 3	0 : 2	0 : 3	116
PI/NRTI/nnRTI/NtRTI/InSTI	0 : 7	0 : 0	0 : 0	0 : 0	7
PI/NRTI/NtRTI/EI/InSTI	0 : 6	0 : 0	0 : 0	0 : 0	6
PI/NRTI/NtRTI/InSTI/PKE	0 : 12	0 : 1	0 : 0	0 : 0	13
NRTI/nnRTI/NtRTI/InSTI/PKE	0 : 2	0 : 0	0 : 0	0 : 1	3
PI/NRTI/nnRTI/NtRTI/InSTI/PKE	0 : 1	0 : 0	0 : 0	0 : 1	2

[1] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion.
[2] PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, telbivudine, zalcitabine, and zidovudine.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, etravirine, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, tenofovir alafenamide, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes dolutegravir, elvitegravir, and raltegravir.
PKE=pharmacokinetic enhancer, which includes cobicistat.
[3] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[4] Includes cases where the occurrence of a birth defect was not reported.
[5] Includes 320 multiple births.
[6] Data is not included for birth defect cases with an unknown trimester of exposure.
Note: Treatment regimens for which no exposures were reported are excluded from the table.

Table 5: Number of Birth Defects [1] By Trimester of Earliest Exposure to Each Drug – Prospective Registry Cases with Follow-Up Data Closed Through 31 January 2017
Individuals may appear in more than one category, as exposures are not mutually exclusive

	Earliest Trimester of Exposure			
	First Trimester		Second/Third Trimester	
	Defects/ live births	Prevalence (95% CI) [2]	Defects/ live births	Prevalence (95% CI) [2]
Proportion of defects reported with an exposure to any ART [3]	240/8583		254/9220	
Proportion of defects reported with an exposure to: [3,4]				
Any PI containing regimen	127/4657		174/5902	
Any Amprenavir regimen	1/29		0/12	
Any Atazanavir regimen	26/1227	2.1% (1.4%, 3.1%)	17/678	2.5% (1.5%, 4.0%)
Any Darunavir regimen	10/407	2.5% (1.2%, 4.5%)	5/246	2.0% (0.7%, 4.7%)
Any Fosamprenavir calcium regimen	2/109		2/36	
Any Indinavir regimen	7/289	2.4% (1.0%, 4.9%)	3/163	1.8% (0.4%, 5.3%)
Any Lopinavir regimen	30/1400	2.1% (1.4%, 3.0%)	76/2518	3.0% (2.4%, 3.8%)
Any Nelfinavir regimen	47/1212	3.9% (2.9%, 5.1%)	86/2733	3.1% (2.5%, 3.9%)
Any Ritonavir regimen	67/3056	2.2% (1.7%, 2.8%)	99/3367	2.9% (2.4%, 3.6%)
Any Saquinavir regimen	7/182		9/221	
Any Tipranavir regimen	0/4		0/2	
Any NRTI containing regimen	232/8157		257/9236	
Any Abacavir regimen	30/1063	2.8% (1.9%, 4.0%)	35/1271	2.8% (1.9%, 3.8%)
Any Didanosine regimen	20/427	4.7% (2.9%, 7.2%)	20/462	4.3% (2.7%, 6.6%)
Any Emtricitabine regimen	60/2523	2.4% (1.8%, 3.1%)	23/1142	2.0% (1.3%, 3.0%)
Any Entecavir regimen [5]	2/58		0/2	
Any Lamivudine regimen	145/4763	3.0% (2.6%, 3.6%)	209/7326	2.9% (2.5%, 3.3%)
Any Stavudine regimen	21/811	2.6% (1.6%, 3.9%)	6/196	3.1% (1.1%, 6.6%)
Any Telbivudine regimen [5]	2/59		0/11	
Any Zalcitabine regimen	2/41		0/12	
Any Zidovudine regimen	133/4161	3.2% (2.7%, 3.8%)	266/9451	2.8% (2.5%, 3.2%)
Any nnRTI containing regimen	57/2272		53/1827	
Any Delavirdine regimen	0/11		0/3	
Any Efavirenz regimen [6]	22/978	2.2% (1.4%, 3.4%)	3/196	1.5% (0.3%, 4.4%)
Any Etravirine regimen	1/62		0/37	
Any Nevirapine regimen	32/1134	2.8% (1.9%, 4.0%)	49/1520	3.2% (2.4%, 4.2%)
Any Rilpivirine regimen	3/247	1.2% (0.3%, 3.5%)	2/143	1.4% (0.2%, 5.0%)
Any NtRTI containing regimen	75/3288		30/1485	
Any Adefovir dipivoxil regimen [5]	0/55		0/2	
Any Tenofovir Alafenamide regimen	1/8		0/10	
Any Tenofovir Disoproxil Fumarate regimen	75/3229	2.3% (1.8%, 2.9%)	30/1480	2.0% (1.4%, 2.9%)

Table 5 continued:

Number of Birth Defects [1] By Trimester of Earliest Exposure to Each Drug – Prospective Registry Cases with Follow-Up Data Closed Through 31 January 2017

Individuals may appear in more than one category, as exposures are not mutually exclusive

	Earliest Trimester of Exposure			
	First Trimester		Second/Third Trimester	
	Defects/ live births	Prevalence (95% CI) [2]	Defects/ live births	Prevalence (95% CI) [2]
Proportion of defects reported with an exposure to any ART [3]	240/8583		254/9220	
Proportion of defects reported with an exposure to: [3,4]				
Any EI containing regimen	1/46		0/20	
Any Enfuvirtide regimen	0/21		0/15	
Any Maraviroc regimen	1/26		0/5	
Any InSTI containing regimen	11/455		10/333	
Any Dolutegravir regimen	2/77		2/56	
Any Elvitegravir regimen	2/120		0/38	
Any Raltegravir regimen	7/263	2.7% (1.1%, 5.4%)	8/250	3.2% (1.4%, 6.2%)
Any PKE containing regimen	2/132		0/42	
Any Cobicistat regimen	2/132		0/42	

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[2] Prevalence and 95% confidence intervals are reported for drugs with a denominator of >= 200 first trimester exposed live births.
[3] Proportion of defects calculated by dividing the number of defects meeting the CDC Criteria by the number of live births reported.
[4] There were 89 outcomes with an exposure to a medication occurring in an unknown trimester. These cases are excluded where trimester is unknown, however they may be represented in a known trimester to another medication.
[5] For treatment of HBV.
[6] The 22 infants with defects reported with first trimester exposure to efavirenz had the following defects:
1) polydactyly, 2) hydronephrosis, 3) bilateral hip dislocation and umbilical hernia, 4) bilateral hip dislocation, 5) urinary obstruction, duplicated right collecting system with obstructed upper pole moiety, possibly associated with vesicoureteral reflux, 6) polydactyly, 7) long bones malformation, 8) sacral myelomeningocele and hydrocephalus with fetal alcohol syndrome, 9) shortening of right leg, 10) cutis aplasia (scalp), 11) hip dysplasia and pulmonary stenosis, 12) bilateral facial cleft, anophthalmia and amniotic band, 13) postaxial polydactyly both hands, 14) unspecified heart anomaly, 15) Klinefelter, 47, XXY, 16) patent ductus arteriosus and nevus, 17) congenital hydronephrosis and variations of vesicoureteral reflux, 18) polydactyly, 19) undefined abnormality of the cerebellar vermis, 20) trisomy 21 and AV septal defect, 21) postaxial skin tag of left hand and foot, and 22) polydactyly.

Note: For each exposure category (drug classification) counts represent the number of outcomes with at least one exposure in that classification, though other classes of ARTs could have been included in the regimen. Additionally, any individual ART may have been used in combination with other ARTs, therefore, the counts represent the number of exposures to the individual ART contained in the regimen. Hence, counts are not mutually exclusive across classifications or individual ART.

Note: Data is not included for birth defect cases with an unknown trimester of exposure.

Table 6: Summary of Birth Defects [1] By Organ System and Antiretroviral Treatment Regimen – All Prospective Registry Cases with Follow-up Data Closed Through 31 January 2017

	Earliest Antiretroviral Therapy (ART) Exposure in First Trimester								
	Any PI(s) [3]	Any NRTI(s) [3]	Any NNRTI(s) [3]	Any NtRTI(s) [3]	Any EI(s) [3]	Any InSTI(s) [3]	Any PKE (s) [3]	Overall First Tri-mester Exposure	Earliest ART Exposure in Second and/or Third Trimester
Pregnancies Identified	5085	9041	2541	3728	52	515	142	9581	9204
Number of Pregnancies with Multiple Gestations	90	159	40	67	0	8	2	162	158
Number of Outcomes [2]	5175	9202	2583	3795	52	523	144	9745	9365
Number of Live Births	4657	8157	2272	3288	46	455	132	8583	9220
Number of Outcomes with Defects [1,2]	127	232	57	75	1	11	2	240	254
CNS	8	15	4	4	0	0	0	15	27
Eye, ear, face and neck	15	27	5	8	0	2	0	29	33
Cleft lip and/or palate	6	11	1	5	0	2	0	11	16
Conotruncal heart defects	5	8	1	4	0	1	0	8	9
Obstructive heart defects - right sided	5	8	4	3	0	1	1	9	13
Obstructive heart defects - left sided	4	6	1	3	0	1	1	6	6
Heart - other defects	25	46	12	12	0	4	1	46	60
Other circulatory system	10	18	5	7	0	1	0	18	15
Respiratory system	0	1	0	0	0	0	0	1	1
Upper gastrointestinal system	1	3	0	0	0	0	0	3	3
Lower gastrointestinal system	7	7	0	1	0	1	0	9	6
Female genitalia	3	5	0	3	0	0	0	5	1
Male genitalia	13	25	2	4	0	0	0	27	11
Renal and urinary system	16	27	6	12	0	1	0	27	22
Limb reduction/addition defects	20	32	7	18	0	3	1	34	40
Other musculoskeletal defects	19	54	17	16	1	3	0	55	58
Skin and skin derivatives	5	7	3	2	0	0	0	7	11
Chromosome anomaly	15	21	6	11	0	2	0	23	23
Other organs and organ systems	10	12	3	4	0	1	0	13	8
Specified syndromes/sequences/associations	11	18	2	7	0	1	0	19	11

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[2] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion.
[3] PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, telbivudine, zalcitabine, and zidovudine.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, etravirine, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, tenofovir alafenamide, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes dolutegravir, elvitegravir, and raltegravir.
PKE=pharmacokinetic enhancer, which includes cobicistat.
Note: For each organ system, counts represent the number of outcomes with at least one defect occurring in that organ system. For each defect, counts represent the number of outcomes manifesting at least one occurrence of the defect. Hence, counts are not mutually exclusive across organ systems.
Note: The cardiovascular organ systems reflect separate types of structural heart defects therefore, it is not appropriate to add them together.
Note: Data is not included for birth defect cases with an unknown trimester of exposure.

In summary, Table 7 shows that the prevalence of birth defects per 100 live births among women with a first trimester exposure to any of the antiretroviral therapies included in the Registry is 240 outcomes with defects among 8583 live births or 2.8% (95% CI: 2.4 - 3.2). Measured against 17805 live births with exposure at any time during pregnancy, there were 496 outcomes with birth defects, a prevalence of 2.8 birth defects per 100 live births (95% CI: 2.5 - 3.0). This proportion is not substantially different than the MACDP (3, 4, 5, 6) where total prevalence of birth defects identified among births from 1989 through 2003 was 2.72 per 100 live births (95% CI: 2.68, 2.76), and the prevalence of birth defects per 100 live births diagnosed during the first seven days of life ("early diagnosis") was 2.09 (95% CI: 2.07, 2.12). Because population-based surveillance does not involve sampling, MACDP does not publish CIs. The CIs reported around MACDP rates in this report were calculated by the Registry. The second population comparator, TBDR, reports an overall prevalence of birth defects of 4.17% (95% CI: 4.15, 4.19) for deliveries during 2000 through 2009 (7). Although the Registry prevalence is statistically significantly lower than the Texas Birth Defects Registry, the inclusion of major malformations in outcomes of any gestational age increases the baseline prevalence in the Texas population. Additionally, the prevalence of defects among offspring of women with first trimester exposure to antiretroviral medications (2.8 per 100 live births) is not substantially different from the prevalence of defects among women with the first exposure during the second and/or third trimester (2.8 per 100 live births) (prevalence ratio: 1.02, 95% CI: 0.85, 1.21).

For frequency monitoring, the Registry has adopted the convention of the "Rule of Three": once three or more prospective similar individual defects have been accumulated with any specific exposure or exposure combination, these cases will be flagged for immediate review.

Table 7: Confidence Intervals for Birth Defects [1] – All Prospective Registry Cases with Follow-up Data Closed Through 31 January 2017

	Overall
Number of Live Births	17805
Number of Outcomes with at Least One Defect [1, 2]	496 (2.8%)
95% Confidence Intervals for Prevalence of Birth Defects for Exposures in:	
First Trimester	240/8583 (2.8%) 2.4% - 3.2%
Second/Third Trimester	254/9220 (2.8%) 2.4% - 3.1%
Any Trimester	496/17805 (2.8%) 2.5% - 3.0%
Risk of Defects for First Trimester Exposures Relative to Second/Third Trimester Exposures	1.02 (0.85, 1.21)

[1] Defects meeting the CDC Criteria only. Excludes reported defects in pregnancy losses < 20 weeks.
[2] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion.
Note: See Table 4 for the other pregnancy outcomes.
Note: Due to unknown trimester of exposure data for 2 case(s) with birth defects, the specific counts may not sum to the overall total.

Summary of Hepatitis B Virus Mono-infected Pregnancies

In 1998, the antiviral activity of lamivudine against the Hepatitis B virus was recognized by the FDA as a supplemental indication for that drug followed by tenofovir disoproxil fumarate in 2008. With the FDA approval of adefovir dipivoxil with the sole indication of treatment for infection with hepatitis B virus (HBV), the APR agreed to provide a repository for reports of pregnancy exposures for these drugs and to include the results as part of the APR's semi-annual interim report. Based on this, and the likely future rise in the use of ARVs to treat HIV/HBV co-infected individuals as well as mono-infected HBV patients, the APR began to systematically collect hepatitis B infection status in 2003. Since the addition of adefovir dipivoxil (2002), two additional HBV drugs, entecavir (2005) and telbivudine (2006), have been added to the Registry.

Since the addition of the hepatitis B indication, the APR has received 581 prospective reports of diagnosed hepatitis B patients with or without concurrent HIV infection, all of which are included in the overall registry data. This sub-analysis is limited to the hepatitis B mono-infected population. Through 31 January 2017, a total of 393 prospective reports of hepatitis B mono-infected pregnancies with outcome have been reported (Table 2). Seven birth defect cases have been reported among 355 live births, including 246 live births with initial exposure during the first trimester of pregnancy. All 7 birth defect cases were initially exposed during the first trimester of pregnancy. There is no pattern among the types of births defects reported.

These numbers do not permit definitive conclusions regarding the possible teratogenicity of these agents for this indication. For lamivudine and tenofovir disoproxil fumarate they should be viewed through the perspective of wide use in HIV-infected pregnant women without emerging signals. Further reports from the hepatitis treating community are urged.

Overview of Clinical Studies Data Included in the Primary Analysis

Complete data from three observational studies ACTG 367, WITS (Women and Infants Transmission Study), and the NISDI Perinatal Study (Maternal Antiretroviral Use During Pregnancy and Infant Congenital Anomalies), are included in the primary Registry analysis. The WITS and NISDI studies have ended and all data have been provided to the Registry. The rationale for including these reports was that these reports were a priori no different from the Registry reports as no intervention or extended follow-up occurs for subjects in these studies.

In a published analysis from the Women and Infants Transmission Study, an elevated rate of hypospadias after first trimester zidovudine exposure was detected (9). The WITS included HIV-infected pregnant women enrolled during pregnancy or within seven days after delivery, and this analysis included women enrolled between 1 January 1990 and 30 June 2004. Anomalies identified during the prenatal, neonatal, and follow-up periods were classified using the criteria of the APR. From 1 January 1990 through 30 June 2004, 2527 live births (LB) with known ARV exposure occurred to 2353 women. Defects were identified in 90 infants for a rate of 3.56 defects/100 LB. The rate of defects was 24/752, 3.19 /100 LB for women with first trimester ARV exposure, 41/1158, 3.54/100 LB with exposure beginning in the second or third trimester, and 25/617, 4.05/100 LB for women with no ARV use during pregnancy. While the overall rate of hypospadias (3.29/1000 LB) was not increased, hypospadias was significantly increased among infants born to women with first trimester exposure to antiretroviral therapy (7/382 male LB) compared to those with second or third trimester exposure (2/578 male LB, p=0.033). Exposure to zidovudine in the first trimester was associated with hypospadias (univariate p= 0.014). Seven cases of hypospadias were grade 1 (mild); two cases were severe, one after first trimester zidovudine and lamivudine exposure and one after first trimester didanosine, stavudine, and nelfinavir exposure. While the differences in rates of this specific defect have reached statistical significance in the case of this one

comparison (in the face of multiple simultaneous comparisons), their importance remains unclear. The signal has not appeared in the primary analysis of the Registry. Further, WITS did not collect detailed information on concomitant medications such as opportunistic infection prophylaxis, which would be expected to be more common among women with more severe illness and first trimester antiretroviral exposure. Thus, the association noted between first trimester zidovudine exposure and hypospadias must be explored further as alternate explanations are possible. A detailed analysis was undertaken following the report of a single additional case of first trimester exposure to zidovudine/lamivudine in the 31 January 2012 period (see page 19). The Registry continues to monitor this defect closely.

The NICHD International Site Development Initiative Perinatal Study (NISDI) is an ongoing prospective cohort study of HIV-infected pregnant women and their infants conducted at multiple Latin American and Caribbean sites where antiretroviral therapy and replacement infant feeding are available. Women are enrolled as early as possible during pregnancy and followed with study visits during each trimester, at delivery, and at 6-12 weeks postpartum. Infants are evaluated at delivery, 6-12 weeks and 6 months of age by history and physical examination and testing for HIV, but no additional evaluations for birth defects such as echocardiograms are included in the protocol. An analysis of the rates and types of birth defects according to earliest trimester of antiretroviral exposures was done including infants born to women enrolled in Brazil and Argentina (the majority of subjects) between September, 2002 and October, 2007 for their first pregnancy on study with a pregnancy outcome at or above 20 weeks of gestation (10). Among the 995 women included, there were 974 live births, one induced abortion, and 20 stillbirths. Data from these 995 pregnancies have been provided from the NISDI study to the APR, and the data have been incorporated into the prospective portion of the APR. APR determined in advance to include these cases into the prospective portion of the APR, based on the non-interventional, observational design, the lack of exclusion criteria for birth defects, and the lack of specified additional infant testing for birth defects in the protocol. While the overall rate of birth defects was increased in the NISDI data compared to the APR and US surveillance data, the rate of defects did not differ by trimester of earliest exposure to antiretroviral drugs. The prevalence of birth defects detected within the first seven days of life, 2.4%, was similar to the rate in APR and in the Latin American Collaborative Study of Congenital Malformations (ECLAMC), suggesting that the increased rate overall was related to enhanced detection of asymptomatic defects with extended follow up.

The Registry has received 322 cases from a prospective clinical study in Africa (the Development of AntiRetroviral Therapy in Africa study – DART), which is a recently completed six year clinical trial of antiretroviral therapy in 3300 patients in Uganda and Zimbabwe. It is the Registry's policy that individual pregnancy exposures from clinical trials of antiretroviral drugs outside of pregnancy are included in the prospective analysis if they are prospectively reported and otherwise meet the criteria for inclusion. Therefore, the DART pregnancy cases are included in the prospective analysis.

Bussmann and colleagues (12) reported 71 pregnancies that occurred in a randomized clinical trial comparing efficacy, tolerability, and adherence rates of 6 highly active antiretroviral therapy (HAART) regimens in urban Botswana. Three of the 6 HAART regimens included efavirenz. Of the 650 subjects enrolled between 2002 and 2004, 451 were women and as of January 2006, 71 pregnancies were reported. Thirty-eight of the 71 pregnancies were exposed to efavirenz in the first trimester and 22 of these 38 pregnancies resulted in live births; one was reported to have a birth defect (right limb shortening) that was determined to be unrelated to efavirenz exposure. Two of the 17 live births not exposed to efavirenz were reported to have birth defects (polydactyly and umbilical hernia). APR has received all of the reported pregnancies from this study, and a single additional case not previously reported. All of these are included in the primary analysis section of this report.

RETROSPECTIVE REPORTS

Though the Registry is a prospective registry, data from retrospective reports (pregnancies with a known outcome at the time of reporting) are also reviewed to assist in the detection of any unusual patterns in birth defects. Retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population experience. Therefore, the calculation of prevalence from these reports is inappropriate. See Appendix C for a list of birth defects reported retrospectively to the Registry with a temporality assessment indicated where possible. As with the prospective reports, these assessments were made in an initial review by the consultant medical geneticist with agreement by the Advisory Committee. Because of animal data, particular emphasis is placed on review of central nervous system (CNS) defects. Special attention is given to neural tube defects, the Registry has received retrospective reports of seven myelomeningocele (neural tube) defects, four with efavirenz exposure.

REPORTS FROM CLINICAL STUDIES IN PREGNANCY

The Registry receives reports of subjects enrolled in clinical studies conducted in pregnant women. These reports are important in evaluating and detecting potential signals. However, these data are examined separately from the primary Registry analysis due to the potential for selection or ascertainment bias. That is, the inclusion/exclusion criteria, severity of disease at the time of maternal enrollment, and the potentially longer, more rigorous follow-up process of these clinical studies may differ from the prospective Registry cases included in the primary analysis. For instance, the inclusion/exclusion criteria for some of these studies may exclude women with abnormal prenatal tests, so subjects may have a lower risk for defects than the Registry group. Regarding severity of disease at enrollment, women in clinical studies with first trimester exposure appear to have more advanced disease (13). Additionally, infants born to women enrolled in these studies continue to be seen for several months after delivery and often undergo additional tests. These additional tests may reveal defects that would not typically be seen by the maternal provider, such as an atrial septal defect diagnosed at 14 months of age on an echocardiogram done as part of a research protocol in an asymptomatic infant. In a comparison of the time to receipt of follow-up information after the outcome of pregnancy, there was a significantly longer time interval to receipt of follow-up on the clinical study reports than for the Registry cases.

The source of the clinical study reports varies. For example, some reports come from individual providers who happen to be participating in a clinical trial and other reports come from a single source, such as the clinical study data coordinating center or the study sponsor. The Registry has received data on all women enrolled in the PACTG 185 study and a South African study. Data from those studies as well as from several clinical studies including ACTG 082, PACTG 326, ACTG 5084, and NIH 00861, as well as data from a German multi-site clinical study with intensive follow-up of infants for 18 months are included in Tables 8-12. The Registry pools all clinical trials data for the purposes of reporting data in this report. However, when possible, the Registry evaluates individual study results separately.

Pooled Clinical Study Data

Table 8 provides a summary of the maternal age and disease status at the time of pregnancy.

Table 8: Maternal Demographics at Registration – Reports from Clinical Studies in Pregnancy with Follow-up Data Closed Through 31 January 2017

	Clinical Studies in Pregnancy
Pregnancies Reported	2285
Age (years)	
N	2276
Median (Interquartile Range)	27.0 (8.0)
Min - Max	13 - 47
Missing	9
Indication for ARV at Start of Pregnancy	
HIV Infected [1]	853 (37.3%)
HIV Uninfected [2]	1 (0.0%)
Post-Exposure Prophylaxis (PEP)	0 (0.0%)
Pre-Exposure Prophylaxis (PrEP)	0 (0.0%)
Hepatitis B mono-infected	654 (28.6%)
Unknown	345 (15.1%)
Missing	432 (18.9%)
Clinical Indicators	
CD4+ T-cell Categories at Start of Pregnancy	
≥ 500 cells/µL	441 (19.3%)
200-499 cells/µL	905 (39.6%)
<200 cells/µL	250 (10.9%)
Unknown	503 (22.0%)
N/A	14 (0.6%)
Missing	172 (7.5%)
Worst Disease Severity by History	
HIV	
A. Asymptomatic, acute (primary) HIV or PGL	714 (31.2%)
B. Symptomatic, not (A) or (C) conditions	50 (2.2%)
C. Other AIDS-indicator conditions	57 (2.5%)
D. CD4 < 200 cells/µL	24 (1.1%)
Not applicable	191 (8.4%)
Unknown	353 (15.4%)
Missing	895 (39.2%)
Hepatitis B	
Compensated liver disease (Pugh score < 7)	511 (22.4%)
Compensated liver disease (Pugh score ≥ 7)	1 (0.0%)
Unknown	581 (25.4%)
Not applicable	11 (0.5%)
Missing	1181 (51.7%)

[1] Includes 3 patients co-infected with HIV and Hepatitis B. Includes 11 patients co-infected with HIV and Hepatitis C.
[2] Where antiretroviral drugs have been used for prophylaxis.
Note: The Registry started systematically collecting data on Hepatitis B in January 2003.
Note: The Registry began to collect data to distinguish between pre- and post-exposure prophylaxis in December 2013.

Table 9 summarizes the exposure classifications and earliest trimester of exposure. As in the primary analysis, only the therapy or combination of therapies taken in the earliest trimester of exposure are included. Some individuals may have received other therapies in a later trimester.

Table 9: Summary of Treatment Classes [1] by Trimester of Earliest Exposure [2] – Reports from Clinical Studies in Pregnancy with Follow-Up Data Closed Through 31 January 2017

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Reported	398	918	969	2285
PI	3	3	2	8
NRTI	153	583	829	1565
PI/NRTI	68	174	17	259
PI/nnRTI	0	7	1	8
NRTI/nnRTI	36	85	59	180
NRTI/InSTI	2	4	39	45
PI/NRTI/nnRTI	7	1	2	10
PI/NRTI/NtRTI	70	17	3	90
NRTI/nnRTI/NtRTI	26	32	8	66
NRTI/NtRTI/InSTI	5	1	2	8
PI/NRTI/nnRTI/NtRTI	10	3	1	14
NRTI/NtRTI/InSTI/PKE	8	6	0	14
Other Combination	10	2	6	18

[1] PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, telbivudine, zalcitabine, and zidovudine.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, etravirine, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, tenofovir alafenamide, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes dolutegravir, elvitegravir, and raltegravir.
PKE=pharmacokinetic enhancer, which includes cobicistat.
[2] Exposures represent earliest trimester of exposure to an antiretroviral drug. Pregnant women may have been on other medications during the pregnancy.
Note: Treatment regimens for which no exposures were reported are excluded from the table.
Note: Treatment regimens with fewer than 5 exposures have been collapsed into the Other category.
Note: Due to unknown trimester of exposure data for 0 case(s), the specific counts may not sum to the overall total.

Table 10 presents a pooled summary of pregnancy exposures and outcome data from all reported studies. Among the 2313 prospectively reported outcomes in this group, there were 401 live births with a first trimester exposure, with 18 defects reported. The prevalence of birth defects per 100 live births among women with first trimester exposures to an antiretroviral (primarily nucleoside analog reverse transcriptase inhibitors) is 4.5 (95% CI: 2.7 - 7.0) (Table 12). The number of defects identified with an initial exposure in the second or third trimester was 31/1892. The prevalence of birth defects per 100 live births among women in this group was 1.6 (95% CI: 1.1 - 2.3). The prevalence of defects among offspring of women with first trimester exposure to antiretroviral medications (4.5 per 100 live births) was significantly higher than the prevalence of defects among women with the first exposure during the second and/or third trimester (1.6 per 100 live births) (prevalence ratio: 2.74, 95% CI: 1.55, 4.85). This increased rate is an artifact of pooling the results from these individual studies. When the studies are analyzed separately, differences are only apparent in the following two studies.

The PACTG 185 study identified 4 reports of various forms of ventricular septal defects (VSD) (included in Heart – Other Defects category in Table 11). The Registry has instituted a thorough re-analysis of these reports with the investigators. The defects were apparently not major; all resolved within the first year without treatment. Several of the biases described in this section may contribute to these findings. Mothers with more advanced disease, who became pregnant while being treated with zidovudine, are differentially included in the group (severity bias). Further, the likelihood of receiving an echocardiogram, and hence a diagnosis of VSD was high (ascertainment bias) and follow-up was often intensive. The finding of an excess rate of VSD has not been repeated in the other major study data, nor is there an apparent excess of VSD to date in the primary analysis of the Registry. Thus, this finding is viewed as not establishing a signal. The Registry will continue its regular review of VSD reports from all sources. To date, we have received 53 prospective cases of VSD, distributed across trimesters and drug exposures. Thus, the overall rate remains low and there is no apparent excess of cases among zidovudine or any drug exposure group or relevant trimester of exposure.

The other study with an increased prevalence of birth defects after first trimester exposure was a German multi-site study, which also makes extensive use of echocardiography and follows infants intensively for 18 months after birth. This study identified 3 heart defects on echocardiogram including VSD, atrial septal defect, and patent ductus arteriosus. The Registry has conducted a thorough evaluation of these and other cardiovascular reports from studies and from our primary analysis. Though no signal has been detected, monitoring continues for these and related cardiovascular defects.

As in the primary analysis, Table 11 summarizes the number of outcomes with defects by therapy classification and organ system of the defect. See Appendix C for a list of all defect reports from clinical studies in pregnancy with, where possible, the temporal assessment made by the consultant defect evaluator with agreement from the Advisory Committee.

Recognizing the difficulties in comparing the findings from prospective clinical studies with population-based data, separate review of the available information from the clinical studies remains inconclusive, and warrants further examination.

Table 10: Summary of Pregnancy Outcomes [1] By Antiretroviral Treatment Regimen [2] – Reports from Clinical Studies in Pregnancy with Follow-up Data Closed Through 31 January 2017

	With Birth Defects[3] : Without Birth Defects[4]				
	Live Births	Spontaneous Losses	Still-births	Induced Abortions	Overall
Number of Outcomes [5]	49 : 2244	0 : 4	0 : 12	0 : 4	2313
Earliest Exposure [6]					
First Trimester	18 : 383	0 : 4	0 : 0	0 : 4	409
Second/Third Trimester	31 : 1861	0 : 0	0 : 12	0 : 0	1904
First Trimester					
PI	0 : 3	0 : 0	0 : 0	0 : 0	3
NRTI	7 : 150	0 : 0	0 : 0	0 : 0	157
PI/NRTI	3 : 62	0 : 2	0 : 0	0 : 2	69
NRTI/nnRTI	2 : 37	0 : 1	0 : 0	0 : 0	40
NRTI/InSTI	0 : 2	0 : 0	0 : 0	0 : 0	2
PI/NRTI/nnRTI	1 : 6	0 : 0	0 : 0	0 : 0	7
PI/NRTI/NtRTI	1 : 69	0 : 1	0 : 0	0 : 1	72
PI/NRTI/InSTI	0 : 3	0 : 0	0 : 0	0 : 0	3
PI/nnRTI/InSTI	1 : 0	0 : 0	0 : 0	0 : 0	1
NRTI/nnRTI/NtRTI	2 : 24	0 : 0	0 : 0	0 : 0	26
NRTI/NtRTI/InSTI	0 : 5	0 : 0	0 : 0	0 : 0	5
PI/NRTI/nnRTI/NtRTI	0 : 10	0 : 0	0 : 0	0 : 0	10
PI/NRTI/NtRTI/InSTI	0 : 3	0 : 0	0 : 0	0 : 0	3
NRTI/NtRTI/InSTI/PKE	1 : 6	0 : 0	0 : 0	0 : 1	8
PI/NRTI/nnRTI/NtRTI/EI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/NRTI/nnRTI/NtRTI/InSTI	0 : 1	0 : 0	0 : 0	0 : 0	1
NRTI/NtRTI/EI/InSTI/PKE	0 : 1	0 : 0	0 : 0	0 : 0	1

[1] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion.
[2] PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, telbivudine, zalcitabine, and zidovudine.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, etravirine, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, tenofovir alafenamide, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes dolutegravir, elvitegravir, and raltegravir.
PKE=pharmacokinetic enhancer, which includes cobicistat.
[3] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[4] Includes cases where the occurrence of a birth defect was not reported.
[5] Includes 28 multiple births.
[6] Data is not included for birth defect cases with an unknown trimester of exposure.
Note: Treatment regimens for which no exposures were reported are excluded from the table.

Table 11: Summary of Clinical Study Reports of Birth Defects [1] By Organ System and Treatment Regimen – First Trimester Exposures. All Reports with Follow-up Data Closed Through 31 January 2017

	Earliest Antiretroviral Therapy (ART) Exposure in First Trimester								
	Any PI(s) [3]	Any NRTI(s) [3]	Any NNRTI(s) [3]	Any NtRTI(s) [3]	Any EI(s) [3]	Any InSTI(s) [3]	Any PKE (s) [3]	Overall First Tri-mester Exposure	Earliest ART Exposure in Second and/or Third Trimester
Pregnancies Enrolled	167	394	82	125	2	24	9	398	1887
Number of Pregnancies with Multiple Gestations	3	11	4	2	0	0	0	11	17
Number of Outcomes [2]	170	405	86	127	2	24	9	409	1904
Number of Live Births	164	397	85	124	2	23	8	401	1892
Number of Outcomes with Defects [1,2]	6	17	6	4	0	2	1	18	31
Eye, ear, face and neck	0	0	0	0	0	0	0	0	1
Cleft lip and/or palate	1	1	0	1	0	0	0	1	1
Obstructive heart defects - right sided	0	0	0	0	0	0	0	0	1
Heart - other defects	3	12	2	2	0	1	1	12	8
Other circulatory system	1	2	1	0	0	0	0	2	2
Respiratory system	0	0	0	0	0	0	0	0	1
Female genitalia	0	0	0	0	0	0	0	0	1
Male genitalia	2	4	2	2	0	1	1	4	3
Renal and urinary system	1	1	2	1	0	1	0	2	0
Limb reduction/addition defects	0	0	0	0	0	0	0	0	9
Other musculoskeletal defects	0	4	1	1	0	0	0	4	11
Skin and skin derivatives	0	2	0	0	0	0	0	2	0
Chromosome anomaly	1	1	0	1	0	0	0	1	1
Other organs and organ systems	0	0	0	0	0	0	0	0	1
Specified syndromes/sequences/associations	0	0	0	0	0	0	0	0	1

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[2] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion.
[3] PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, telbivudine, zalcitabine, and zidovudine.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, etravirine, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, tenofovir alafenamide, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes dolutegravir, elvitegravir, and raltegravir.
PKE=pharmacokinetic enhancer, which includes cobicistat.
Note: For each organ system, counts represent the number of outcomes with at least one defect occurring in that organ system. For each defect, counts represent the number of outcomes manifesting at least one occurrence of the defect. Hence, counts are not mutually exclusive across organ systems.
Note: The cardiovascular organ systems reflect separate types of structural heart defects therefore, it is not appropriate to add them together.
Note: Data is not included for birth defect cases with an unknown trimester of exposure.

Table 12: Confidence Intervals for Birth Defects [1] – Reports from Clinical Studies in Pregnancy with Follow-up Data Closed Through 31 January 2017

	Overall
Number of Live Births	2293
Number of Outcomes with at Least One Defect [1, 2]	49 (2.1%)
95% Confidence Intervals for Prevalence of Birth Defects for Exposures in:	
First Trimester	18/401 (4.5%) 2.7% - 7.0%
Second/Third Trimester	31/1892 (1.6%) 1.1% - 2.3%
Any Trimester	49/2293 (2.1%) 1.6% - 2.8%
Risk of Defects for First Trimester Exposures Relative to Second/Third Trimester Exposures	2.74 (1.55, 4.85)

[1] Defects meeting the CDC Criteria only. Excludes reported defects in pregnancy losses < 20 weeks.
[2] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion.

Individual Clinical Study Data

The Registry generally excludes reports from studies where one or more of the therapies are still blinded, as the complete exposure information is not available. The exception is PACTG 316 which is a blinded perinatal transmission trial in which nevirapine or placebo was given to the mother at delivery and to the newborn following delivery. All women in this study were on an antiretroviral therapy at enrollment into the study. This first exposure is of primary interest to the Registry since the Registry categorizes exposures by earliest trimester of exposure as most structural defects or major malformations would have occurred prior to labor and delivery.

PACTG 316

PACTG 316 was a study conducted from 1997-2000 evaluating the effects on maternal-to-child transmission of HIV-1 of addition of a single dose of nevirapine to the mother during labor and a single dose to the neonate compared to placebos for each among women otherwise on background antiretroviral therapy during pregnancy. Many of the women were already taking a variety of antiretroviral regimens (excluding non-nucleoside agents) at the outset of pregnancy; others started antiretroviral therapy later in pregnancy. Information regarding antiretroviral use during pregnancy was captured in detail. All observed defects were reviewed by the protocol team and categorized using APR criteria.

During the January 2009 reporting period, the Registry received data tables describing pregnancy outcomes and birth defects among women enrolled in the PACTG 316 study. With the addition of the PACTG 316 study data, all prior individual case reports from PACTG 316 (N=122) were removed from Registry Tables 8-12 and are presented here as unduplicated case summaries in Tables 13 and 14 including 1283 exposed pregnancies and 1311 outcomes with 60 defect cases. Tables 13 and 14 were updated in the July 31, 2011 interim report following publication of final PACTG 316 study results (14). The results presented in the interim report differ slightly from those in the published manuscript as the definition of first trimester (14 vs. 12 weeks gestation) and the denominator for the prevalence rate calculation (number of live births vs. number of outcomes) were adjusted to maintain consistency with APR methodology. In addition, to avoid duplicate reporting, 110 live births (none with reported defects) have been excluded from the data reported here.

Birth defects after first trimester exposure to any antiretroviral agent were detected among 27 infants, a rate of 6.5% (95% CI: 4.3, 9.3) of 417 live births. Birth defects were detected in 33 infants with second/third trimester exposure, a rate of 3.7% (95% CI: 2.6, 5.2) of 889 live births. The rate of birth defects overall was not increased after first trimester exposure compared to later exposure (ratio 1.75, 95% CI: 1.07-2.87). The relatively higher rate of defects in this study compared to the APR and MACDP rates is not unexpected, given participation of the women and infants in a research protocol with enhanced follow up of the infants. This study's rate is not elevated when compared to the TBDR.

A slightly increased frequency of the most common heart defects, primarily atrial septal defects and ventricular septal defects, was noted after first trimester exposure compared to later exposure to antiretroviral agents and is being evaluated further. This finding was noted also in the PACTG 185 study and may be related to severity bias, in that demographic and treatment data suggest that sicker women would be more likely to have started therapy before pregnancy. A recent detailed analysis of APR cases of ventricular septal defects among prospective cases found no association between first trimester antiretroviral exposure and risk of these defects. These regular analyses are conducted as data accumulate. To date we have sufficient power overall and for 2 individual drugs most commonly used in PACTG 316.

Table 13: Summary of Birth Defects by Organ System and Antiretroviral Treatment Regimen, PACTG 316 Data [collection period: 13 May 1997 to 19 June 2000]

	Earliest Antiretroviral Therapy (ART) Exposure in First Trimester						
	Any NRTI(s) [3]	Any NtRTI(s) [3]	Any NNRTI(s) [3]	Any PI(s) [3]	Any EI(s) [3]	Overall First Tri-mester Exposure	Earliest ART Exposure in Second and/or Third Trimester
Pregnancies Identified	378	0	0	186	0	411	872
Number of Pregnancies with Multiple Gestations	5	0	0	3	0	6	22
Number of Outcomes [2]	383	0	0	189	0	417	894
Number of Live Births	382	0	0	189	0	416	889
Number of Outcomes with Defects [1,2]	26	0	0	16	0	27	33
CNS	0	0	0	0	0	0	1
Face and neck	2	0	0	2	0	2	2
Cleft lip and/or palate	0	0	0	0	0	0	2
Conotruncal heart defects	2	0	0	1	0	2	0
Obstructive heart defects - right sided	3	0	0	2	0	3	3
Obstructive heart defects - left sided	2	0	0	2	0	2	0
Heart - other defects	11	0	0	3	0	11	4
Other circulatory system	0	0	0	0	0	0	0
Respiratory system	1	0	0	1	0	1	0
Upper gastrointestinal system	1	0	0	1	0	1	1
Lower gastrointestinal system	0	0	0	0	0	0	1
Male genitalia	3	0	0	3	0	3	3
Female genitalia	0	0	0	0	0	0	1
Renal and urinary system	1	0	0	1	0	2	4
Limb reduction/addition defects	2	0	0	1	0	2	1
Other musculoskeletal defects	2	0	0	2	0	2	10
Skin and skin derivatives	1	0	0	0	0	1	4
Chromosome anomaly	2	0	0	2	0	2	2
Other organs and organ systems	0	0	0	0	0	0	0
Specified syndromes/sequences/ associations	0	0	0	0	0	0	0

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[2] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion ≥20 weeks gestation.
[3] PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, telbivudine, zalcitabine and zidovudine.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, and nevirapine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.
Note: For each organ system, counts represent the number of outcomes with at least one defect occurring in that organ system. For each defect, counts represent the number of outcomes manifesting at least one occurrence of the defect. Hence, counts are not mutually exclusive across organ systems.
Note: Organ systems for which no defects were reported are excluded from the table.
Note: Treatment regimens for which no exposures were reported are excluded from the table.
Note: The cardiovascular organ systems reflect separate types of structural heart defects therefore, it is not appropriate to add them together.

Table 14: Confidence Intervals for Birth Defects, PACTG 316 Data [collection period: 13 May 1997 to 19 June 2000]

	Overall
Number of Live Births	1305
Number of Outcomes with at least one defect [1,2]	60
95% Confidence Intervals for prevalence of Birth Defects for exposures in:	
First Trimester	27/416 (6.5%) (4.3% -- 9.3%)
Second/Third Trimester	33/889 (3.7%) (2.6% -- 5.2%)
Any Trimester	60/1305 (4.6%) (3.5% -- 5.9%)
Risk of defects for first trimester exposures relative to second/third trimester exposures	1.75 (1.07 – 2.87)

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions < 20 weeks.
[2] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion ≥20 weeks gestation.

Update to Related Sponsor Studies

Elevated levels of ethyl methanesulfonate (EMS) were found in some lots of nelfinavir manufactured and marketed by Roche in Europe which led to a recall in Europe only. Nelfinavir manufactured by Pfizer for the US, Puerto Rico, Canada, and by Japan was not recalled. EMS at high exposures is known to be an animal carcinogen, mutagen and teratogen.

Following the review of toxicology studies conducted by Roche, European Medicines Agency (EMA) concluded in July 2008 that there was no need to monitor patients who had been exposed to high levels of contaminated Viracept through specific patient registries and confirmed that there is no increased risk of development of cancer for patients who have taken contaminated Viracept. Concerning exposure during pregnancy the EMA noted the following: "The CHMP noted that patients or children born to mothers who had taken contaminated Viracept were exposed to ethyl mesilate levels well below this threshold, and therefore that there was no increased risk of developing cancer for these patients compared with those patients who were not exposed to the contaminant (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000292.jsp&mid=WC0b01ac058004d5c1).

Please note that Viracept by Roche is not available in Europe anymore since June 2014 (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000164/human_med_001140.jsp&mid=WC0b01ac058001d124)

For information pertaining specifically to nelfinavir manufactured by Pfizer supplied to the US, Canada, Puerto Rico, and by Japan, a Dear Healthcare Professional letter was issued in the US on September 10th, 2007 with information available at http://www.fda.gov/medwatch/safety/2007/safety07.htm#nelfinavir and http://www.fda.gov/cder/drug/infopage/nelfinavir/qa.htm, or Healthcare professionals with medical inquiries on nelfinavir can also contact Pfizer Medical Information at (800) 438-1985.

On May 6th, 2008, Pfizer issued a Dear Health Care Provider letter to health care professionals in the United States to announce that Pfizer and FDA had agreed on a final limit for EMS in nelfinavir mesylate (active ingredient in nelfinavir and to provide guidance on the use of nelfinavir in patients. Effective March

31, 2008, all nelfinavir released by Pfizer meets the new final limits established by the FDA for prescribing to all patient populations, including pregnant female and pediatric patients.

For information pertaining specifically to nelfinavir manufactured by Pfizer for the US and Puerto Rico, is available at: http://www.pfizer.com.

US healthcare professionals with medical inquiries on nelfinavir are advised to contact Pfizer's US Medical Information at (800) 438-1985.

In Canada, nelfinavir is not recommended for use in pregnant women. For information and use of nelfinavir approved in Canada, please contact Pfizer Canada's Medical Information line at (800) 463-6001.

For additional information refer to http://aidsinfo.nih.gov.

REPORTS FROM THE PUBLISHED LITERATURE

There is a growing body of literature on the potential association between prenatal antiretroviral exposure and birth defects. This section summarizes the studies that have been identified by the Registry through an annual systematic literature search of MEDLINE, the US National Library of Medicine electronic bibliographic database, from 1966 through the present. The following search terms were used: antiretroviral therapy or anti-HIV agents and congenital malformations or birth defects or pregnancy outcome. This section is not necessarily a comprehensive review of the international literature on this topic.*

Studies with Large Sample Sizes: The European Collaborative Study initiated in 1986 is a prospective cohort study of HIV-infected pregnant women seen at 26 centers in nine European countries (15, 16, 17). Infants are followed for at least 18 months. In a 2005 publication (2005) (17), the 3740 mother-infant pairs, including 1973 infants exposed to antiretroviral therapy in utero of whom 602 were exposed to highly active antiretroviral therapy (HAART). The prevalence of birth defects among infants exposed to antiretroviral therapy in utero (31/1973, 1.6%) was similar to those not exposed (24/1767, 1.4%). The prevalence among those exposed in the first trimester of pregnancy (14/789, 1.8%) was similar to those exposed later in pregnancy (17/1184, 1.4%) and to those exposed to HAART in the first trimester (11/546, 2.0%). A multivariable analysis controlling for potential risk factors confirmed that there were no differences in the prevalence of birth defects between the therapy groups. The birth defects reported in the 14 infants exposed to antiretroviral therapy in the first trimester included ventricular septal defects (3), other heart defects (2), other circulatory defects (1), renal defects (3), gastrointestinal defects (4), male genitalia defect (1), other (unspecified) defect (1). The numbers do not add to 14 because one infant had both a heart defect and male genitalia defect. There were no birth defects reported in infants exposed to efavirenz in the first trimester of pregnancy (17). In March 2007, the European Collaborative Study coordinating center produced Tables 15 and 16 specifically for the Registry to provide updated data following the format of tables 11 and 12. In a joint study with the National Study of HIV in Pregnancy Childhood, they reported on 7573 singleton births to HIV-infection women diagnosed between 2000 and 2009 taking HAART with or without zidovudine. There was no difference in the overall rate of congenital anomalies in the zidovudine-sparing compared to zidovudine-containing regimens (2.7%, adjusted odds ratio [AOR] 0.98, 95% CI 0.66-1.45) or when limited to first trimester exposures (AOR 0.79, 95% CI 0.48-1.30) (18).

The National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland is a population-based surveillance study of HIV positive women and their children (19, 20). In their most recent publication (20), they reported data on over 8200 infants born between 1990 and 2007. Overall 232 of 8242 infants reportedly had congenital anomalies (2.8%, 95% CI: 2.5 - 3.2), and there were no significant differences between those not exposed to ART in utero (14/498, 2.8%) and those exposed in the first trimester (53/1708, 3.1%) or later in pregnancy (147/5427, 2.7%). There were no significant differences in congenital anomalies between infants exposed to various classes of ART. A multivariable analysis controlling for potential risk factors confirmed that there were no differences in the prevalence of birth defects between therapy groups. There were no significant differences in infants exposed in the first trimester to efavirenz (5/205, 2.4%) or to didanosine (6/174, 3.4%) compared with infants with first trimester exposure to other ART. For infants exposed in the first trimester to any ART, the most commonly reported types of congenital anomalies were musculoskeletal, heart and circulatory, and urinary and digestive systems.

* In addition to the studies and case series summarized in this section, individual case reports from the literature may be included in this report in the primary analysis section as prospective cases or in the retrospective listing of defects in Appendix C if they meet the inclusion criteria. Case reports from the literature are identified as such in a footnote.

The National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland produced Tables 17 and 18 annually for the Registry.

Table 15: European Collaborative Study Data: Summary of Birth Defects by Organ System and Treatment Regimen – First Trimester Exposures. Data Reporting Period December 1984 – March 2007

	Earliest Antiretroviral Therapy (ART) in First Trimester						
	Any NRTI(s)	Any NtRTI(s)	Any NNRTI(s)	Any PI(s)	Any FI(s)	Overall First Trimester Exposure	Earliest ART Exposure in Second or Third Trimester
Pregnancies Reported	872	24	278	350	2	872	1748
Number of Pregnancies with Multiple Gestations	15	0	4	7	0	15	20
Number of Outcomes	887	24	282	357	2	887	1768
Number of Live Births	880	24	279	354	2	880	1765
Number of Outcomes with Defects [1,2]	18	0	7	8	0	18	21
CNS	0	0	0	0	0	0	1
Eye, ear, face and neck	2	0	1	0	0	2	1
Cleft lip and/or palate	0	0	0	0	0	0	2
Conotruncal heart defects	0	0	0	0	0	0	1
Obstructive heart defects, right-sided	1	0	0	1	0	1	0
Obstructive heart defects, left-sided	0	0	0	0	0	0	0
Heart - other defects	6	0	2	2	0	6	4
Other circulatory system	1	0	0	1	0	1	0
Respiratory system	0	0	0	0	0	0	0
Upper gastrointestinal system	3	0	2	1	0	3	0
Lower gastrointestinal system	1	0	0	1	0	1	0
Female genitalia	0	0	0	0	0	0	0
Male genitalia	1	0	1	0	0	1	0
Renal and urinary system	3	0	2	1	0	3	2
Limb reduction/addition	0	0	0	0	0	0	4
Other musculoskeletal defects	0	0	0	0	0	0	0
Skin and skin derivatives	0	0	0	0	0	0	0
Chromosome anomaly	0	0	0	0	0	0	3
Other organ systems - specified	0	0	0	0	0	0	1
Specified syndromes	0	0	0	0	0	0	0
Unspecified abnormality	1	0	0	1	0	1	2

* one child had 2 defects (hydrocele and atrial septal defect)

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[2] An outcome is defined as a live infant, spontaneous abortion, induced abortion, or a stillbirth.
Note: For each organ system, counts represent the number of outcomes with at least one defect occurring in that organ system. For each defect, counts represent the number of outcomes manifesting at least one occurrence of the defect. Hence, counts are not mutually exclusive across organ systems.
Note: Organ systems for which no defects were reported are excluded from the table.
Note: The cardiovascular organ systems reflect separate types of structural heart defects; therefore, it is not appropriate to add them together.

Table 16: European Collaborative Study Data: Confidence Intervals for Birth Defects. Data Reporting Period December 1984 – March 2007

	Overall
Number of Live Births	2645
Number of Live Births with at least one defect [1]	39 (1.5%)
95% Confidence Intervals [2] for % of Birth Defects for exposures in:	
First Trimester	18/880 (2.0%) 1.2 – 3.2
Second/Third Trimester	21/1765 (1.2%) 0.7 – 1.8
Any Trimester	39/2645 (1.5%) 1.1 – 2.0
Risk of defects for first trimester exposures relative to second/third trimester exposures	1.7 (0.9, 3.2)

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[2] Confidence intervals based on exact methods for the binomial distribution.
Note: Only upper confidence limits are presented when no defects were observed.

Table 17: Surveillance Data Collected Through the National Study of HIV in Pregnancy and Childhood (United Kingdom and Ireland): Summary of Birth Defects by Organ System and Treatment Regimen: Pregnancies with Delivery/Outcome 1990-2016, Reported by the End of December 2016

	Earliest Antiretroviral Therapy (ART) in First Trimester							
	Any NRTI(s)	Any NtRTI(s)	Any NNRTI (s)	Any PI(s)	Any EI(s)	Any InSTI	Overall First Trimester Exposure [3]	Earliest ART Exposure in Second or Third Trimester
Pregnancies Reported	7132	3720	3553	3498	39	228	7301	9857
Number of Pregnancies with Multiple Gestations	172	93	72	100	0	7	177	171
Number of Outcomes	7308	3815	3628	3599	36	187	7482	10029
Number of Live Births	7145	3745	3542	3520	32	170	7304	9897
Number of Outcomes with Defects [1,2]	223	110	105	116	0	5	231	289
CNS	21	13	9	12	0	0	22	22
Eye, ear, face and neck	7	5	3	3	0	0	7	12
Cleft lip and/or palate	4	3	2	2	0	0	4	10
Conotruncal heart defects	3	1	2	0	0	0	2	3
Obstructive heart defects, right-sided	5	0	3	2	0	0	5	4
Obstructive heart defects, left-sided	0	0	0	0	0	0	0	3
Heart - other defects	27	11	9	15	0	2	28	25
Other circulatory system	8	2	4	5	0	1	8	6
Respiratory system	3	1	3	1	0	0	3	9
Upper gastrointestinal system	1	0	1	0	0	0	1	4
Lower gastrointestinal system	13	4	5	6	0	1	15	13
Female genitalia	2	0	1	1	0	0	2	0
Male genitalia	14	8	8	9	0	0	14	18
Renal and urinary system	17	8	7	11	0	0	18	25
Limb reduction/addition	30	15	19	10	0	0	30	53
Other musculoskeletal defects	33	15	17	16	0	0	34	50
Skin and skin derivatives	10	4	2	7	0	0	10	16
Chromosome anomaly	34	25	13	20	0	0	34	27
Other organ systems - specified	2	0	1	1	0	0	2	3
Specified syndromes	2	0	0	2	0	0	2	3
Unspecified abnormality	8	7	4	3	0	1	8	6
	244	122	113	126	0	5	249	312

[1] Defects meeting WHO International Classification of Diseases (ICD-10) criteria only
[2] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion at ≥20 week gestation
[3] 143 pregnancies had first trimester exposure to unspecified antiretroviral drugs, 6 with abnormalities reported (both lower gastrointestinal system).
Note: Pregnancies/outcomes with missing information on exposure to ART or defects are excluded.

Table 18: Surveillance Data Collected Through the National Study of HIV in Pregnancy and Childhood (United Kingdom and Ireland): Confidence Intervals for Birth Defects: Pregnancies with Delivery/Outcome 1990-2016, Reported by the End of December 2016

	Overall
Number of live births	17201
Number of outcomes with at least one defect *	520 (3.0%)
95% confidence intervals for % birth defects for exposures in:	
First Trimester	231/7482 (3.1%) 2.8, 3.6
Second/Third Trimester	289/10029 (2.9%) 2.6, 3.2
Any Trimester	520/17502 (3.0%) 2.8, 3.3
Risk of defects for first trimester exposures relative to second/third trimester exposures	1.04 (0.87, 1.23)

* An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion at ≥20 weeks gestation

Newschaffer and colleagues (21) conducted a study on prenatal zidovudine use and birth defects among 3037 live births to HIV-infected women enrolled in the Medicaid program in New York State. Maternal and infant Medicaid claims records were linked and longitudinal Medicaid claims files were created for the infants from delivery through two years of age. Birth defects were obtained from the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). Of the 3037 live born infants in the cohort, 278 were excluded due to multiple gestations or multiple births in the study period, and 827 were excluded due to missing Medicaid data, leaving 1932 infants in the study group. Of the 1932 infants, approximately 140 had a first trimester exposure to zidovudine, 430 had a second or third trimester exposure to zidovudine, and 1362 had no prenatal exposure to zidovudine based on Medicaid claims. Overall, infants of HIV-infected women in the study group were significantly more likely to have a birth defect than infants of women in the general population of New York State. However, there was no increased risk of birth defects among infants exposed to zidovudine in the first trimester (adjusted odds ratio 1.20 and 95% CI 0.58, 2.51), the period of organogenesis when susceptibility to drug exposure is greatest.

No defects were observed in any of the outcomes of the 344 pregnancies with first trimester exposure to either efavirenz (n=213) or nevirapine (n=131) from the International epidemiological Database to Evaluate AIDS [IeDEA] West Africa, ANRS 1269 and ANRS 12136 study groups (22).

The Pediatric AIDS Clinical Trials Protocols (PACTG) 219 and 219C studies found an overall birth defect prevalence of 5.3% (95% CI: 4.4-6.3) (23). A higher defect rate was noted among those with first trimester exposure to efavirenz compared to those without a first trimester efavirenz exposure (adjusted OR 4.31, 95% CI: 1.56-11.86). Given the small number of efavirenz cases (n=32) more studies are needed. The Pediatric Adolescent AIDS Clinical Trials Group protocol P1025 is a companion study of PACTG 219 with considerable overlap of the cases enrolled (24). While they report a significant increased risk of congenital anomalies among infants born between 2002 and 2007 with first trimester exposure to efavirenz, there is overlap in the defect cases between the two studies as well as a significantly smaller denominator count in the P1025.

In a recently published meta-analysis of 9 prospective cohort studies, a nonsignificant pooled relative risk of birth defects (0.87, 95% CI: 0.61-1.24, p=0.45) was reported among first trimester efavirenz exposed pregnancies (1132 live births) compared to those without a first trimester efavirenz exposure (7163 live births). APR data are included in this meta-analysis. Given the APR's large size, the results of this meta-analysis mirror the findings of the APR to a large degree (25).

An independent group not affiliated with the FDA or the APR conducted a disproportionality analysis and reported that a signal had been generated from the AERS data between cleft lip and palate defects and prenatal antiretroviral exposure (26). In follow-up, the APR undertook a careful review of our data and confirmed that there is no signal and responded with a Letter to the Editor (27).

Other Studies Reviewed by the Registry: In addition to the above studies with sample sizes large enough to calculate rates of birth defects, a number of descriptive studies have also been published. It is inappropriate to attempt to calculate rates of birth defects from these studies due to the small number of cases. Following is a list of these studies.

Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? Sex Transm Inf 77:441-3, 2001. (28)

Lorenzi P, Spicher VM, Laubereau B, et al. Antiretroviral therapies in pregnancy: Maternal, fetal and neonatal effects. AIDS 1998;12(18):241. (29)

Simon T, Funke AM, Hero B, Reiser-Hartwig S, Fuhrmann U. Efficiency and side effects of antiretroviral treatment of HIV infected pregnant women. Zentralbl Gynakol 2002 Aug-Sep;124(8-9):413-7. (30)

Conclusion: The Registry has not identified a signal in any of the published case series reviewed to date.

SUMMARY AND ADVISORY COMMITTEE CONSENSUS

EXECUTIVE SUMMARY

Background

The purpose of the Antiretroviral Pregnancy Registry (Registry) is to detect any major teratogenic effects involving any of the Registry drugs* to which pregnant women are exposed (1). Registration is voluntary and confidential with information obtained from the health care provider. A Registry-assigned identifier allows for follow-up capability. Information on subjects is provided to the Registry prospectively (prior to the outcome of pregnancy being known) through their health care provider, with follow-up obtained from the health care provider after the outcome is determined. (For more details, see Appendix F: Methods beginning on page 158.) Providers are strongly urged to enroll their patients as early in pregnancy as possible to maximize the validity of the data. In addition, the Registry is very interested in assembling a group of providers who are willing to make a commitment to report all of their site's antiretroviral pregnancy exposures to the Registry, thereby assuring all cases can be considered prospective. Providers are encouraged to contact the Registry for more information about this group. The Registry is informed in its analysis by other data, for example, retrospective reports and clinical studies.

Prospective tracking of fetal drug exposure during pregnancy, particularly newer agents and new combinations of therapies remains critically important in evaluating the safety of these agents among reproductive-age women and the exposed fetus.

Each year the Registry has enrolled approximately 1300 pregnant women in the US exposed to antiretroviral drugs. This number represents approximately 15% of the 8,700 HIV positive women who give birth to live infants annually in the US (2)[γ]. Each year the Registry also enrolls approximately 200 pregnant women from other countries. Given the continued emergence of newer therapies used for treatment and prevention for which there is an ongoing need for evidence of their safety in pregnancy, sustained reporting is vital to the registry's ability to fulfill its mission of early detection of a birth defect signal, if present. Health care providers are strongly encouraged to continue reporting eligible patients to the Registry.

Data Summary

Primary Registry Analysis (Prospective Reports): In review of the data through 31 January 2017, among the prospective Registry reports, the prevalence of birth defects per 100 live births among women with a first trimester exposure to any of the antiretroviral therapies included in the Registry is 2.8 (95% confidence interval (CI): 2.4 - 3.2, i.e., 240 outcomes with defects of 8583 live births (Table 7). The prevalence of defects is not significantly different from the prevalence of defects among women with an

* Drugs included: abacavir (ZIAGEN®, ABC), abacavir/lamivudine combination (EPZICOM®, EPZ), abacavir/lamivudine/zidovudine combination (TRIZIVIR®, TZV), abacavir/dolutegravir/lamivudine combination (TRIUMEQ®, TRI), adefovir dipivoxil (HEPSERA®, ADV), amprenavir (AGENERASE®, APV), atazanavir (REYATAZ®, ATV), atazanavir/cobicistat combination (EVOTAZ®, EVO), cobicistat (TYBOST®, COBI), darunavir (PREZISTA®, DRV), darunavir/cobicistat combination (PREZCOBIX™, PCX), delavirdine mesylate (RESCRIPTOR®, DLV), didanosine (VIDEX®, VIDEX® EC, ddI), dolutegravir (TIVICAY®, DTG), emtricitabine/ tenofovir alafenamide (Descovy®,DVY), efavirenz (SUSTIVA®, STOCRIN®, EFV), efavirenz/emtricitabine/ tenofovir disoproxil combination (ATRIPLA® ATR), elvitegravir (VITEKTA®, EVG), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide combination (GENVOYA®, GEN), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate combination (STRIBILD®, STB), emtricitabine (EMTRIVA®, FTC), enfuvirtide (FUZEON®, T-20), entecavir (BARACLUDE®, ETV), etravirine (INTELENCE®, ETR), fosamprenavir calcium (LEXIVA®, FOS), indinavir (CRIXIVAN®, IDV), lamivudine (EPIVIR®, 3TC), lamivudine/raltegravir combination (DUTREBIS™, DUT), lamivudine/zidovudine combination (COMBIVIR®, ZDV+3TC), lopinavir/ritonavir combination (KALETRA®, ALUVIA®, LPV/r), maraviroc (SELZENTRY®, CELSENTRI®, MVC), nelfinavir (VIRACEPT®, NFV), nevirapine (VIRAMUNE®, VIRAMUNE® XR™, NVP), raltegravir (ISENTRESS®, RAL), rilpivirine (EDURANT®, RPV), rilpivirine/emtricitabine/tenofovir alafenamide (Odefsey®,ODE), rilpivirine/emtricitabine/tenofovir disoproxil combination (COMPLERA®, CPA; EVIPLERA®, EPA), ritonavir (NORVIR®, RTV), saquinavir (FORTOVASE®, SQV-SGC), saquinavir mesylate (INVIRASE®, SQV-HGC), stavudine (ZERIT®, d4T), telbivudine (SEBIVO®, TYZEKA®, LdT), tenofovir alafenamide (VEMLIDY®, TAF), tenofovir DF (VIREAD®, TDF), tenofovir disoproxil fumarate /emtricitabine (TRUVADA®, TVD), tipranavir (APTIVUS®, TPV), zalcitabine (HIVID®, ddC), and zidovudine (RETROVIR®, ZDV).

γ Whitemore SK, Zhang X, Taylor A, Blair JM. Estimated number of infants born to HIV-infected women in the United States and five dependent areas, 2006. J Acquir Immune Defic Syndr. 2011, 57(3):218-222.

initial exposure during the second and/or third trimester (2.8 per 100 live births) (prevalence ratio: 1.02, 95% CI: 0.85, 1.21).

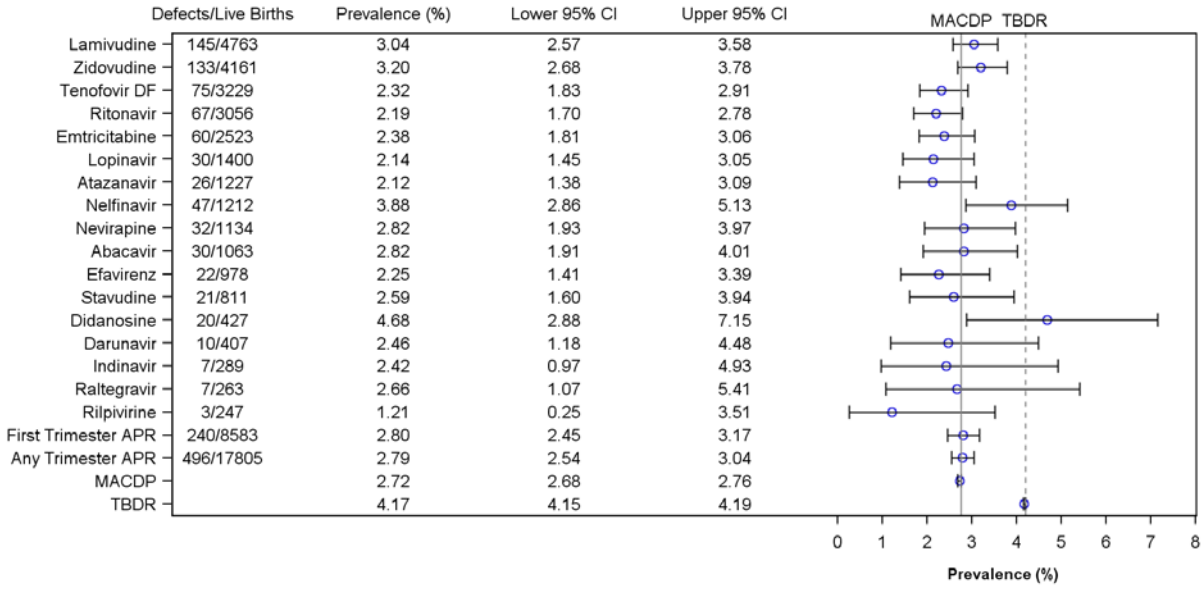
Measured against 17805 live births with exposure at any time during pregnancy, there were 496 outcomes with birth defects identified, a prevalence of 2.8 birth defects per 100 live births (95% CI: 2.5 - 3.0). This proportion is not significantly higher than those reported in the Registry's two population based comparators, the CDC's birth defects surveillance system (MACDP) (3, 4, 5, 6) (2.72 per 100 live births), and the Texas Birth Defects Registry (TBDR) (7) (4.17 per 100 live births). No increases in risk of specific defects have been detected to date when compared with observed MACDP or TBDR rates or with rates among those with earliest exposure in the second or third trimester. In analyzing individual drugs with sufficient data to warrant a separate analysis with the exception of didanosine and nelfinavir, no increases of concern in risk have been detected. For didanosine and nelfinavir, there is a modest but statistically significant increase in overall rates of defects when compared with the MACDP though not the TBDR. These defects are listed in Appendix C. No pattern of birth defects has been detected with didanosine or nelfinavir. The clinical relevance of this statistical finding is unclear. The Registry will continue to monitor didanosine and nelfinavir for any signal or pattern of birth defects.

A previously noted transient increase in the rate of hypospadias cases from the addition of data from one large clinical study (WITS) has not persisted and detailed analysis does not confirm that signal. There are no additional cases of hypospadias with relevant exposure in this update.

For darunavir, didanosine, efavirenz, indinavir, nevirapine, raltegravir, rilpivirine, and stavudine sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date. For abacavir, atazanavir, emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, tenofovir disoproxil fumarate, and zidovudine sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date. (See table below for number of defects and prevalence per 100 live births for first trimester exposures to all drugs with sufficient data to warrant separate analysis. See Appendix A for additional data.) There are insufficient data to make similar comparisons for other drugs or specific subgroups of defects.

The Advisory Committee pays particular attention to findings from animal studies. Therefore, the Advisory Committee is closely monitoring first trimester exposures to efavirenz for anomalies including central nervous system defects. Defects have been reported in 22 among the 978 infants with first trimester exposure to efavirenz, including a single case of myelomeningocele and a single case of anophthalmia with severe oblique facial clefts and amniotic banding. During this report period an undefined abnormality of the cerebellar vermis seen on prenatal ultrasound was reported. At birth, the infant's physical exam was normal. Upon February 2015 follow-up, it was reported that the infant was developing normally and that the parents have declined further imaging at this time. Without postnatal imaging, a central nervous system abnormality cannot be confirmed.

Figure 1: Summary of Birth Defects among Trimester Exposures, Prospective Registry Cases Closed with Outcome through 31 January 2017



Supplemental Analyses

Retrospective Reports: Though the Registry is a prospective registry, data from retrospective reports (pregnancies with a known outcome at the time of reporting) are also reviewed to assist in the detection of any unusual patterns in birth defects. Retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population experience. Therefore, the calculation of prevalence from these reports is inappropriate. Isolated cases of neural tube defects with efavirenz exposure have been reported. No other pattern of defects (isolated or syndromic) has been found in the overall evaluation of retrospective reports and Registry cases of birth defects.

Clinical Studies: In the analysis of reports from clinical studies in pregnancy, 18 infants with defects were identified among 401 live births with first trimester exposures to an antiretroviral therapy. The prevalence of birth defects per 100 live births among women with first trimester exposures to an antiretroviral (primarily nucleoside reverse transcriptase inhibitors) is 4.5 (95% CI: 2.7 - 7.0) (Table 12). The number of defects identified with an initial exposure in the second or third trimester is 31 among1892 live births, and the prevalence of birth defects per 100 live births is 1.6 (95% CI: 1.1 - 2.3). It is not surprising that the rate of detection of birth defects was relatively high among infants born to women enrolled in clinical studies conducted in pregnant women, as this group is often very different compared with either the CDC population-based surveillance system or the Registry. Differences include severity of disease at the time of maternal enrollment in clinical studies and rigorous infant follow-up and evaluation (e.g., echocardiography). In addition, women with first trimester exposures appeared to have more advanced disease. The higher rates of defects observed in clinical studies compared to the primary analysis are principally minor, spontaneously resolving cardiovascular defects that were detected on echocardiogram. To date, we have received 53 prospective cases of VSD, distributed across trimesters and drug exposures. Thus, the overall rate remains low and there is no apparent excess of cases among zidovudine or any drug exposure group or relevant trimester of exposure.

Reports from the Published Literature: There is a growing body of literature on the potential association between prenatal antiretroviral exposure and birth defects. The Registry attempts to identify

these studies through a systematic literature search conducted annually. The Registry has not identified a signal in any of the published studies reviewed to date.

Data Limitations

The Registry is designed to detect teratogenic effects of antiretroviral medications used in pregnancy. The occurrence of other developmental or functional defects is not systematically collected, although the Advisory Committee carefully reviews each pregnancy outcome received by the Registry. Potential limitations of registries such as this should be recognized. The limitations include, but are not limited to, underreporting (i.e., not every report of an exposure is obtained), differential reporting (i.e., there may be reasons why one report would be provided to the Registry and another would not), underascertainment of birth defects (i.e., not every birth defect is identified, e.g., reporter may not see the defect at birth), differential ascertainment of birth defects (e.g., variable use of diagnostic tests), and loss to follow-up (e.g., reports where no outcome information is obtained). Despite these limitations, such reports have been useful to supplement animal toxicology studies and clinical trial data, and to assist clinicians in weighing the risks and benefits of antiretroviral treatment during pregnancy and in counseling women with exposure during the first trimester. Moreover, accrual of additional patient experience over time will provide more definitive information regarding risks, if any, of exposure during pregnancy to the antiretroviral therapies followed in the Registry.

ADVISORY COMMITTEE CONSENSUS*

In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Given the emergence of new therapies about which data are still insufficient, health care providers are strongly encouraged to report eligible patients to the Registry at www.APRegistry.com.

PRÉCIS*

The Antiretroviral Pregnancy Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause; however, potential limitations of registries should be recognized. Providers are strongly encouraged to report eligible patients to www.APRegistry.com.

* Those wishing to cite data from this Report are encouraged to do so. However, to ensure consistency of reporting, you are required to include the consensus statement verbatim. Shorter presentations of Registry data (i.e., abstracts) may use the abbreviated précis. Editors should be reminded of this requirement and encouraged to exempt the sentence from any word count restrictions. Suggested citation: Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 1 January 2017. Wilmington, NC: Registry Coordinating Center; 2017. Available from URL: www.APRegistry.com.

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AERS – Adverse Events Reporting System

Birth Defect – A "birth defect" in this Registry 1) follows the CDC guidelines and is defined as any major structural malformation or chromosomal defect diagnosed or with signs/symptoms before six years of age, in addition 2) on a case by case basis, subject to independent review, any cluster of two or more conditional abnormalities, or 3) on a case by case basis, subject to independent review, any structural or chromosomal defect detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, fetus, or deceased infant. The Registry excludes birth defects attributed to prematurity itself (e.g., patent ductus arteriosus, patent foramen ovale, and inguinal hernias).

Birth Outcome – A birth outcome is defined as a live birth, spontaneous abortion, induced abortion, or stillbirth.

CDC – Centers for Disease Control and Prevention

Cirrhosis – Liver disease that involves scarring and damage of the liver cells and interruption of the blood flow through the liver.

Clinical Studies in Pregnancy – Prospective reports of women exposed to one or more of the Registry drugs during the course of a clinical study conducted in pregnant women are included in the Registry.

Compensated Liver Disease – The liver is diseased or cirrhotic but is still functioning relatively normally.

Corrected EDD – Estimated date of delivery obtained by prenatal test (e.g., ultrasound).

Decompensated Liver Disease – The liver is damaged and is not functioning properly. The subject is getting constantly worse and may have repeated episodes of gastrointestinal bleeding, marked fluid retention in the abdomen (ascites), and episodic confusion.

EDD – Estimated date of delivery

EI – Entry Inhibitor. Entry inhibitors are compounds designed to disrupt the interactions between the HIV virus and the cell surface. These compounds can block or prevent binding to human cell surface receptors (CD4, CCR5, and CXCR4, for instance), or prevent fusion of the HIV virus to the cell. There are currently three types of HIV entry inhibitors being researched and they work at three key steps in the HIV entry process.

Attachment Inhibitor – The first step in the process of viral entry involves the interaction between HIV's external "viral envelope" and the area of the CD4 cells that allow HIV to bind and attach to the cell. Attachment inhibitors try to disrupt the process that leads to the next step in viral entry – coreceptor binding.

Coreceptor Inhibitor – Following the attachment step, a change in the "viral envelope" occurs that allows the virus to interact with parts of CD4 cells known as coreceptors (e.g., CCR5, CXCR4). Coreceptor inhibitors act as antagonists and block binding to coreceptors on the cell surface. (Represented in this Registry by maraviroc)

Fusion Inhibitor – Once attachment and coreceptor binding have occurred, the HIV envelope then drives the "fusion" of the viral membrane with the CD4 cell membrane. Successful fusion of these membranes delivers into the cell the viral machinery required for a virus to replicate.

Fusion inhibitors bind to envelope proteins and block the structural changes necessary for the virus to fuse with the host CD4 cell. When the virus cannot penetrate the host cell membrane and infect the cell, HIV replication within that host cell is prevented. (Represented in this Registry by enfuvirtide)

Evaluable report – An evaluable report is a case, confirmed by a Provider, containing at least the minimum criteria for a report, and is not lost to follow-up. Prospectively reported evaluable cases with known outcomes are included in the analysis for the Interim Report produced semi-annually. Also included in this group are reports where the patient is in a clinical study in pregnancy. However, these reports are evaluated separately.

FDA – Food and Drug Administration

FDA Pregnancy Category – The FDA's revised Pregnancy and Lactation Labelling Rule (PLLR) or Final Rule, published 04 Dec 2014, will eliminate the current pregnancy letter categories over the next 3-5 years. Additional information is available at www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm:

- **Pregnancy Category A –** Controlled studies show no risk: Adequate, well-controlled studies in pregnant women failed to demonstrate risk to the fetus.
- **Pregnancy Category B –** No evidence of risk in humans: Either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative.
- **Pregnancy Category C –** Risk cannot be ruled out: Human studies are lacking, and animal studies are either positive for fetal risk, or lacking as well. However, potential benefits may justify the potential risk.
- **Pregnancy Category D –** Positive evidence of risk: Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
- **Pregnancy Category X –** Contraindicated in pregnancy: Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk which clearly outweighs any possible benefit to the patient.

HIPAA – Health Insurance Portability and Accountability Act

Induced Abortion – Voluntary interruption of pregnancy, includes pregnancy termination which occurs electively, to preserve maternal health, or due to fetal abnormalities.

INSTI – Integrase strand transfer inhibitor. INSTIs block a middle step in HIV's lifecycle. After HIV has entered a CD4 cell (T cell) and its RNA has been reverse transcribed to viral DNA, it must then be integrated into the CD4 cell's DNA. The HIV DNA can then hijack the CD4 cell, turning it into a viral factory. INSTIs block the viral DNA integration, hence their classification as integrase inhibitors. (Represented in this Registry by dolutegravir, elvitegravir and raltegravir)

IRB – Institutional Review Board

LMP – Last menstrual period

Lost to follow-up – A prospective report where follow-up information on the outcome (live birth, fetal loss) is never obtained, is unavailable, and/or where the indication of a defect is designated as "unknown" is considered "lost to follow-up".

MACDP (Metropolitan Atlanta Congenital Defects Program) – A program that monitors all major birth defects in five counties of the metropolitan Atlanta area (Clayton, Cobb, DeKalb, Fulton, and Gwinnett) with approximately 50,000 annual births from a population of about 2.9 million. MACDP acts as the model for many state-based programs and as a resource for the development of uniform methods and approaches to birth defect surveillance. For the ascertainment of birth defects among deliveries on or after January 1, 2012, MACDP's catchment area consists of 3 counties (DeKalb, Fulton, Gwinnett) with approximately 35,000 births.

MCN – Manufacturer's Control Number

NNRTI – Non-nucleoside analog reverse transcriptase inhibitor. (Represented in this Registry by delavirdine, efavirenz, etravirine, nevirapine and rilpivirine)

NRTI – Nucleoside analog reverse transcriptase inhibitor. (Represented in this Registry by abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, telbivudine, zalcitabine and zidovudine)

NtRTI – Nucleotide analog reverse transcriptase inhibitor. (Represented in this Registry by adefovir dipivoxil, tenofovir alafenamide and tenofovir disoproxil fumarate)

PHI – protected health information

PI – Protease inhibitor. (Represented in this Registry by amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir)

PKE – Pharmacokinetic enhancer. (Represented in this Registry by cobicistat)

Premature Birth – An infant at outcome <37 weeks gestational age or if gestational age not available, weighing <2500 grams as defined by CDC's criteria in the MACDP manual.

Prospective Report – Any report of a pregnancy exposure to a Registry antiretroviral drug(s) reported before the outcome of pregnancy is known.

Retrospective Report – Any report of a pregnancy exposure to a Registry antiretroviral drug(s) reported after the outcome or perceived outcome of the pregnancy is known (i.e., if the results of a prenatal test indicate a birth defect).

Spontaneous Abortion – Fetal death or expulsion of products of conception prior to 20 weeks gestation. Terminology may include: missed abortion, blighted ovum, incomplete abortion, and inevitable abortion.

Stillbirth – A fetal death occurring 20 weeks gestation or greater, or if the gestational age is unknown, a fetus weighing 500 grams or more.

Temporality Assessment – The determination of the probable association or non-association of the timing of the maternal antiretroviral exposure in pregnancy relative to the probable timing of organogenesis of a defect.

TBDR (Texas Birth Defects Registry) – A population-based active surveillance system that monitors all major birth defects among women who are residents of the state of Texas at the time of delivery. Approximately 400,000 live births occur annually.

WIRB – Western Institutional Review Board

APPENDICES

Appendix A: Prevalence of Birth Defects

Prevalence of Birth Defects, 95% Exact Confidence Intervals, and Raw Numbers for
Antiretroviral Drugs that have exceeded the Threshold of N ≥ 200 First Trimester Exposed Live Births

Report Date	Lamivudine	Zidovudine	Nelfinavir	Stavudine	Nevirapine	Abacavir	Efavirenz	Didanosine	Ritonavir	Lopinavir	Tenofovir disoproxil fumarate	Indinavir	Emtricitabine	Atazanavir	Darunavir	Raltegravir	Rilpivirine
Jan 02	2.6% (1.6, 4.1) 18/687	2.5% (1.5, 4.0) 17/684	3.1% (1.4, 6.1) 8/256	2.0% (0.7, 4.6) 5/250													
Jul 02	2.9% (1.8, 4.3) 23/807	2.7% (1.7, 4.1) 21/782	3.0% (1.4, 5.6) 9/301	1.8% (0.6, 4.1) 5/283	1.9% (0.5, 4.7) 4/216												
Jan 03	3.0% (2.0, 4.3) 28/940	2.8% (1.8, 4.1) 25/886	2.9% (1.4, 5.3) 10/343	2.2% (0.9, 4.4) 7/323	2.0% (0.7, 4.7) 5/248												
Jul 03	2.7% (1.8, 3.9) 29/1075	2.7% (1.8, 3.9) 27/1003	2.9% (1.4, 5.1) 11/381	2.3% (1.0, 4.5) 8/345	2.1% (0.8, 4.5) 6/289												
Jan 04	2.9% (2.0, 4.0) 34/1185	3.1% (2.2, 4.3) 34/1088	3.6% (2.0, 5.9) 15/416	2.9% (1.4, 5.1) 11/381	2.1% (0.9, 4.3) 7/332	4.0% (1.9, 7.5) 9/223											
Jul 04	2.8% (2.0, 3.9) 37/1318	3.0% (2.1, 4.2) 36/1185	4.0% (2.4, 6.2) 18/455	2.6% (1.3, 4.7) 11/418	2.1% (0.9, 4.1) 8/383	3.5% (1.6, 6.6) 9/254											
Jan 05	2.7% (1.9, 3.7) 39/1432	3.0% (2.1, 4.1) 38/1278	3.8% (2.3, 5.9) 19/496	2.6% (1.3, 4.5) 11/431	2.1% (1.0, 4.0) 9/419	3.1% (1.4, 5.9) 9/286	2.4% (0.8, 5.6) 5/206	6.3% (3.4, 10.6) 13/205									
Jul 05	2.8% (2.0, 3.7) 43/1554	3.0% (2.2, 4.0) 41/1371	3.7% (2.3, 5.7) 20/534	2.7% (1.4, 4.7) 12/446	2.0% (0.9, 3.8) 9/449	3.4% (1.7, 6.0) 11/322	2.2% (0.7, 5.1) 5/228	6.4% (3.5, 10.5) 14/220	2.9% (1.2, 5.9) 7/243								
Jan 06	2.7% (2.0, 3.6) 45/1663	2.9% (2.1, 4.0) 43/1459	3.7% (2.3, 5.6) 21/572	2.7% (1.4, 4.6) 12/451	1.9% (0.9,3.5) 9/479	3.2% (1.6, 5.6) 11/345	2.5% (0.9 5.3) 6/244	6.0% (3.3, 9.8) 14/234	3.1% (1.4, 5.8) 9/291								
Jul 06	2.8% (2.0, 3.6) 49/1776	3.0% (2.2, 4.0) 47/1550	3.7% (2.3, 5.5) 22/601	2.6% (1.4, 4.5) 12/459	1.9% (0.9, 3.6) 10/515	2.9% (1.5, 5.2) 11/378	2.4% (0.9, 5.1) 6/255	5.6% (3.1, 9.3) 14/248	2.8% (1.3, 5.1) 10/359	2.9% (1.1, 6.2) 6/206	2.6% (1.0, 5.6) 6/231						
Jan 07	2.9% (2.2, 3.8) 55/1888	3.1% (2.3, 4.1) 51/1643	3.8% (2.4, 5.6) 24/638	2.8% (1.5, 4.7) 13/468	2.4% (1.3, 4.1) 13/543	3.2% (1.7, 5.4) 13/404	2.5% (1.0, 5.1) 7/281	5.8% (3.3, 9.4) 15/259	2.7% (1.3, 4.8) 11/410	2.6% (1.0, 5.6) 6/232	2.6% (1.1, 5.4) 7/266						
Jul 07	2.7% (2.1, 3.6) 57/2076	2.9% (2.2, 3.8) 53/1816	3.6% (2.3, 5.3) 24/670	2.7% (1.4, 4.6) 13/480	2.4% (1.3, 4.0) 14/584	3.2% (1.8, 5.3) 14/436	2.4% (1.0, 4.8) 7/295	5.3% (2.9, 8.7)* 14/266	2.1% (1.0, 3.8)* 10/476	1.9% (0.6, 4.3)* 5/267	1.6% (0.6, 3.4)* 6/380						
Jan 08	3.1% (2.4, 3.8) 85/2784	3.1% (2.5, 3.8) 87/2808	3.4% (2.3, 4.7) 33/972	2.9% (1.8, 4.5) 19/651	2.4% (1.5, 3.8) 18/737	3.3% (1.9, 5.3) 17/512	2.7% (1.3, 5.0) 10/364	4.5% (2.6, 7.3) 16/353	2.5% (1.5, 4.1) 16/628	1.8% (0.7, 3.9) 6/328	2.2% (1.1, 4.0) 11/491	2.2% (0.8, 4.7) 6/272					
Jul 08	2.9% (2.4, 3.6) 91/3089	3.1% (2.5, 3.7) 94/3068	3.5% (2.5, 4.8) 37/1066	2.7% (1.7, 4.2) 19/696	2.3% (1.4, 3.6) 18/785	3.1% (1.9, 4.9) 18/578	3.2% (1.7, 5.4) 13/407	4.4% (2.5, 7.1) 16/362	2.3% (1.4, 3.6) 18/783	1.9% (0.8, 3.7) 8/420	2.3% (1.3, 3.9) 14/606	2.2% (0.8, 4.7) 6/275	3.2% (1.4, 6.2) 8/252	2.0% (0.7, 4.7) 5/246			
Jan 09	2.9% (2.3, 3.5) 93/3226	3.1% (2.5, 3.7) 95/3108	3.4% (2.4, 4.7) 37/1074	2.5% (1.5, 3.9) 19/754	2.2% (1.3, 3.5) 18/817	3.0% (1.8, 4.6) 18/608	2.9% (1.6, 4.9) 14/477	4.4% (2.5, 7.0) 16/365	2.3% (1.4, 3.5) 20/883	1.7% (0.7, 3.3) 8/470	2.4% (1.4, 3.8) 16/678	2.2% (0.8, 4.7) 6/276	2.9% (1.3, 5.4) 9/313	2.4% (1.0, 4.9) 7/292			
Jul 09	2.9% (2.3, 3.5) 96/3314	3.1% (2.5, 3.7) 97/3167	3.4% (2.4, 4.7) 37/1075	2.5% (1.5, 3.8) 19/771	2.1% (1.3, 3.4) 18/842	3.0% (1.8, 4.7) 19/628	2.8% (1.5, 4.7) 14/501	4.6% (2.7, 7.3) 17/370	2.2% (1.4, 3.3) 22/1000	1.7% (0.8, 3.2) 9/526	2.4% (1.4, 3.7) 18/756	2.2% (0.8, 4.7) 6/276	2.9% (1.4, 5.1) 11/384	2.6% (1.2, 4.9) 9/343			
Jan 10	2.8% (2.3, 3.5) 99/3481	3.0% (2.5, 3.7) 100/3289	3.4% (2.4, 4.7) 37/1080	2.4% (1.4, 3.7) 19/795	2.2% (1.3, 3.3) 19/882	2.8% (1.7, 4.4) 19/670	2.6% (1.4, 4.3) 14/546	4.5% (2.6, 7.1) 17/380	2.1% (1.4, 3.2) 24/1122	1.7% (0.8, 3.1) 10/590	2.2% (1.3, 3.4) 19/879	2.2% (0.8, 4.7) 6/276	2.6% (1.4, 4.6) 12/456	2.3% (1.0, 4.3) 9/393			

Report Date	Lamivudine	Zidovudine	Nelfinavir	Stavudine	Nevirapine	Abacavir	Efavirenz	Didanosine	Ritonavir	Lopinavir	Tenofovir disoproxil fumarate	Indinavir	Emtricitabine	Atazanavir	Darunavir	Raltegravir	Rilpivirine
Jul 10	3.0% (2.5, 3.6) 113/3754	3.2% (2.6, 3.8) 113/3534	3.8% (2.8, 5.1) 45/1182	2.4% (1.4, 3.7) 19/797	2.6% (1.7, 3.8) 25/970	2.9% (1.8, 4.5) 21/717	2.8% (1.6, 4.5) 17/604	4.7% (2.8, 7.3) 19/404	2.4% (1.6, 3.4) 30/1271	2.1% (1.1, 3.5) 14/676	2.5% (1.6, 3.7) 25/981	2.1% (0.8, 4.6) 6/284	3.0% (1.7, 4.8) 16/542	2.5% (1.2, 4.4) 11/448			
Jan 11	3.1% (2.5, 3.7) 118/3864	3.3% (2.7, 3.9) 118/3620	3.9% (2.8, 5.1) 46/1193	2.4% (1.4, 3.7) 19/797	2.5% (1.6, 3.7) 25/987	3.0% (1.9, 4.5) 22/744	2.7% (1.6, 4.3) 17/623	4.7% (2.8, 7.2) 19/406	2.4% (1.6,3.3) 33/1401	2.2% (1.2, 3.5) 16/738	2.4% (1.6, 3.5) 26/1092	2.1% (0.8, 4.5) 6/285	2.7% (1.5, 4.2) 17/641	2.4% (1.2, 4.1) 12/502			
Jul 11	3.1% (2.6, 3.7) 122/3966	3.2% (2.7, 3.9) 120/3699	3.8% (2.8, 5.1) 46/1196	2.4% (1.4, 3.7) 19/799	2.6% (1.7, 3.8) 26/1002	3.2% (2.1, 4.7) 25/781	2.6% (1.5, 4.2) 17/644	4.6% (2.8, 7.2) 19/409	2.2% (1.6, 3.1) 35/1567	2.2% (1.3, 3.5) 18/816	2.2% (1.5, 3.2) 27/1219	2.1% (0.8, 4.5) 6/285	2.4% (1.4, 3.7) 18/764	2.1% (1.1, 3.6) 12/576			
Jan 12	3.1% (2.6, 3.7) 127/4088	3.3% (2.7, 3.9) 124/3789	3.9% (2.9, 5.2) 47/1204	2.5% (1.5, 3.8) 20/801	2.7% (1.8, 4.0) 28/1020	3.0% (2.0, 4.5) 25/823	2.7% (1.6, 4.2) 18/679	4.6% (2.8, 7.2) 19/409	2.2% (1.6, 3.0) 39/1741	2.4% (1.5, 3.6) 21/883	2.3% (1.5, 3.2) 31/1370	2.1% (0.8, 4.5) 6/286	2.3% (1.4, 3.5) 21/899	1.9% (1.0, 3.3) 13/669			
Jul 12	3.2% (2.7, 3.8) 133/4185	3.3% (2.7, 3.9) 127/3864	3.9% (2.9, 5.2) 47/1207	2.6% (1.6, 4.0) 21/802	3.0% (2.0, 4.2) 31/1036	3.1% (2.0, 4.5) 26/848	2.6% (1.5, 4.0) 18/702	4.8% (3.0, 7.4) 20/413	2.3% (1.7, 3.1) 45/1923	2.4% (1.5, 3.5) 23/969	2.4% (1.7, 3.3) 39/1612	2.4% (1.0, 5.0) 7/287	2.5% (1.7, 3.7) 27/1068	2.1% (1.2, 3.5) 16/.746			
Jan 13	3.2% (2.6, 3.7) 135/4273	3.3% (2.7, 3.9) 128/3932	3.9% (2.9, 5.1) 47/1210	2.6% (1.6, 4.0) 21/803	3.0% (2.0, 4.2) 31/1049	3.1% (2.0, 4.4) 27/880	2.4% (1.4, 3.9) 18/735	4.8% (3.0, 7.4) 20/413	2.2% (1.6, 3.0) 47/2096	2.3% (1.5, 3.4) 24/1049	2.3% (1.7, 3.1) 42/1800	2.4% (1.0, 5.0) 7/288	2.4% (1.6, 3.5) 30/1230	2.1% (1.2, 3.3) 17/813			
Jul 13	3.1% (2.6, 3.7) 136/4360	3.2% (2.7, 3.8) 129/4000	3.9% (2.9, 5.1) 47/1211	2.6% (1.6, 4.0) 21/805	2.9% (2.0, 4.1) 31/1061	3.0% (2.0, 4.3) 27/905	2.3% (1.4, 3.7) 18/766	4.8% (3.0, 7.3) 20/416	2.3% (1.7, 3.0) 52/2260	2.3% (1.5, 3.4) 26/1125	2.3% (1.7, 3.1) 46/1982	2.4% (1.0, 4.9) 7/289	2.4% (1.7, 3.4) 34/1400	2.2% (1.3, 3.4) 19/878	2.4% (0.8, 5.4) 5/212		
Jan 14	3.1% (2.6, 3.7) 137/4418	3.2% (2.7, 3.8) 129/4034	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 4.0) 21/809	2.9% (2.0, 4.1) 31/1068	3.0% (2.0, 4.4) 28/925	2.3% (1.3, 3.5) 18/797	4.8% (2.9, 7.3) 20/418	2.2% (1.7, 2.9) 53/2391	2.2% (1.4, 3.2) 26/1174	2.2% (1.6, 2.9) 47/2141	2.4% (1.0, 4.9) 7/289	2.3% (1.6, 3.1) 35/1543	2.2% (1.3, 3.3) 20/922	2.3% (0.9, 5.0) 6/258		
Jul 14	3.1% (2.6, 3.7) 140/4485	3.2% (2.7, 3.8) 132/4069	3.9% (2.8, 5.1) 47/1214	2.6% (1.6, 3.9) 21/810	2.9% (1.9, 4.0) 31/1083	2.9% (1.9, 4.2) 28/957	2.3% (1.4, 3.6) 19/825	4.7% (2.9, 7.2) 20/423	2.4% (1.8, 3.0) 60/2542	2.4% (1.6, 3.4) 29/1218	2.3% (1.7, 3.0) 53/2330	2.4% (1.0, 4.9) 7/289	2.4% (1.7, 3.2) 41/1721	2.2% (1.4, 3.3) 22/993	2.7% (1.2, 5.3) 8/293		
Jan 15	3.1% (2.6, 3.7) 142/4527	3.3% (2.7, 3.9) 133/4092	3.9% (2.8, 5.1) 47/1214	2.6% (1.6, 3.9) 21/810	2.9% (2.0, 4.1) 32/1096	3.0% (2.0, 4.2) 29/976	2.3% (1.4, 3.6) 20/852	4.7% (2.9, 7.2) 20/423	2.4% (1.8, 3.0) 62/2628	2.3% (1.6, 3.3) 29/1242	2.4% (1.8, 3.0) 58/2452	2.4% (1.0, 4.9) 7/289	2.5% (1.8, 3.3) 46/1834	2.2% (1.4, 3.3) 23/1037	2.9% (1.3, 5.4) 9/314		
Jul 15	3.1% (2.6, 3.7) 143/4566	3.2% (2.7, 3.8) 133/4113	3.9% (2.8, 5.1) 47/1215	2.6% (1.6, 3.9) 21/810	2.9% (2.0, 4.1) 32/1105	2.9% (2.0, 4.2) 29/993	2.4% (1.5, 3.6) 21/883	4.7% (2.9, 7.2) 20/423	2.3% (1.8, 3.0) 63/2720	2.3% (1.5, 3.3) 29/1261	2.3% (1.8, 3.0) 60/2608	2.4% (1.0, 4.9) 7/289	2.4% (1.7, 3.1) 47/1984	2.2% (1.4, 3.2) 24/1093	2.7% (1.2, 5.1) 9/333		
Jan 16	3.1% (2.6, 3.7) 143/4589	3.2% (2.7, 3.8) 133/4128	3.9% (2.9, 5.1) 47/1213	2.6% (1.6, 3.9) 21/810	2.9% (2.0, 4.0) 32/1113	3.0% (2.0, 4.2) 30/1007	2.4% (1.5, 3.7) 22/902	4.7% (2.9, 7.2) 20/422	2.3% (1.7, 2.9) 64/2815	2.2% (1.5, 3.2) 29/1290	2.2% (1.7, 2.8) 61/2779	2.4% (1.0, 4.9) 7/289	2.2% (1.6, 3.0) 48/2145	2.1% (1.3, 3.1) 24/1142	2.8% (1.4, 5.2) 10/352	3.0% (1.1, 6.4) 6/201	
Jul 16	3.1% (2.6, 3.6) 144/4671	3.2% (2.7, 3.8) 133/4144	3.9% (2.9, 5.1) 47/1211	2.6% (1.6, 3.9) 21/811	2.8% (1.9, 4.0) 32/1124	2.9% (2.0, 4.1) 30/1031	2.4% (1.5, 3.5) 22/934	4.7% (2.9, 7.2) 20/426	2.2% (1.7, 2.8) 65/2983	2.1% (1.4, 3.0) 29/1384	2.2% (1.7, 2.8) 67/3007	2.4% (1.0, 4.9) 7/289	2.2% (1.7, 3.0) 54/2326	2.1% (1.4, 3.1) 25/1187	2.6% (1.2, 4.7) 10/385	2.8% (1.1, 5.8) 7/247	0.5% (0.0, 2.7) 1/202
Jan 17	3.0% (2.6, 3.6) 145/4763	3.2% (2.7, 3.8) 133/4161	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	2.8% (1.9, 4.0) 32/1134	2.8% (1.9, 4.0) 30/1063	2.2% (1.4, 3.4) 22/978	4.7% (2.9, 7.2) 20/427	2.2% (1.7, 2.8) 67/3056	2.1% (1.4, 3.0) 30/1400	2.3% (1.8, 2.9) 75/3229	2.4% (1.0, 4.9) 7/289	2.4% (1.8, 3.1) 60/2523	2.1% (1.4, 3.1) 26/1227	2.5% (1.2, 4.5) 10/407	2.7% (1.1, 5.4) 7/263	1.2% (0.3, 3.5) 3/247

* Updated information was received on a case that changed the status to retrospective and it is no longer included in this table.

Appendix B: Summary of Treatment Regimens

Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 January 2017

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Enrolled	9581	6853	2351	18787
3TC	5234	5531	1801	12609
ABC	1165	914	340	2428
ADV	73	0	2	75
APV	32	5	8	45
ATV	1316	519	154	1993
COBI	142	30	10	183
d4T	912	112	87	1120
ddC	62	8	5	76
ddI	488	297	168	963
DLV	13	1	2	16
DRV	451	157	85	699
DTG	88	23	31	142
EFV	1134	127	63	1333
ETR	72	29	9	111
ETV	77	2	0	79
EVG	129	28	8	165
FOS	122	23	13	159
FTC	2774	825	313	3917
IDV	335	116	47	505
LdT	68	7	4	79
LPV	1571	1856	666	4100
MVC	27	5	0	32
NFV	1266	1990	734	4003
NVP	1244	973	560	2793
RAL	304	120	129	556
RPV	266	115	30	412
RTV	3346	2478	890	6730
SQV	204	137	86	428
T20	26	6	9	41
TAF	10	7	2	19
TDF	3651	988	488	5135
TPV	4	0	2	6
ZDV	4555	6278	3153	14016

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Enrolled	9581	6853	2351	18787
3TC & NFV & ZDV	693	1531	465	2689
3TC & LPV & RTV & ZDV	506	1256	352	2114
ZDV	539	658	401	1598
3TC & NVP & ZDV	537	651	247	1436
ABC & 3TC & ZDV	256	572	168	996
ATV & FTC & RTV & TDF	681	272	42	995
3TC & ZDV	310	383	108	801
FTC & LPV & RTV & TDF	250	104	24	378
FTC & RPV & TDF	215	86	8	309
EFV & FTC & TDF	261	38	8	307
DRV & FTC & RTV & TDF	217	47	2	266
TDF	184	12	64	260
IDV & 3TC & ZDV	139	58	17	214
FTC & TDF	188	10	13	211
3TC & TDF & ZDV	193	10	6	209
EFV & 3TC & ZDV	96	56	12	164
ABC & ATV & 3TC & RTV	103	25	1	129
FTC & RAL & TDF	86	32	10	128
COBI & EVG & FTC & TDF	104	17	3	124
3TC & NVP & d4T	102	11	3	116
3TC	86	12	14	112
EFV & 3TC & d4T	111	0	0	111
ATV & 3TC & RTV & ZDV	57	45	5	107
3TC & NFV & d4T	95	8	0	103
ABC & 3TC & LPV & RTV & ZDV	45	47	10	102
ddI	21	59	11	91
3TC & NFV & NVP & ZDV	27	40	16	83
FTC & NVP & TDF	74	5	1	80
3TC & LPV & RTV & TDF	68	4	0	72
3TC & RTV & SQV & ZDV	18	42	12	72
LdT	61	5	4	70
ABC & 3TC & LPV & RTV	52	13	4	69
ETV	68	1	0	69
ABC & 3TC & NVP	63	4	0	67
ADV	56	0	0	56
ABC & 3TC & NVP & ZDV	24	16	12	52
EFV & 3TC & NVP & ZDV	52	0	0	52
EFV & FTC & LPV & RTV & TDF	48	1	1	50
3TC & LPV & RTV & TDF & ZDV	25	17	6	48
3TC & SQV & ZDV	31	11	5	47
ABC & 3TC & NFV & ZDV	20	22	5	47
ABC & ATV & 3TC	40	6	1	47
EFV & FTC & 3TC & LPV & RTV & TDF & ZDV	44	2	1	47
3TC & LPV & NFV & RTV & ZDV	12	23	8	43
ATV & 3TC & LPV & RTV & ZDV	21	19	2	42
ATV & 3TC & ZDV	32	8	2	42
DRV & 3TC & RTV & ZDV	12	28	1	41
3TC & d4T	36	4	0	40
EFV & 3TC & NFV & ZDV	40	0	0	40
LPV & RAL & RTV	38	2	0	40

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
EFV & 3TC & TDF	36	3	0	39
EFV & 3TC & NVP & d4T	38	0	0	38
FTC & FOS & RTV & TDF	32	4	2	38
LPV & RTV	30	7	1	38
ddI & NFV & ZDV	18	15	5	38
ddI & NFV & d4T	32	4	1	37
ABC & DTG & 3TC	29	5	1	35
NFV	27	7	0	34
DRV & FTC & RAL & RTV & TDF	20	7	6	33
ATV & FTC & 3TC & LPV & RTV & TDF & ZDV	24	6	2	32
IDV & 3TC & d4T	31	1	0	32
FTC & 3TC & LPV & RTV & TDF & ZDV	18	11	2	31
ddI & 3TC & NFV & ZDV	5	16	10	31
ABC & 3TC & TDF & ZDV	20	8	2	30
ABC & EFV & 3TC	28	2	0	30
ATV & FTC & RTV & TDF & ZDV	5	2	23	30
DTG & FTC & TDF	22	3	3	28
IDV	25	3	0	28
ddI & 3TC & NVP & ZDV	0	10	18	28
ddI & ZDV	17	9	2	28
ABC & DRV & 3TC & RTV	20	7	0	27
EFV	27	0	0	27
ATV & EFV & FTC & RTV & TDF	23	2	0	25
ATV & FTC & RAL & RTV & TDF	11	9	5	25
ATV & FTC & TDF	15	7	1	23
FTC & NFV & TDF	18	4	0	22
ddC & ZDV	20	2	0	22
3TC & NVP & TDF	19	2	0	21
3TC & d4T & TDF	21	0	0	21
NVP	16	3	2	21
NVP & ZDV	2	0	19	21
ddI & NFV	4	10	7	21
3TC & LPV & NVP & RTV & ZDV	3	11	6	20
3TC & LPV & RTV & d4T	16	1	3	20
ABC & ATV & 3TC & RTV & TDF	18	2	0	20
FTC & LPV & RTV & TDF & ZDV	10	0	10	20
ddI & NVP & d4T	14	6	0	20
3TC & NFV & d4T & ZDV	13	4	2	19
3TC & RAL & ZDV	6	9	4	19
3TC & RTV & ZDV	13	5	1	19
ABC & FOS & 3TC & RTV	16	1	0	17
EFV & 3TC & LPV & RTV & ZDV	16	1	0	17
FTC & LPV & RTV & ZDV	2	10	5	17
ddI & 3TC & ZDV	6	9	2	17
3TC & NFV & TDF & ZDV	6	8	2	16
ATV & 3TC & RTV & TDF	15	1	0	16
ddI & NFV & NVP	3	8	5	16
ddI & NVP & ZDV	13	2	1	16
3TC & NVP & d4T & ZDV	5	7	3	15
ABC & ATV & 3TC & RTV & ZDV	10	3	2	15
ATV & FTC & LPV & RTV & TDF	13	2	0	15
FOS & 3TC & RTV & ZDV	10	4	1	15

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
DRV & ETR & RAL & RTV	12	2	0	14
ETR & 3TC & ZDV	7	7	0	14
IDV & 3TC & RTV & ZDV	10	4	0	14
LPV & RTV & TDF & ZDV	8	4	2	14
d4T	14	0	0	14
ddI & LPV & RTV & TDF	11	3	0	14
ABC & 3TC & d4T	12	1	0	13
ABC & EFV & 3TC & ZDV	13	0	0	13
IDV & 3TC & NFV & ZDV	9	3	1	13
3TC & LPV & RAL & RTV & ZDV	5	0	7	12
ABC & ATV & 3TC & ZDV	8	3	1	12
ABC & ddI & LPV & RTV	12	0	0	12
ATV & FTC & 3TC & RTV & TDF & ZDV	10	2	0	12
EFV & FTC & RAL & TDF	8	3	1	12
ATV & RTV	10	1	0	11
FTC & RTV & SQV & TDF	7	4	0	11
FTC & RTV & TDF	10	1	0	11
3TC & NFV	6	2	2	10
ABC & 3TC & LPV & RTV & TDF	7	3	0	10
ABC & 3TC & NFV	8	2	0	10
ATV & DRV & FTC & RTV & TDF	5	3	2	10
ATV & RTV & TDF & ZDV	7	2	1	10
COBI & EVG & FTC & TAF	5	4	1	10
FTC & LPV & RAL & RTV & TDF	4	4	2	10
IDV & 3TC & RTV & d4T	10	0	0	10
LPV & RTV & ZDV	4	3	3	10
ddI & 3TC & LPV & RTV & ZDV	7	3	0	10
ddI & 3TC & NVP	4	5	1	10
3TC & NFV & NVP & d4T & ZDV	7	2	0	9
3TC & NVP & TDF & ZDV	5	2	2	9
3TC & TDF	9	0	0	9
ABC & EFV & d4T	9	0	0	9
ABC & LPV & RTV & TDF	8	1	0	9
ATV & 3TC & RTV & TDF & ZDV	7	2	0	9
ATV & ddI & RTV & TDF	9	0	0	9
EFV & 3TC & NFV & d4T	9	0	0	9
FTC & ETR & TDF	6	3	0	9
FTC & RPV & TDF & ZDV	3	3	3	9
SQV & ddC & ZDV	9	0	0	9
ddI & EFV & d4T	9	0	0	9
ddI & LPV & RTV & ZDV	4	5	0	9
ddI & SQV & ZDV	3	5	1	9
3TC & LPV & RTV & d4T & ZDV	4	3	1	8
3TC & NFV & TDF	6	2	0	8
3TC & RTV & SQV & d4T	7	1	0	8
3TC & d4T & ZDV	8	0	0	8
ABC & 3TC & RAL	6	2	0	8
ADV & 3TC	8	0	0	8
ATV & FTC & 3TC & NFV & RTV & TDF & ZDV	8	0	0	8
DRV & DTG & FTC & RTV & TDF	4	2	2	8
ddC	8	0	0	8
ddI & 3TC & LPV & RTV	4	3	1	8

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
ddI & 3TC & NFV	4	3	1	8
ddI & 3TC & NFV & NVP & ZDV	2	4	2	8
ABC & 3TC & RTV & SQV	7	0	0	7
ABC & EFV & 3TC & NFV & ZDV	7	0	0	7
ABC & FTC & d4T	7	0	0	7
ATV & COBI & EVG & FTC & RTV & TDF	7	0	0	7
DRV & FTC & 3TC & LPV & RTV & TDF & ZDV	5	0	2	7
DRV & FTC & ETR & RTV & TDF	5	1	1	7
DRV & FTC & RTV & TDF & ZDV	0	1	6	7
DRV & FTC & TDF	5	2	0	7
DRV & RAL & RTV	7	0	0	7
EFV & 3TC & NVP & d4T & ZDV	7	0	0	7
EFV & FTC & RPV & TDF	6	1	0	7
ETV & TDF	7	0	0	7
FOS & 3TC & ZDV	5	2	0	7
IDV & 3TC & d4T & ZDV	7	0	0	7
RAL	4	3	0	7
ddI & 3TC & NFV & d4T & ZDV	7	0	0	7
ddI & IDV & d4T	7	0	0	7
3TC & RAL & TDF	6	0	0	6
3TC & SQV & d4T	6	0	0	6
ABC & ATV & 3TC & LPV & RTV & ZDV	4	1	1	6
ABC & EFV & 3TC & NVP	6	0	0	6
ABC & NVP & ZDV	5	1	0	6
ADV & LdT	6	0	0	6
ATV & 3TC & d4T	6	0	0	6
ATV & DTG & FTC & RTV & TDF	6	0	0	6
DRV & RTV	6	0	0	6
EFV & FTC & 3TC & NFV & TDF & ZDV	5	1	0	6
EFV & IDV	6	0	0	6
FTC & TDF & ZDV	2	4	0	6
FTC & d4T	6	0	0	6
IDV & ZDV	5	1	0	6
SQV & ZDV	6	0	0	6
ddI & 3TC & NVP & d4T & ZDV	5	1	0	6
ddI & EFV & LPV & RTV	6	0	0	6
ddI & EFV & NVP & ZDV	6	0	0	6
ddI & LPV & RTV & d4T	6	0	0	6
3TC & LPV & RTV	5	0	0	5
3TC & NFV & NVP	5	0	0	5
3TC & NFV & SQV & d4T	5	0	0	5
ABC & 3TC	5	0	0	5
ABC & 3TC & LPV & NFV & RTV & ZDV	2	3	0	5
ABC & ATV & 3TC & LPV & RTV	3	2	0	5
ABC & ATV & FTC & 3TC & RTV & TDF	3	2	0	5
ABC & ATV & FTC & RTV & TDF	3	2	0	5
ABC & ATV & RTV & TDF	5	0	0	5
ABC & FOS & 3TC	5	0	0	5
ABC & FTC & 3TC & LPV & RTV & TDF	3	2	0	5
ABC & NFV & d4T	5	0	0	5
ABC & NVP & d4T	2	2	1	5
ATV	4	1	0	5

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
ATV & FTC & RPV & RTV & TDF	4	1	0	5
COBI & EVG & FTC & TAF & TDF	4	0	1	5
DRV & FTC & 3TC & RTV & TDF & ZDV	4	0	1	5
DRV & RAL & RTV & TDF	5	0	0	5
DRV & RTV & TDF	5	0	0	5
EFV & 3TC & LPV & RTV	5	0	0	5
EFV & FTC & 3TC & NVP & TDF & ZDV	5	0	0	5
EFV & FTC & NVP & TDF	5	0	0	5
FTC & 3TC & LPV & RTV & TDF	4	0	1	5
FTC & 3TC & NVP & TDF & ZDV	5	0	0	5
FTC & ETR & RAL & TDF	5	0	0	5
FTC & RAL & TDF & ZDV	1	1	3	5
NVP & TDF & ZDV	1	3	1	5
ddI & EFV & NVP & d4T	5	0	0	5
ddI & EFV & ZDV	5	0	0	5
ddI & LPV & NVP & RTV	5	0	0	5
ddI & NFV & d4T & ZDV	4	0	1	5
ddI & NVP & TDF	5	0	0	5
3TC & NFV & RTV & SQV & ZDV	1	3	0	4
3TC & NFV & SQV & ZDV	3	1	0	4
3TC & ddC & ZDV	4	0	0	4
ABC & 3TC & LPV & RTV & TDF & ZDV	2	2	0	4
ABC & 3TC & RAL & ZDV	1	2	1	4
ABC & 3TC & TDF	4	0	0	4
ABC & ATV & ddI & RTV	4	0	0	4
ABC & EFV & FTC & 3TC & TDF & ZDV	2	1	1	4
ABC & NFV & TDF	3	1	0	4
ABC & ddI & NFV	4	0	0	4
ATV & ddI & 3TC	4	0	0	4
ATV & ddI & 3TC & RTV	4	0	0	4
DRV & FTC & ETR & RAL & RTV & TDF	4	0	0	4
DRV & FTC & LPV & RTV & TDF	3	1	0	4
DRV & FTC & MVC & RAL & RTV & TDF	4	0	0	4
DRV & FTC & RPV & RTV & TDF	4	0	0	4
DRV & RTV & TDF & ZDV	4	0	0	4
EFV & 3TC	4	0	0	4
EFV & 3TC & LPV & RTV & TDF	4	0	0	4
EFV & 3TC & LPV & RTV & TDF & ZDV	4	0	0	4
EFV & 3TC & NFV & TDF & ZDV	4	0	0	4
EFV & 3TC & TDF & ZDV	4	0	0	4
EFV & FTC & TDF & ZDV	0	0	4	4
ETR & 3TC & LPV & RTV & ZDV	2	2	0	4
FOS & 3TC & RTV & TDF	2	0	2	4
FTC & 3TC & LPV & RAL & RTV & TDF & ZDV	3	0	1	4
FTC & 3TC & LPV & RPV & RTV & TDF & ZDV	4	0	0	4
FTC & 3TC & NFV & TDF & ZDV	0	4	0	4
FTC & RAL & RPV & TDF	1	1	2	4
IDV & 3TC & NVP & ZDV	2	2	0	4
LPV & NVP & RTV & TDF	4	0	0	4
LPV & RTV & d4T & TDF	4	0	0	4
SQV	3	1	0	4
ddI & 3TC	4	0	0	4

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
3TC & LPV & RAL & RTV & TDF	3	0	0	3
3TC & LPV & RTV & d4T & TDF	3	0	0	3
3TC & NFV & NVP & d4T	3	0	0	3
3TC & NFV & ddC & ZDV	2	1	0	3
3TC & NVP & RTV & SQV & ZDV	1	1	1	3
3TC & RTV & SQV	3	0	0	3
ABC & 3TC & NFV & NVP & ZDV	2	0	1	3
ABC & 3TC & NVP & d4T	2	1	0	3
ABC & 3TC & RTV & SQV & ZDV	1	2	0	3
ABC & ATV & DTG & 3TC & RTV	3	0	0	3
ABC & ATV & EFV & FTC & 3TC & RTV & TDF	3	0	0	3
ABC & EFV & 3TC & NVP & d4T & ZDV	3	0	0	3
ABC & FOS & 3TC & RTV & ZDV	2	0	1	3
ABC & FTC & LPV & RTV & TDF	3	0	0	3
ABC & IDV & 3TC & ZDV	2	1	0	3
ABC & LPV & RTV & d4T	2	1	0	3
ABC & NVP & TDF	3	0	0	3
ABC & ddI & NVP & d4T	3	0	0	3
ABC & ddI & T20 & FOS & 3TC & TDF	3	0	0	3
APV & 3TC & d4T	3	0	0	3
ATV & 3TC & RTV	1	2	0	3
ATV & EFV & FTC & 3TC & RTV & TDF & ZDV	3	0	0	3
ATV & FTC & FOS & RTV & TDF	3	0	0	3
ATV & FTC & RAL & RTV & TDF & ZDV	1	0	2	3
ATV & FTC & RPV & TDF	3	0	0	3
ATV & ddI & FTC	3	0	0	3
ATV & ddI & FTC & RTV & TDF	3	0	0	3
COBI & DRV & FTC & TDF	2	1	0	3
COBI & EVG & FTC & RPV & TDF	2	1	0	3
DLV & 3TC & ZDV	2	0	1	3
DRV & 3TC & LPV & RTV & ZDV	1	2	0	3
DRV & EFV & FTC & RTV & TDF	3	0	0	3
DRV & FTC & NVP & RTV & TDF	2	1	0	3
DRV & MVC & RTV	3	0	0	3
EFV & 3TC & NFV & NVP & ZDV	3	0	0	3
EFV & 3TC & NFV & d4T & ZDV	3	0	0	3
EFV & 3TC & NVP & TDF	3	0	0	3
EFV & FTC & NFV & TDF	3	0	0	3
FTC	3	0	0	3
FTC & 3TC & LPV & NFV & RTV & TDF & ZDV	1	1	1	3
FTC & 3TC & NVP & d4T	2	1	0	3
FTC & FOS & LPV & RTV & TDF	3	0	0	3
FTC & NVP & TDF & ZDV	2	0	1	3
FTC & NVP & d4T	3	0	0	3
IDV & 3TC & NFV & d4T & ZDV	3	0	0	3
IDV & NVP & ZDV	2	1	0	3
IDV & d4T & ZDV	3	0	0	3
LPV & RTV & TDF	3	0	0	3
NFV & NVP & d4T	3	0	0	3
NFV & ZDV	1	2	0	3
RTV	2	0	1	3
ddI & 3TC & NFV & RTV & SQV & ZDV	2	1	0	3

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
ddI & 3TC & SQV & ZDV	1	2	0	3
ddI & 3TC & SQV & d4T & ZDV	2	0	1	3
ddI & 3TC & TDF	1	2	0	3
ddI & 3TC & d4T	3	0	0	3
ddI & EFV & FTC	3	0	0	3
ddI & EFV & LPV & NVP & RTV	3	0	0	3
ddI & FOS & RTV & TDF	2	1	0	3
ddI & d4T	3	0	0	3
ddI & ddC & ZDV	3	0	0	3
3TC & LPV & NFV & RTV & TDF	2	0	0	2
3TC & LPV & NFV & RTV & TDF & ZDV	0	2	0	2
3TC & LPV & NVP & RTV & TDF	2	0	0	2
3TC & LPV & NVP & RTV & TDF & ZDV	1	0	1	2
3TC & LPV & NVP & RTV & d4T	1	0	1	2
3TC & LPV & RTV & SQV & ZDV	1	1	0	2
3TC & NFV & NVP & SQV & d4T & ZDV	2	0	0	2
3TC & NVP & SQV & ZDV	2	0	0	2
3TC & RTV & SQV & TDF & ZDV	1	1	0	2
3TC & RTV & SQV & d4T & ZDV	1	1	0	2
3TC & RTV & TDF	2	0	0	2
3TC & RTV & d4T	2	0	0	2
3TC & SQV & d4T & ZDV	2	0	0	2
ABC & 3TC & LPV & RTV & d4T	2	0	0	2
ABC & 3TC & LPV & RTV & d4T & TDF	2	0	0	2
ABC & 3TC & NFV & TDF & ZDV	1	0	1	2
ABC & 3TC & NVP & TDF & ZDV	0	2	0	2
ABC & 3TC & RPV	2	0	0	2
ABC & 3TC & RTV & SQV & TDF & ZDV	2	0	0	2
ABC & 3TC & SQV	2	0	0	2
ABC & 3TC & d4T & ZDV	1	1	0	2
ABC & APV & ddI & NVP & RTV	2	0	0	2
ABC & ATV & EFV & 3TC & RTV & TDF & ZDV	2	0	0	2
ABC & ATV & EFV & FTC & 3TC & RTV & TDF & ZDV	2	0	0	2
ABC & ATV & FTC & 3TC & RPV & RTV & TDF	2	0	0	2
ABC & ATV & RTV	2	0	0	2
ABC & ATV & TDF	2	0	0	2
ABC & ATV & ZDV	2	0	0	2
ABC & ATV & ddI	2	0	0	2
ABC & ATV & ddI & 3TC & RTV	2	0	0	2
ABC & DRV & 3TC	2	0	0	2
ABC & DRV & 3TC & RTV & TDF	2	0	0	2
ABC & DRV & 3TC & RTV & ZDV	1	1	0	2
ABC & DRV & FTC & 3TC & RAL & RTV & TDF & ZDV	1	0	1	2
ABC & DRV & FTC & 3TC & RTV & TDF	2	0	0	2
ABC & DRV & FTC & RTV & TDF	2	0	0	2
ABC & DTG & 3TC & TDF	2	0	0	2
ABC & EFV & 3TC & LPV & RTV	2	0	0	2
ABC & EFV & FTC & 3TC & LPV & RTV & TDF & ZDV	2	0	0	2
ABC & EFV & NVP & d4T	2	0	0	2
ABC & ETR & 3TC	2	0	0	2
ABC & FOS & 3TC & LPV & RTV	2	0	0	2
ABC & FOS & 3TC & LPV & RTV & ZDV	1	1	0	2

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
ABC & FOS & 3TC & RTV & TDF & ZDV	1	1	0	2
ABC & FOS & 3TC & ZDV	2	0	0	2
ABC & FTC & 3TC & LPV & RPV & RTV & TDF	2	0	0	2
ABC & FTC & LPV & RTV	2	0	0	2
ABC & IDV & 3TC & RTV & ZDV	2	0	0	2
ABC & IDV & 3TC & RTV & d4T	2	0	0	2
ABC & LPV & RTV	2	0	0	2
ABC & NFV & NVP	1	1	0	2
ABC & NFV & ZDV	0	2	0	2
ABC & d4T	2	0	0	2
ABC & ddI & EFV & NVP	2	0	0	2
ABC & ddI & NVP	2	0	0	2
ABC & ddI & d4T	2	0	0	2
ATV & 3TC & NFV & RTV & TDF & ZDV	1	1	0	2
ATV & 3TC & NFV & ZDV	1	1	0	2
ATV & 3TC & NVP & RTV & ZDV	1	1	0	2
ATV & COBI & FTC & TDF	2	0	0	2
ATV & EFV & FTC & TDF	2	0	0	2
ATV & FTC & 3TC & NVP & RTV & TDF & ZDV	2	0	0	2
ATV & FTC & ETR & RTV & TDF	2	0	0	2
ATV & FTC & TDF & ZDV	1	0	1	2
ATV & LPV & RTV & ZDV	2	0	0	2
ATV & RAL & RTV	2	0	0	2
ATV & RAL & RTV & ZDV	2	0	0	2
ATV & RPV & RTV & TDF	2	0	0	2
ATV & RPV & RTV & ZDV	1	1	0	2
ATV & RTV & d4T & TDF	2	0	0	2
ATV & ddI & d4T	2	0	0	2
COBI & DRV	1	0	1	2
COBI & DRV & DTG & FTC & RTV & TDF	1	0	1	2
COBI & DRV & FTC & RTV & TDF	2	0	0	2
COBI & EVG & FTC & RAL & TDF	1	0	1	2
COBI & EVG & FTC & TDF & ZDV	0	1	1	2
DLV & 3TC & NFV & ZDV	2	0	0	2
DRV	1	0	0	2
DRV & 3TC & RAL & RTV & ZDV	2	0	0	2
DRV & 3TC & RTV	1	1	0	2
DRV & 3TC & RTV & TDF & ZDV	2	0	0	2
DRV & DTG & RTV	2	0	0	2
DRV & ETR & 3TC & RTV	2	0	0	2
DRV & FTC & 3TC & NFV & RTV & TDF & ZDV	2	0	0	2
DRV & FTC & 3TC & NVP & RTV & TDF & ZDV	2	0	0	2
DRV & FTC & MVC & RTV & TDF	1	1	0	2
DRV & FTC & RAL & RTV	2	0	0	2
DRV & FTC & RAL & RTV & TDF & ZDV	1	0	1	2
DRV & MVC & RAL & RTV	2	0	0	2
DTG & FTC & RAL & TDF	2	0	0	2
DTG & FTC & RPV & TDF	0	1	1	2
EFV & 3TC & LPV & NFV & RTV & ZDV	1	1	0	2
EFV & 3TC & d4T & TDF & ZDV	2	0	0	2
EFV & FTC & 3TC & TDF	2	0	0	2
EFV & FTC & RTV & SQV & TDF	2	0	0	2

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
EFV & IDV & 3TC & d4T	2	0	0	2
EFV & LPV & NVP & RTV & d4T & TDF	2	0	0	2
EFV & LPV & RTV	2	0	0	2
EFV & NVP	2	0	0	2
ETR & RAL	1	1	0	2
FTC & 3TC & LPV & RTV & ZDV	1	1	0	2
FTC & 3TC & TDF & ZDV	0	2	0	2
FTC & FOS & TDF	2	0	0	2
FTC & LPV & RAL & RTV & TDF & ZDV	0	1	1	2
FTC & LPV & RPV & RTV & TDF	2	0	0	2
FTC & LPV & RTV & SQV & TDF	2	0	0	2
FTC & LPV & RTV & SQV & TDF & ZDV	1	1	0	2
FTC & LPV & RTV & d4T & TDF	1	1	0	2
FTC & MVC & RAL & TDF	2	0	0	2
FTC & MVC & TDF	2	0	0	2
FTC & NFV & TDF & ZDV	0	2	0	2
FTC & NVP & RAL & TDF	1	1	0	2
FTC & RPV & TAF	0	2	0	2
IDV & 3TC & NVP & RTV & ZDV	0	2	0	2
IDV & 3TC & RTV & d4T & ZDV	2	0	0	2
IDV & 3TC & SQV & d4T & ZDV	2	0	0	2
IDV & 3TC & d4T & ddC	2	0	0	2
IDV & LPV & RTV & TDF	2	0	0	2
IDV & NVP & d4T	1	1	0	2
IDV & RTV & d4T	2	0	0	2
IDV & d4T	2	0	0	2
LPV & NVP & RTV	1	1	0	2
LPV & RTV & SQV & TDF	1	1	0	2
NFV & NVP & ZDV	0	2	0	2
NFV & TDF & ZDV	1	1	0	2
NFV & d4T	2	0	0	2
NVP & RTV & SQV	2	0	0	2
NVP & d4T	2	0	0	2
RTV & SQV	2	0	0	2
RTV & SQV & d4T	1	0	1	2
RTV & d4T	2	0	0	2
d4T & ZDV	2	0	0	2
ddI & 3TC & LPV & NFV & RTV & d4T	2	0	0	2
ddI & 3TC & LPV & RTV & TDF	2	0	0	2
ddI & 3TC & LPV & RTV & TDF & ZDV	2	0	0	2
ddI & 3TC & NFV & d4T	2	0	0	2
ddI & 3TC & RTV & SQV & d4T & ZDV	2	0	0	2
ddI & 3TC & d4T & ZDV	2	0	0	2
ddI & EFV & 3TC	2	0	0	2
ddI & EFV & 3TC & NFV & ZDV	2	0	0	2
ddI & EFV & 3TC & NFV & d4T & ZDV	2	0	0	2
ddI & EFV & NFV & d4T	2	0	0	2
ddI & EFV & NVP	2	0	0	2
ddI & EFV & TDF	2	0	0	2
ddI & FOS & 3TC & RTV	2	0	0	2
ddI & FTC & LPV & RTV & TDF	2	0	0	2
ddI & FTC & NVP	2	0	0	2

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
ddI & FTC & RTV & TDF	1	1	0	2
ddI & IDV & 3TC & NFV & ZDV	2	0	0	2
ddI & IDV & 3TC & d4T & ZDV	2	0	0	2
ddI & IDV & RTV & d4T	2	0	0	2
ddI & NFV & TDF	1	1	0	2
ddI & NVP	0	2	0	2
ddI & RTV & SQV & TDF	2	0	0	2
3TC & LPV & MVC & RTV & ZDV	1	0	0	1
3TC & LPV & NFV & RTV & SQV & ZDV	0	0	1	1
3TC & LPV & NVP & RTV & d4T & ZDV	0	0	1	1
3TC & LPV & RAL & RTV & TDF & ZDV	1	0	0	1
3TC & LPV & RTV & SQV & TDF & ZDV	0	1	0	1
3TC & LPV & RTV & SQV & d4T	1	0	0	1
3TC & MVC & RAL	1	0	0	1
3TC & MVC & ZDV	0	1	0	1
3TC & NFV & NVP & RTV & SQV & d4T & ZDV	1	0	0	1
3TC & NFV & NVP & TDF & ZDV	0	1	0	1
3TC & NFV & SQV & d4T & ZDV	1	0	0	1
3TC & NFV & d4T & TDF	1	0	0	1
3TC & NVP	1	0	0	1
3TC & NVP & RAL & ZDV	0	1	0	1
3TC & NVP & RTV & SQV & d4T & ZDV	1	0	0	1
3TC & NVP & RTV & ZDV	1	0	0	1
3TC & NVP & SQV & d4T & TDF & ZDV	1	0	0	1
3TC & NVP & d4T & TDF	1	0	0	1
3TC & RAL	1	0	0	1
3TC & RPV & TDF	1	0	0	1
3TC & RPV & ZDV	0	1	0	1
3TC & RTV	1	0	0	1
3TC & RTV & SQV & TDF	1	0	0	1
3TC & RTV & d4T & ZDV	1	0	0	1
3TC & SQV	1	0	0	1
3TC & SQV & ddC & ZDV	1	0	0	1
3TC & d4T & TDF & ZDV	1	0	0	1
3TC & d4T & ddC & ZDV	1	0	0	1
ABC	1	0	0	1
ABC & 3TC & LPV & NFV & NVP & RTV & ZDV	1	0	0	1
ABC & 3TC & LPV & NFV & RTV & TDF	1	0	0	1
ABC & 3TC & LPV & NFV & RTV & TDF & ZDV	1	0	0	1
ABC & 3TC & LPV & NFV & RTV & d4T	1	0	0	1
ABC & 3TC & LPV & RAL & RTV & TDF	1	0	0	1
ABC & 3TC & LPV & RAL & RTV & ZDV	1	0	0	1
ABC & 3TC & LPV & RPV & RTV	1	0	0	1
ABC & 3TC & LPV & RTV & SQV & TDF & ZDV	0	1	0	1
ABC & 3TC & LPV & RTV & d4T & TDF & ZDV	1	0	0	1
ABC & 3TC & LPV & RTV & d4T & ZDV	1	0	0	1
ABC & 3TC & NFV & NVP & d4T & ZDV	1	0	0	1
ABC & 3TC & NFV & RTV & d4T & ZDV	1	0	0	1
ABC & 3TC & NFV & TDF	1	0	0	1
ABC & 3TC & NFV & d4T	1	0	0	1
ABC & 3TC & NFV & d4T & TDF	1	0	0	1
ABC & 3TC & NFV & d4T & ZDV	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
ABC & 3TC & NVP & RTV & SQV	1	0	0	1
ABC & 3TC & NVP & d4T & TDF & ZDV	0	1	0	1
ABC & 3TC & RPV & TDF	0	1	0	1
ABC & 3TC & RTV	1	0	0	1
ABC & 3TC & RTV & ZDV	0	1	0	1
ABC & 3TC & d4T & TDF	1	0	0	1
ABC & APV & 3TC & NFV & RTV & ZDV	0	1	0	1
ABC & APV & 3TC & RTV	1	0	0	1
ABC & APV & 3TC & TDF & ZDV	1	0	0	1
ABC & APV & 3TC & d4T	1	0	0	1
ABC & APV & FOS & 3TC	1	0	0	1
ABC & APV & RTV & TDF	1	0	0	1
ABC & APV & RTV & d4T	1	0	0	1
ABC & APV & ddI & IDV & 3TC & RTV & ZDV	1	0	0	1
ABC & APV & ddI & RTV	1	0	0	1
ABC & APV & ddI & RTV & d4T	1	0	0	1
ABC & ATV & 3TC & NFV & RTV & TDF & ZDV	1	0	0	1
ABC & ATV & 3TC & NFV & ZDV	0	1	0	1
ABC & ATV & 3TC & RAL & RTV	1	0	0	1
ABC & ATV & 3TC & RTV & SQV	1	0	0	1
ABC & ATV & 3TC & RTV & SQV & ZDV	1	0	0	1
ABC & ATV & EFV & 3TC & RPV & RTV & TDF & ZDV	1	0	0	1
ABC & ATV & EFV & FTC & 3TC & TDF & ZDV	1	0	0	1
ABC & ATV & FOS & 3TC & RTV	1	0	0	1
ABC & ATV & FTC & 3TC & LPV & RTV & TDF & ZDV	1	0	0	1
ABC & ATV & FTC & 3TC & RTV & TDF & ZDV	0	1	0	1
ABC & ATV & FTC & 3TC & TDF & ZDV	0	1	0	1
ABC & ATV & FTC & RTV & TDF & ZDV	1	0	0	1
ABC & ATV & NFV & RTV	1	0	0	1
ABC & ATV & NFV & RTV & TDF & ZDV	0	1	0	1
ABC & ATV & RTV & d4T	0	1	0	1
ABC & ATV & ddI & T20 & IDV & 3TC & RTV & d4T & TDF & ZDV	1	0	0	1
ABC & COBI & DRV & 3TC	1	0	0	1
ABC & DLV & NVP & RTV & SQV & ZDV	1	0	0	1
ABC & DLV & ddI & EFV	1	0	0	1
ABC & DRV & 3TC & LPV & RTV	1	0	0	1
ABC & DRV & 3TC & LPV & RTV & ZDV	1	0	0	1
ABC & DRV & 3TC & RAL & RTV	0	1	0	1
ABC & DRV & 3TC & RAL & RTV & ZDV	1	0	0	1
ABC & DRV & 3TC & ZDV	0	1	0	1
ABC & DRV & DTG & 3TC & RTV	1	0	0	1
ABC & DRV & EFV & 3TC & RTV	0	1	0	1
ABC & DRV & ETR & 3TC & RAL & RTV	1	0	0	1
ABC & DRV & ETR & 3TC & RAL & RTV & TDF & ZDV	1	0	0	1
ABC & DRV & ETR & 3TC & RTV & TDF & ZDV	0	1	0	1
ABC & DRV & ETR & RTV & TDF	1	0	0	1
ABC & DRV & FTC & 3TC & TDF	1	0	0	1
ABC & DRV & FTC & FOS & 3TC & RTV & TDF	1	0	0	1
ABC & DRV & FTC & LPV & RTV & TDF	1	0	0	1
ABC & DRV & MVC & RTV	1	0	0	1
ABC & DRV & RAL & RTV	0	1	0	1
ABC & DRV & RTV & TDF	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
ABC & DRV & T20 & 3TC & RTV & TDF & ZDV	1	0	0	1
ABC & DTG & 3TC & RAL	1	0	0	1
ABC & DTG & EFV & FTC & 3TC & TDF	1	0	0	1
ABC & DTG & FTC & 3TC & LPV & RTV & TDF	1	0	0	1
ABC & DTG & FTC & 3TC & RAL & TDF	0	0	1	1
ABC & DTG & TDF	0	1	0	1
ABC & EFV & 3TC & LPV & NFV & NVP & RTV	1	0	0	1
ABC & EFV & 3TC & LPV & RTV & TDF	1	0	0	1
ABC & EFV & 3TC & LPV & RTV & TDF & ZDV	1	0	0	1
ABC & EFV & 3TC & NFV & d4T	1	0	0	1
ABC & EFV & 3TC & NFV & d4T & ZDV	1	0	0	1
ABC & EFV & 3TC & NVP & TDF & ZDV	1	0	0	1
ABC & EFV & 3TC & NVP & ZDV	1	0	0	1
ABC & EFV & 3TC & TDF	1	0	0	1
ABC & EFV & 3TC & TDF & ZDV	1	0	0	1
ABC & EFV & 3TC & d4T	1	0	0	1
ABC & EFV & 3TC & d4T & ZDV	1	0	0	1
ABC & EFV & FOS & 3TC & RTV & ZDV	1	0	0	1
ABC & EFV & FTC & 3TC & LPV & RTV & TDF	1	0	0	1
ABC & EFV & FTC & TDF	0	1	0	1
ABC & EFV & IDV	1	0	0	1
ABC & EFV & IDV & LPV & RTV	1	0	0	1
ABC & EFV & LPV & RTV	1	0	0	1
ABC & EFV & NFV	1	0	0	1
ABC & EFV & NFV & NVP	1	0	0	1
ABC & EFV & NFV & ZDV	1	0	0	1
ABC & EFV & NFV & d4T	1	0	0	1
ABC & EFV & TDF	1	0	0	1
ABC & ETR & 3TC & RAL	0	1	0	1
ABC & ETV & 3TC & LPV & RAL & RTV	1	0	0	1
ABC & FOS & 3TC & NFV & NVP & d4T	1	0	0	1
ABC & FOS & 3TC & NVP & RTV	1	0	0	1
ABC & FOS & 3TC & RTV & SQV & ZDV	1	0	0	1
ABC & FOS & 3TC & TDF	1	0	0	1
ABC & FOS & RTV & TDF	1	0	0	1
ABC & FTC & 3TC & LPV & RTV & TDF & ZDV	1	0	0	1
ABC & FTC & 3TC & RAL & RPV & TDF & ZDV	1	0	0	1
ABC & FTC & 3TC & RAL & TDF	0	1	0	1
ABC & FTC & FOS & 3TC & RTV & TDF & ZDV	0	0	1	1
ABC & FTC & NVP & TDF	1	0	0	1
ABC & FTC & RPV & TDF	0	1	0	1
ABC & FTC & TDF	1	0	0	1
ABC & IDV & 3TC & NFV & NVP & RTV & ZDV	1	0	0	1
ABC & IDV & 3TC & RAL & RTV	1	0	0	1
ABC & IDV & NFV & RTV	1	0	0	1
ABC & IDV & RTV	1	0	0	1
ABC & IDV & RTV & d4T	0	0	1	1
ABC & IDV & RTV & d4T & ZDV	1	0	0	1
ABC & IDV & ZDV	1	0	0	1
ABC & IDV & d4T	1	0	0	1
ABC & LPV & NFV & RTV & TDF	1	0	0	1
ABC & LPV & NVP & RTV	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
ABC & LPV & NVP & RTV & d4T & TDF	1	0	0	1
ABC & LPV & RAL & RTV	1	0	0	1
ABC & LPV & RTV & SQV	1	0	0	1
ABC & LPV & RTV & TDF & ZDV	1	0	0	1
ABC & NFV & NVP & TDF	1	0	0	1
ABC & NFV & NVP & d4T	1	0	0	1
ABC & NFV & SQV	1	0	0	1
ABC & NVP	0	1	0	1
ABC & RTV & SQV & ZDV	1	0	0	1
ABC & RTV & d4T	1	0	0	1
ABC & SQV	1	0	0	1
ABC & T20 & 3TC & LPV & RTV	1	0	0	1
ABC & T20 & 3TC & RTV & TPV	1	0	0	1
ABC & ddI & 3TC	1	0	0	1
ABC & ddI & 3TC & LPV & RTV	1	0	0	1
ABC & ddI & 3TC & LPV & RTV & SQV & TDF & ZDV	1	0	0	1
ABC & ddI & 3TC & LPV & RTV & ZDV	1	0	0	1
ABC & ddI & 3TC & LPV & RTV & d4T & ZDV	0	1	0	1
ABC & ddI & 3TC & NFV & NVP & ZDV	0	0	1	1
ABC & ddI & 3TC & NFV & NVP & d4T & ZDV	0	1	0	1
ABC & ddI & 3TC & NFV & TDF & ZDV	1	0	0	1
ABC & ddI & 3TC & NFV & ZDV	1	0	0	1
ABC & ddI & 3TC & NFV & d4T	1	0	0	1
ABC & ddI & 3TC & NFV & d4T & ZDV	1	0	0	1
ABC & ddI & 3TC & NVP & TDF & ZDV	1	0	0	1
ABC & ddI & 3TC & SQV & d4T & ZDV	1	0	0	1
ABC & ddI & 3TC & TDF & ZDV	1	0	0	1
ABC & ddI & 3TC & ZDV	1	0	0	1
ABC & ddI & EFV	1	0	0	1
ABC & ddI & EFV & 3TC & NFV & d4T & TDF	1	0	0	1
ABC & ddI & EFV & LPV & RTV	1	0	0	1
ABC & ddI & EFV & NVP & RTV & SQV & d4T	1	0	0	1
ABC & ddI & EFV & d4T	1	0	0	1
ABC & ddI & FOS & 3TC	1	0	0	1
ABC & ddI & FOS & 3TC & LPV & RTV	1	0	0	1
ABC & ddI & FOS & 3TC & LPV & RTV & d4T	1	0	0	1
ABC & ddI & FOS & RTV	1	0	0	1
ABC & ddI & IDV & 3TC & NFV & RTV & ZDV	0	1	0	1
ABC & ddI & IDV & LPV & RTV	1	0	0	1
ABC & ddI & LPV & NFV & NVP & RTV & ZDV	1	0	0	1
ABC & ddI & LPV & RAL & RTV	1	0	0	1
ABC & ddI & LPV & RTV & TDF & ZDV	1	0	0	1
ABC & ddI & NFV & RTV & SQV	1	0	0	1
ABC & ddI & NFV & d4T	1	0	0	1
ABC & ddI & NVP & TDF	1	0	0	1
ABC & ddI & NVP & ZDV	0	1	0	1
ABC & ddI & NVP & ddC	1	0	0	1
ABC & ddI & ZDV	0	1	0	1
ADV & 3TC & ZDV	1	0	0	1
ADV & EFV & IDV	1	0	0	1
ADV & TDF	1	0	0	1
APV & 3TC & LPV & RTV & TDF	0	1	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
APV & 3TC & RTV & SQV & ZDV	1	0	0	1
APV & 3TC & RTV & ZDV	1	0	0	1
APV & 3TC & RTV & d4T & ZDV	1	0	0	1
APV & EFV & 3TC & RTV & ZDV	1	0	0	1
APV & EFV & NFV & NVP & d4T & ddC	1	0	0	1
APV & FOS & 3TC & RTV & TDF	1	0	0	1
APV & LPV & RTV & TDF	1	0	0	1
APV & NFV & d4T	1	0	0	1
APV & NVP & d4T	1	0	0	1
APV & NVP & d4T & ZDV	1	0	0	1
APV & RTV	1	0	0	1
APV & RTV & SQV	1	0	0	1
APV & ddI & 3TC & RTV	1	0	0	1
APV & ddI & 3TC & d4T & ZDV	1	0	0	1
APV & ddI & LPV & RTV	1	0	0	1
APV & ddI & RTV	1	0	0	1
APV & ddI & RTV & d4T	1	0	0	1
APV & ddI & d4T	1	0	0	1
ATV & 3TC & LPV & MVC & RTV & ZDV	1	0	0	1
ATV & 3TC & LPV & RTV & SQV & TDF & ZDV	0	1	0	1
ATV & 3TC & LPV & RTV & SQV & ZDV	0	0	1	1
ATV & 3TC & LPV & RTV & TDF & ZDV	0	1	0	1
ATV & 3TC & LPV & RTV & d4T & ZDV	1	0	0	1
ATV & 3TC & NFV & RTV & ZDV	1	0	0	1
ATV & 3TC & NVP & TDF & ZDV	0	1	0	1
ATV & 3TC & NVP & ZDV	1	0	0	1
ATV & 3TC & RAL & RTV & ZDV	0	0	1	1
ATV & 3TC & RTV & d4T	1	0	0	1
ATV & 3TC & RTV & d4T & ZDV	0	0	1	1
ATV & 3TC & TDF	1	0	0	1
ATV & COBI & DTG & FTC & TDF	1	0	0	1
ATV & COBI & EFV & EVG & FTC & RTV & TDF	1	0	0	1
ATV & COBI & FTC & RTV & TDF	1	0	0	1
ATV & DRV & FTC & RAL & RTV & TDF	0	1	0	1
ATV & DRV & FTC & RPV & RTV & TDF	1	0	0	1
ATV & DRV & T20 & 3TC & RTV & ZDV	1	0	0	1
ATV & DTG & 3TC & RTV & TDF & ZDV	1	0	0	1
ATV & DTG & FTC & RTV & TDF & ZDV	0	0	1	1
ATV & DTG & RTV	1	0	0	1
ATV & DTG & RTV & TDF	1	0	0	1
ATV & EFV & 3TC & RTV & TDF & ZDV	1	0	0	1
ATV & EFV & 3TC & ZDV	1	0	0	1
ATV & EFV & ETR & 3TC & RTV & TDF	1	0	0	1
ATV & EFV & FTC & 3TC & LPV & RTV & TDF & ZDV	1	0	0	1
ATV & EFV & FTC & 3TC & NVP & TDF & ZDV	1	0	0	1
ATV & EFV & FTC & LPV & RTV & TDF	1	0	0	1
ATV & EFV & FTC & NVP & RTV & TDF	1	0	0	1
ATV & EFV & FTC & RTV & TDF & ZDV	1	0	0	1
ATV & EFV & RTV & TDF	1	0	0	1
ATV & ETR & 3TC & LPV & RTV & ZDV	1	0	0	1
ATV & FOS & 3TC & NFV & RTV & TDF & ZDV	1	0	0	1
ATV & FOS & 3TC & RTV & TDF	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
ATV & FTC & 3TC & LPV & RTV & TDF	1	0	0	1
ATV & FTC & 3TC & NFV & TDF & ZDV	1	0	0	1
ATV & FTC & 3TC & RAL & TDF & ZDV	0	0	1	1
ATV & FTC & 3TC & RTV & TDF	1	0	0	1
ATV & FTC & 3TC & TDF & ZDV	1	0	0	1
ATV & FTC & ETR & 3TC & RTV & TDF & ZDV	0	1	0	1
ATV & FTC & FOS & 3TC & RTV & TDF & ZDV	1	0	0	1
ATV & FTC & NFV & RTV & TDF	0	1	0	1
ATV & FTC & NVP & RAL & RTV & TDF	0	1	0	1
ATV & FTC & NVP & RTV & TDF	0	0	1	1
ATV & FTC & NVP & RTV & TDF & ZDV	0	0	1	1
ATV & FTC & NVP & TDF	1	0	0	1
ATV & FTC & NVP & TDF & ZDV	0	0	1	1
ATV & FTC & RTV & SQV & TDF	0	0	1	1
ATV & FTC & RTV & ZDV	0	1	0	1
ATV & IDV & 3TC & RTV & ZDV	0	1	0	1
ATV & LPV & NVP & RTV & TDF & ZDV	0	0	1	1
ATV & LPV & RTV	1	0	0	1
ATV & LPV & RTV & TDF & ZDV	0	1	0	1
ATV & NVP & RAL	1	0	0	1
ATV & RAL & RTV & TDF	1	0	0	1
ATV & RTV & TDF	1	0	0	1
ATV & T20 & RTV	1	0	0	1
ATV & TDF & ZDV	1	0	0	1
ATV & ddI	1	0	0	1
ATV & ddI & 3TC & NFV & ZDV	1	0	0	1
ATV & ddI & 3TC & ZDV	1	0	0	1
ATV & ddI & EFV & FTC & 3TC & RTV & TDF & ZDV	1	0	0	1
ATV & ddI & EFV & FTC & RTV & TDF	1	0	0	1
ATV & ddI & EFV & NVP & RTV	1	0	0	1
ATV & ddI & FOS & 3TC & NFV & NVP & TDF & ZDV	1	0	0	1
ATV & ddI & FTC & 3TC & LPV & RTV & TDF & ZDV	1	0	0	1
ATV & ddI & LPV & RAL & RTV & TDF	1	0	0	1
ATV & ddI & LPV & RTV & TDF	1	0	0	1
ATV & ddI & NFV & RTV & TDF	1	0	0	1
ATV & ddI & RTV & TDF & ZDV	1	0	0	1
ATV & ddI & TDF	1	0	0	1
ATV & ddI & ZDV	1	0	0	1
COBI & DRV & 3TC & ZDV	0	1	0	1
COBI & DRV & DTG & FTC & TDF	1	0	0	1
COBI & DRV & DTG & RPV	1	0	0	1
COBI & DRV & EVG & FTC & RAL & RTV & TDF	1	0	0	1
COBI & DRV & EVG & FTC & RTV & TDF	1	0	0	1
COBI & DRV & EVG & FTC & TDF	0	0	1	1
COBI & EVG & FTC & 3TC & LPV & RPV & RTV & TDF & ZDV	1	0	0	1
COBI & EVG & FTC & 3TC & LPV & RTV & TDF & ZDV	1	0	0	1
COBI & EVG & FTC & 3TC & NFV & TDF & ZDV	0	1	0	1
COBI & EVG & FTC & RPV & TAF & TDF	1	0	0	1
DLV & 3TC & NFV & SQV & ZDV	1	0	0	1
DLV & 3TC & NVP & d4T	1	0	0	1
DLV & 3TC & SQV	1	0	0	1
DLV & NFV & d4T	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
DLV & ddC & ZDV	1	0	0	1
DLV & ddI & LPV & RTV	0	1	0	1
DLV & ddI & NFV	1	0	0	1
DLV & ddI & ZDV	1	0	0	1
DRV & 3TC & LPV & RAL & RTV & TDF & ZDV	1	0	0	1
DRV & 3TC & LPV & RAL & RTV & ZDV	1	0	0	1
DRV & 3TC & NVP & RTV & ZDV	1	0	0	1
DRV & 3TC & RTV & SQV	1	0	0	1
DRV & 3TC & RTV & TDF	1	0	0	1
DRV & DTG & 3TC & MVC & RTV & TDF & ZDV	1	0	0	1
DRV & DTG & 3TC & RTV & TDF	1	0	0	1
DRV & DTG & 3TC & RTV & ZDV	1	0	0	1
DRV & DTG & ETR & RTV	1	0	0	1
DRV & DTG & FTC & RPV & RTV & TDF & ZDV	0	1	0	1
DRV & DTG & MVC & RTV	1	0	0	1
DRV & EFV & FTC & 3TC & RTV & TDF & ZDV	1	0	0	1
DRV & ETR & 3TC & RTV & TDF & ZDV	1	0	0	1
DRV & ETR & 3TC & RTV & ZDV	1	0	0	1
DRV & ETR & RAL	1	0	0	1
DRV & ETR & RAL & RTV & ZDV	1	0	0	1
DRV & ETR & RTV & ZDV	0	1	0	1
DRV & FTC & 3TC & RAL & RTV & TDF & ZDV	1	0	0	1
DRV & FTC & 3TC & RTV & SQV & TDF & ZDV	1	0	0	1
DRV & FTC & 3TC & RTV & TDF	1	0	0	1
DRV & FTC & ETR & TDF	1	0	0	1
DRV & FTC & FOS & 3TC & LPV & RTV & TDF & ZDV	1	0	0	1
DRV & FTC & NVP & RAL & RTV & TDF & ZDV	0	0	1	1
DRV & FTC & RAL & TDF	1	0	0	1
DRV & FTC & RTV & SQV & TDF	1	0	0	1
DRV & FTC & RTV & ZDV	1	0	0	1
DRV & FTC & T20 & ETR & RTV & TDF	0	1	0	1
DRV & FTC & T20 & RAL & RTV & TDF	1	0	0	1
DRV & LPV & RTV	0	1	0	1
DRV & MVC & RAL	1	0	0	1
DRV & MVC & RAL & RTV & ZDV	1	0	0	1
DRV & RTV & SQV	1	0	0	1
DRV & RTV & ZDV	1	0	0	1
DRV & T20 & 3TC & RTV & TDF	1	0	0	1
DRV & T20 & ETR & RTV	1	0	0	1
DRV & T20 & ETR & RTV & TDF	1	0	0	1
DRV & T20 & MVC & RAL & RTV	1	0	0	1
DRV & T20 & RTV & d4T & TDF & ZDV	1	0	0	1
DRV & T20 & TDF	0	1	0	1
DRV & ddI & RAL & RTV & TDF	1	0	0	1
DRV & ddI & RTV & ZDV	1	0	0	1
DTG & EFV & FTC & RPV & TDF	1	0	0	1
DTG & FTC & ETR & RAL & RPV & TDF	1	0	0	1
EFV & 3TC & LPV & NVP & RTV & ZDV	1	0	0	1
EFV & 3TC & LPV & NVP & RTV & d4T	1	0	0	1
EFV & 3TC & LPV & RTV & d4T	1	0	0	1
EFV & 3TC & NFV	1	0	0	1
EFV & 3TC & NFV & NVP & d4T	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
EFV & 3TC & NFV & d4T & TDF	1	0	0	1
EFV & 3TC & NFV & d4T & TDF & ZDV	1	0	0	1
EFV & 3TC & NVP & RTV & TPV	1	0	0	1
EFV & 3TC & NVP & TDF & ZDV	1	0	0	1
EFV & 3TC & NVP & d4T & TDF	1	0	0	1
EFV & 3TC & RAL & ZDV	0	0	1	1
EFV & 3TC & RTV & SQV & ZDV	1	0	0	1
EFV & FTC & 3TC & LPV & RAL & RTV & TDF	1	0	0	1
EFV & FTC & 3TC & LPV & RPV & RTV & TDF & ZDV	1	0	0	1
EFV & FTC & 3TC & NFV & TDF	1	0	0	1
EFV & FTC & 3TC & NVP & d4T & TDF	1	0	0	1
EFV & FTC & 3TC & RPV & TDF	1	0	0	1
EFV & FTC & 3TC & RTV & SQV & TDF & ZDV	1	0	0	1
EFV & FTC & 3TC & SQV & TDF & ZDV	1	0	0	1
EFV & FTC & 3TC & TDF & ZDV	1	0	0	1
EFV & FTC & 3TC & d4T	1	0	0	1
EFV & FTC & RAL & TDF & ZDV	0	0	1	1
EFV & FTC & d4T	1	0	0	1
EFV & IDV & 3TC & NFV & NVP & ZDV	1	0	0	1
EFV & IDV & 3TC & NFV & ZDV	1	0	0	1
EFV & IDV & 3TC & NVP & RTV & ZDV	1	0	0	1
EFV & IDV & 3TC & RTV & ZDV	1	0	0	1
EFV & IDV & 3TC & d4T & ZDV	1	0	0	1
EFV & LPV & RTV & d4T	1	0	0	1
EFV & NFV	1	0	0	1
EFV & NFV & d4T	1	0	0	1
EFV & NVP & RTV & SQV	1	0	0	1
EFV & NVP & d4T	1	0	0	1
EFV & SQV & d4T	1	0	0	1
EFV & ZDV	1	0	0	1
ETR & 3TC & LPV & RAL & RTV & ZDV	0	1	0	1
ETR & 3TC & LPV & RTV & TDF	1	0	0	1
ETR & 3TC & LPV & RTV & TDF & ZDV	1	0	0	1
ETR & 3TC & RAL & ZDV	0	1	0	1
ETR & LPV & RTV & d4T	1	0	0	1
ETR & MVC & RAL	1	0	0	1
ETR & NFV & RAL	0	1	0	1
ETR & RAL & RTV	1	0	0	1
ETR & RAL & TDF	0	1	0	1
FOS & 3TC & RTV & TDF & ZDV	0	0	1	1
FOS & RAL & RTV & TDF & ZDV	1	0	0	1
FOS & RTV	1	0	0	1
FTC & 3TC & LPV & NFV & RTV & d4T & ZDV	1	0	0	1
FTC & 3TC & LPV & RTV & d4T & TDF	0	1	0	1
FTC & 3TC & LPV & RTV & d4T & ZDV	1	0	0	1
FTC & 3TC & NFV & ZDV	0	1	0	1
FTC & 3TC & RAL & TDF & ZDV	1	0	0	1
FTC & 3TC & RTV & SQV & TDF & ZDV	1	0	0	1
FTC & ETR & 3TC & LPV & RTV & TDF & ZDV	0	0	1	1
FTC & ETR & 3TC & RTV & TDF & ZDV	1	0	0	1
FTC & ETR & LPV & RAL & RTV & TDF	1	0	0	1
FTC & ETR & LPV & RTV & TDF	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
FTC & ETR & TDF & ZDV	1	0	0	1
FTC & ETV & MVC & RAL & TDF	1	0	0	1
FTC & ETV & RTV & TDF	0	1	0	1
FTC & FOS & 3TC & LPV & RTV & TDF & ZDV	1	0	0	1
FTC & FOS & LPV & RTV & d4T & TDF	1	0	0	1
FTC & FOS & RAL & TDF	1	0	0	1
FTC & FOS & TDF & ZDV	1	0	0	1
FTC & IDV & LPV & RTV & TDF & ZDV	1	0	0	1
FTC & LPV & NFV & NVP & RTV & TDF	0	1	0	1
FTC & LPV & NFV & RTV & ZDV	0	1	0	1
FTC & LPV & NVP & RTV & TDF	1	0	0	1
FTC & LPV & NVP & RTV & TDF & ZDV	0	0	1	1
FTC & MVC	1	0	0	1
FTC & NFV & ZDV	0	0	1	1
FTC & NFV & d4T	0	1	0	1
FTC & NVP & RAL & RTV & SQV & TDF & ZDV	0	0	1	1
FTC & RAL	1	0	0	1
FTC & RAL & RTV & TDF	0	0	1	1
FTC & RPV & RTV & TDF	1	0	0	1
FTC & T20 & LPV & RTV & TDF	1	0	0	1
FTC & T20 & RTV & TDF	1	0	0	1
FTC & T20 & RTV & TDF & TPV	1	0	0	1
IDV & 3TC & LPV & NFV & RTV & d4T & TDF & ZDV	1	0	0	1
IDV & 3TC & LPV & RTV & ZDV	1	0	0	1
IDV & 3TC & LPV & RTV & d4T & TDF & ZDV	1	0	0	1
IDV & 3TC & NFV	1	0	0	1
IDV & 3TC & NFV & NVP & d4T	1	0	0	1
IDV & 3TC & NFV & SQV & ZDV	1	0	0	1
IDV & 3TC & NFV & d4T	1	0	0	1
IDV & 3TC & NVP & RTV & d4T	1	0	0	1
IDV & 3TC & NVP & RTV & d4T & ZDV	1	0	0	1
IDV & 3TC & RTV	1	0	0	1
IDV & 3TC & SQV & ZDV	1	0	0	1
IDV & 3TC & ddC & ZDV	1	0	0	1
IDV & LPV & RTV	1	0	0	1
IDV & LPV & RTV & d4T & TDF	1	0	0	1
IDV & NFV & NVP & ddC & ZDV	1	0	0	1
IDV & NVP & RTV	1	0	0	1
IDV & RTV & d4T & TDF	1	0	0	1
IDV & d4T & ddC	1	0	0	1
IDV & ddC & ZDV	1	0	0	1
LPV & NFV & RTV	1	0	0	1
LPV & NVP & RTV & d4T	0	1	0	1
LPV & RAL & RTV & ZDV	1	0	0	1
LPV & RTV & SQV & d4T	1	0	0	1
LPV & RTV & d4T & TDF & ZDV	0	1	0	1
LPV & RTV & d4T & ddC	1	0	0	1
LdT & TDF	1	0	0	1
MVC	1	0	0	1
NFV & NVP	1	0	0	1
NFV & NVP & SQV	1	0	0	1
NFV & NVP & SQV & ddC & ZDV	0	1	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
NFV & SQV & d4T	1	0	0	1
NFV & d4T & TDF	0	1	0	1
NFV & d4T & ddC	1	0	0	1
NVP & RTV & SQV & ZDV	1	0	0	1
NVP & SQV	1	0	0	1
NVP & SQV & d4T	1	0	0	1
NVP & TDF	1	0	0	1
NVP & d4T & TDF & ZDV	0	1	0	1
NVP & ddC & ZDV	1	0	0	1
RAL & TDF	1	0	0	1
RAL & TDF & ZDV	1	0	0	1
RPV	0	1	0	1
RTV & SQV & TDF & ZDV	0	1	0	1
RTV & SQV & ddC	1	0	0	1
RTV & TDF	1	0	0	1
RTV & TPV	1	0	0	1
SQV & d4T	1	0	0	1
SQV & d4T & ZDV	1	0	0	1
SQV & d4T & ddC	1	0	0	1
T20 & 3TC & LPV & RTV	1	0	0	1
T20 & 3TC & NVP & TDF	1	0	0	1
T20 & ETR & LPV & RTV & TDF	1	0	0	1
T20 & LPV & RTV & SQV & TDF	1	0	0	1
ddI & 3TC & LPV & NVP & RTV	1	0	0	1
ddI & 3TC & LPV & NVP & RTV & TDF & ZDV	1	0	0	1
ddI & 3TC & LPV & RTV & d4T & ZDV	1	0	0	1
ddI & 3TC & NFV & NVP	1	0	0	1
ddI & 3TC & NFV & NVP & d4T	1	0	0	1
ddI & 3TC & NFV & NVP & d4T & ZDV	1	0	0	1
ddI & 3TC & NFV & SQV	1	0	0	1
ddI & 3TC & NFV & SQV & d4T & ZDV	1	0	0	1
ddI & 3TC & NVP & RTV & d4T	1	0	0	1
ddI & 3TC & NVP & SQV & TDF & ZDV	1	0	0	1
ddI & 3TC & NVP & TDF & ZDV	1	0	0	1
ddI & 3TC & NVP & d4T	0	1	0	1
ddI & 3TC & RTV & SQV	1	0	0	1
ddI & EFV & 3TC & LPV & RTV	1	0	0	1
ddI & EFV & 3TC & LPV & RTV & d4T & TDF	1	0	0	1
ddI & EFV & 3TC & NFV	1	0	0	1
ddI & EFV & 3TC & NFV & TDF & ZDV	1	0	0	1
ddI & EFV & 3TC & NVP	1	0	0	1
ddI & EFV & 3TC & NVP & TDF	1	0	0	1
ddI & EFV & 3TC & NVP & d4T	1	0	0	1
ddI & EFV & 3TC & TDF	1	0	0	1
ddI & EFV & FTC & 3TC & NFV & NVP	0	1	0	1
ddI & EFV & FTC & 3TC & NVP & ZDV	1	0	0	1
ddI & EFV & FTC & LPV & NFV & RTV & TDF	1	0	0	1
ddI & EFV & FTC & LPV & RTV & TDF	1	0	0	1
ddI & EFV & FTC & RTV & TDF	1	0	0	1
ddI & EFV & FTC & d4T	1	0	0	1
ddI & EFV & IDV & 3TC & NVP & d4T	1	0	0	1
ddI & EFV & IDV & 3TC & ZDV	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

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Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2017

	First Trimester	Second Trimester	Third Trimester	Overall
ddI & EFV & LPV & NFV & RTV & d4T & TDF & ZDV	1	0	0	1
ddI & EFV & NFV & NVP & RTV	1	0	0	1
ddI & EFV & NFV & NVP & d4T	1	0	0	1
ddI & FOS & 3TC & RTV & SQV & d4T	1	0	0	1
ddI & FOS & LPV & RTV & TDF	1	0	0	1
ddI & FOS & RTV	1	0	0	1
ddI & FOS & RTV & ZDV	0	1	0	1
ddI & FOS & ZDV	0	1	0	1
ddI & FTC & NVP & TDF	1	0	0	1
ddI & IDV & 3TC	1	0	0	1
ddI & IDV & 3TC & NFV & d4T	1	0	0	1
ddI & IDV & 3TC & NVP & d4T & ZDV	1	0	0	1
ddI & IDV & 3TC & RTV	1	0	0	1
ddI & IDV & 3TC & RTV & ZDV	0	0	1	1
ddI & IDV & 3TC & TDF & ZDV	1	0	0	1
ddI & IDV & 3TC & ZDV	1	0	0	1
ddI & IDV & NFV	1	0	0	1
ddI & IDV & RTV & ZDV	1	0	0	1
ddI & IDV & ZDV	0	1	0	1
ddI & IDV & d4T & ZDV	1	0	0	1
ddI & LPV & NFV & RTV	1	0	0	1
ddI & LPV & NVP & RTV & TDF	1	0	0	1
ddI & LPV & NVP & RTV & ZDV	0	1	0	1
ddI & NFV & NVP & ZDV	0	1	0	1
ddI & NFV & d4T & TDF	1	0	0	1
ddI & NVP & RTV	1	0	0	1
ddI & NVP & RTV & SQV	1	0	0	1
ddI & RTV & SQV & ZDV	1	0	0	1
ddI & RTV & SQV & d4T	1	0	0	1
ddI & RTV & TDF	1	0	0	1
ddI & RTV & TDF & ZDV	1	0	0	1
ddI & SQV	1	0	0	1
ddI & SQV & d4T	1	0	0	1
ddI & T20 & 3TC & RTV	1	0	0	1
ddI & T20 & FOS & RAL & RTV	1	0	0	1
ddI & T20 & LPV & RTV	1	0	0	1
ddI & T20 & LPV & RTV & TDF	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir, COBI=cobicistat, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, DTG=dolutegravir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, EVG=elvitegravir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LdT=telbivudine, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, T20=enfuvirtide, TAF=tenofovir alafenamide, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

Appendix C: List of Defects as Reported to the Registry

Prospective Reports of Defects

The following lists the individual prospective reports of defects made to the Registry, listed by the trimester of exposure and treatment regimen:

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) Only Regimen:

	1.	Agenesis of right kidney and cyst in thymic gland tissue	Temporality: Cannot rule out a possible association [1]
¥	2.	Pectus excavatum, other specified anomaly of respiratory system	Temporality: Cannot rule out a possible association [1]
	3.	Hypoplasia of the right femur, agenesis of the right fibula, a bend in the middle of the right tibia, and a right pes valgus	Temporality: Cannot rule out a possible association [1]
	4.	Congenital giant nevus of anterior abdominal wall with high risk of malignant degeneration	Temporality: Cannot rule out a possible association [1]
	5.	Bilateral skin tags – ears, Preauricular sinus - left ear	Temporality: Cannot rule out a possible association [1]
	6.	Hemangioma (2"x1"x1") on upper right arm	Temporality: Cannot rule out a possible association [1]
	7.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
	8.	Midline cleft lip and palate	Temporality: Cannot rule out a possible association [1]
	9.	Left unilateral cleft lip and palate	Temporality: Cannot rule out a possible association [1]
	10.	Hypospadias	Temporality: Cannot rule out a possible association [1]
	11.	Hypospadias	Temporality: Cannot rule out a possible association [1]
	12.	Hypospadias, cleft in scrotum, micrognathia, microcephaly	Temporality: Cannot rule out a possible association [1]
	13.	Hypospadias	Temporality: Cannot rule out a possible association [1]
	14.	Hypospadias variant	Temporality: Cannot rule out a possible association [1]
	15.	Heart arrhythmia	Temporality: Cannot rule out a possible association [1]
	16.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association [1]
	17.	Hip dysplasia/dislocation	Temporality: Cannot rule out a possible association [1]
	18.	Abnormal genitalia in genetic female	Temporality: Cannot rule out a possible association [1]
	19.	Polydactyly	Temporality: Cannot rule out a possible association [1]
	20.	Polydactyly	Temporality: Cannot rule out a possible association [1]
	21.	Ambiguous genitalia	Temporality: Cannot rule out a possible association [1]
	22.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association [1]
	23.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	24.	Micrognathia	Temporality: Cannot rule out a possible association [1]
	25.	Split Uvula, Down Syndrome, Duodenal atresia	Temporality: Cannot rule out a possible association [1]
	26.	Ascites, Cogenital cardiomegaly, Hydrops fetalis	Temporality: Cannot rule out a possible association [1]
	27.	Cystic Hygroma/webbed neck, secundum ASD, dysplastic tricuspid valve, main pulmonary artery hypoplasia, ventriculomegaly, PDA, low set ears	Temporality: Cannot rule out a possible association [1]
	28.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
¥	29.	Hydrocele, inguinal hernia	Temporality: Cannot rule out a possible association [1]
	30.	Other and unspecified cranio-synostosis	Temporality: Cannot rule out a possible association [1]
*	31.	Right congenital dislocation of knee	Temporality: Cannot rule out a possible association [1]
*	32.	Facial asymmetry, micropenis, right retained testis, widening of toe gap	Temporality: Cannot rule out a possible association [1]
	33.	Ventricular Septal Defect (VSD), Fetal alcohol syndrome	Temporality: Cannot rule out a possible association [1]
		Pyloric stenosis	Temporality: Unable to assess [2]
	34.	Pyloric stenosis, hydrocephaly, hepatomegaly, hydrocele	Temporality: Unable to assess [2]
	35.	Club Foot	Temporality: Unable to assess [2]
	36.	Club Foot	Temporality: Unable to assess [2]

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[2] Insufficient data to assess temporality

[3] No temporal association

‡	37.	Club Foot	Temporality: Unable to assess [2]
	38.	Club Foot	Temporality: Unable to assess [2]
	39.	Hydrocele, stenosis/obstruction of lacrimal duct	Temporality: Unable to assess [2]
	40.	Congenital adrenal hyperplasia	Temporality: No temporal association [3]
	41.	Truncus arteriosis	Temporality: No temporal association [3]
	42.	Hypoplastic left ventricle	Temporality: No temporal association [3]
	43.	Polydactyly	Temporality: No temporal association [3]
	44.	Balanced AV Septal Defect	Temporality: Cannot rule out a possible association [1]
		Trisomy 21	Temporality: No temporal association [3]
	45.	Congenital Hearing Loss	Temporality: Cannot rule out a possible association [1]
		Sotos Syndrome	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to PI(s) Only Regimen:

	1.	Pulmonary Atresia, Aplastic right heart	Temporality: Cannot rule out a possible association [1]
	2.	Hydrocele, Hepatomegaly	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NtRTI(s) Only Regimen:

	1.	Ankyloglossia, natal teeth	Temporality: Cannot rule out a possible association [1]
		Bilateral post axial polydactyly	Temporality: No temporal association [3]
	2.	Glandular hypospadias/retracted foreskin	Temporality: No temporal association [3]
*	3.	Congenital disorder of glycosylation	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + PI(s) Regimen:

	1.	Transposition of the great vessels, right malformed pinna/atretic canal, hepatosplenomegaly, Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
	2.	Severe pericardial effusion, cardiomegaly (congestive heart failure), hyaline membrane disease, velocardiofacial syndrome, undescended testicle	Temporality: Cannot rule out a possible association [1]
	3.	Bowing of right and left femurs, subluxable left hip	Temporality: Cannot rule out a possible association [1]
	4.	Polydactyly (both hands)	Temporality: Cannot rule out a possible association [1]
	5.	Multicystic dysplastic kidney	Temporality: Cannot rule out a possible association [1]
	6.	Hearing deficit	Temporality: Cannot rule out a possible association [1]
¥	7.	Lobulated/fused/horseshoe kidney	Temporality: Cannot rule out a possible association [1]
¥	8.	Spinal muscular atrophy	Temporality: Cannot rule out a possible association [1]
	9.	Polycystic kidneys (induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
	10.	Achondroplasia	Temporality: Cannot rule out a possible association [1]
	11.	Chronic Granulomatous disease	Temporality: Cannot rule out a possible association [1]
	12.	Atrial Septal Defect (ASD) with atrial wall aneurysm	Temporality: Cannot rule out a possible association [1]
	13.	Cardiac arrythmia	Temporality: Cannot rule out a possible association [1]
	14.	Bilateral club feet	Temporality: Cannot rule out a possible association [1]
¥	15.	Anomaly of calf	Temporality: Cannot rule out a possible association [1]
	16.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
¥	17.	Chordee and hypospadias NOS	Temporality: Cannot rule out a possible association [1]
¥	18.	Anomaly in cardiac rhythm	Temporality: Cannot rule out a possible association [1]
	19.	Ascites, imperforate external auditory meatus, low-set ears	Temporality: Cannot rule out a possible association [1]
¥	20.	Trisomy 21, Patent Ductus Arterious (PDA)	Temporality: Cannot rule out a possible association [1]
¥	21.	Trisomy 21, Ventricular Septal Defect (VSD), other specified anomaly of nose	Temporality: Cannot rule out a possible association [1]
	22.	Ureteropelvic junction obstruction with mild bilateral pyelectasis noted on prenatal ultrasound (unconfirmed at outcome)	Temporality: Cannot rule out a possible association [1]
	23.	Polydactyly (Extra 5th digit bilateral hands)	Temporality: Cannot rule out a possible association [1]
‡	24.	Anotia/Microtia	Temporality: Cannot rule out a possible association [1]

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	25.	Hydrocephalus, smooth philtrum, low-set ears, accessory nipple, bilateral club feet, undescended testes, and polycystic kidney disease	Temporality: Cannot rule out a possible association [1]
	26.	Atrial Septal Defect (ASD), biventricular hypertrophy, dilated renal pelvis, and dilated cerebral ventricle	Temporality: Cannot rule out a possible association [1]
	27.	Brain growth retardation, Microcephaly, Micropenis, 2 vessel cord	Temporality: Cannot rule out a possible association [1]
	28.	Right hydronephrosis	Temporality: Cannot rule out a possible association [1]
	29.	Hypospadias	Temporality: Cannot rule out a possible association [1]
	30.	Hirschprung's Disease	Temporality: Cannot rule out a possible association [1]
	31.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
	32.	Hypospadias on the glans	Temporality: Cannot rule out a possible association [1]
¥	33.	Trisomy 21 (induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
¥	34.	Hypospadias	Temporality: Cannot rule out a possible association [1]
¥	35.	Hypospadias	Temporality: Cannot rule out a possible association [1]
	36.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
	37.	Pyloric stenosis	Temporality: Cannot rule out a possible association [1]
	38.	Tetralogy of Fallot	Temporality: Cannot rule out a possible association [1]
	39.	Single kidney	Temporality: Cannot rule out a possible association [1]
	40.	Micrognathia	Temporality: Cannot rule out a possible association [1]
	41.	Syndactyly, polydactyly	Temporality: Cannot rule out a possible association [1]
	42.	Double outlet of right ventricle, transposition of Great Vessels, membraneous/malalignment Ventricular Septal Defect (VSD), Patent Foramen Ovale (PFO), Patent Ductus Arteriosus (PDA), subvalvar pulmonary stenosis, valvar pulmonary stenosis	Temporality: Cannot rule out a possible association [1]
	43.	Hepatomegaly, Splenomegaly, Alpha thalassemia, Ventricular Septal Defect (VSD), Patent ductus arteriosus (PDA), Dilated coronary arteries	Temporality: Cannot rule out a possible association [1]
	44.	Cleft Lip L Upper	Temporality: Cannot rule out a possible association [1]
	45.	Abdominal mass	Temporality: Cannot rule out a possible association [1]
	46.	Muscular Ventricular Septal Defect (VSD), Secundum Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
	47.	Aortic Atresia, Atrial Septal Defect (ASD), Hypoplastic Left Ventricle, Mitral Atresia, Patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association [1]
	48.	Absence of hand/fingers	Temporality: Cannot rule out a possible association [1]
	49.	Hypospadias	Temporality: Cannot rule out a possible association [1]
	50.	Asymmetry of cortical sulcation, Colpocephaly, Dysgenesis of Corpus Callosum, Suspected Dandy Walker Syndrome	Temporality: Cannot rule out a possible association [1]
	51.	Abnormal cerebellum, abnormal cisterna magna, suspected cardiac anomaly	Temporality: Cannot rule out a possible association [1]
	52.	Ileal Atresia	Temporality: Cannot rule out a possible association [1]
¥	53.	Polydactyly – B preaxial toes, polydactyly – L postaxial finger, cleft lip	Temporality: Cannot rule out a possible association [1]
	54.	Bilateral Eye Ptosis	Temporality: Cannot rule out a possible association [1]
	55.	Polydactyly NOS – hand	Temporality: Cannot rule out a possible association [1]
	56.	Muscular VSDs	Temporality: Cannot rule out a possible association [1]
¥	57.	Primary hypospadias	Temporality: Cannot rule out a possible association [1]
	58.	Primary hypospadias with chordee	Temporality: Cannot rule out a possible association [1]
	59.	Inguinal hernia	Temporality: Cannot rule out a possible association [1]
	60.	Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
	61.	Patent Foramen Ovale, Sacral Dimple, VSD Muscular	Temporality: Cannot rule out a possible association [1]
	62.	Right Ventricular Hypertrophy	Temporality: Cannot rule out a possible association [1]
	63.	Long thin toes	Temporality: Cannot rule out a possible association [1]
	64.	Midmuscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
		Benign external hydrocephalus, frontal bossing	Temporality: Unable to assess [2]

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	65.	Abnormal posturing of hands and wrists, Unilateral left choroids plexus cysts, Unilateral ventriculomegaly	Temporality: Cannot rule out a possible association [1]
		Questionable abnormality of cavum septum pellucidum, Questionable forniceal fusion, Qustionable septo-optic dysplasia	Temporality: Unable to assess [2]
	66.	Patent Ductus Arteriosus (PDA), suspect Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
		Left club foot, spine curvature	Temporality: Unable to assess [2]
		Low-set/widespread thumb, hypoplastic left leg	Temporality: No temporal association [3]
	67.	Chromosomic aberration, no karyotype done (induced abortion <20 weeks gestation)	Temporality: Unable to assess [2]
	68.	Developmental hip dysplasia	Temporality: Unable to assess [2]
	69.	Muscular Ventricular Septal Defect (VSD)	Temporality: Unable to assess [2]
	70.	Congenital myotonic dystrophy, Hip dysplasia/dislocation	Temporality: Unable to assess [2]
	71.	Club foot	Temporality: Unable to assess [2]
	72.	Microcephaly	Temporality: Unable to assess [2]
	73.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
		AV Canal	Temporality: No temporal association [3]
	74.	Epispadias	Temporality: No temporal association [3]
	75.	Digeorge Syndrome	Temporality: No temporal association [3]
	76.	Syndactyly toes	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + nnRTI(s) Regimen:

	1.	Hydrocephalus, holoprosencephaly	Temporality: Cannot rule out a possible association [1]
	2.	Patent Foramen Ovale (PFO - or possible small secundum Atrial Septal Defect - ASD), small Patent Ductus Arteriosis (PDA)	Temporality: Cannot rule out a possible association [1]
	3.	Mild hydronephrosis	Temporality: Cannot rule out a possible association [1]
	4.	Talipes (positional, both feet)	Temporality: Cannot rule out a possible association [1]
	5.	Hypoplastic right ventricle, Pulmonary atresia	Temporality: Cannot rule out a possible association [1]
	6.	Urinary obstruction, duplicated right collecting system with obstructed upper pole moiety (possibly with associated vesicoureteral reflux)	Temporality: Cannot rule out a possible association [1]
	7.	Small muscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
¥	8.	Long bones malformation	Temporality: Cannot rule out a possible association [1]
	9.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association [1]
	10.	Hearing loss, congenital CMV	Temporality: Cannot rule out a possible association [1]
	11.	AV canal	Temporality: Cannot rule out a possible association [1]
	12.	Postaxial polydactyly – both hands	Temporality: Cannot rule out a possible association [1]
	13.	Polydactyly	Temporality: Cannot rule out a possible association [1]
	14.	Umbilical hernia, hypopigmentation	Temporality: Cannot rule out a possible association [1]
¥	15.	Shortening of right leg	Temporality: Cannot rule out a possible association [1]
	16.	AVSD, Trisomy 21, Distal phalax left thumb does not flex	Temporality: Cannot rule out a possible association [1]
	17.	Micropenis	Temporality: Cannot rule out a possible association [1]
	18.	Intraventricular communication	Temporality: Cannot rule out a possible association [1]
	19.	Right multicystic kidney	Temporality: Cannot rule out a possible association [1]
	20.	ASD, VSD	Temporality: Cannot rule out a possible association [1]
	21.	Congenital hydronephrosis, vesicoureteral reflux	Temporality: Cannot rule out a possible association [1]
	22.	Mesenteric Cyst	Temporality: Cannot rule out a possible association [1]
	23.	Ventricular Septal Defect Muscular	Temporality: Cannot rule out a possible association [1]
	24.	Umbilical hernia with a small granuloma	Temporality: Cannot rule out a possible association [1]
		Bilateral hip dislocation	Temporality: Unable to assess [2]
¥	25.	Hip dysplasia/dislocation	Temporality: Unable to assess [2]
	26.	Bilateral congenital dislocation of hips	Temporality: Unable to assess [2]
	27.	Hemangioma on nostril	Temporality: Unable to assess [2]

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	28.	Congenital talipies	Temporality: Unable to assess [2]
	29.	Left club foot	Temporality: Unable to assess [2]
	30.	Talipes equinovarus	Temporality: Unable to assess [2]
	31.	Failed hearing test, Trisomy 21	Temporality: Cannot rule out a possible association [1]
	32.	Omphalocele (spontaneous abortion <20 weeks gestation)	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + NtRTI(s) Regimen:

¥	1.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association [1]
	2.	Polydactyly (postaxial - bilateral hands)	Temporality: Cannot rule out a possible association [1]
	3.	Polydactyly (postaxial hand), hypospadias (NOS)	Temporality: Cannot rule out a possible association [1]
*	4.	Right renal agenesis	Temporality: Cannot rule out a possible association [1]
*	5.	Hypospadia (urethra on the penis)	Temporality: Cannot rule out a possible association [1]
	6.	Right club foot	Temporality: Unable to assess [2]
	7.	Club foot	Temporality: Unable to assess [2]
	8.	Positional Talipes – Right Unilateral Talipes	Temporality: Unable to assess [2]
	9.	Small ears, small eyes	Temporality: Cannot rule out a possible association [1]
		Syndactyly digits of both hands	Temporality: No temporal association [3]
	10.	Hemangioma	Temporality: Unable to assess [2]
		Umbilical hernia	Temporality: No temporal association [3]
	11.	Omphalocele	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to PI(s) + InSTI(s) Regimen:

	1.	Bilateral polydactyly post-axial to both hands	Temporality: Cannot rule out a possible association [1]
	2.	Bilateral talipes equinovarus	Temporality: Unable to assess [2]
		Low set eyes, long slender fingers, hepatomegaly, splenomegaly, probably trisomy 21	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + InSTI(s) Regimen:

	1.	Facial Aysmmetry, low set ears, Microstomia, possible Antley-Bixler	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + EI(s) Regimen:

	1.	Syndactyly defect of feet	Temporality: No temporal association [3]
		Syndactyly defect of hands	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + nnRTI(s) + PI(s) Regimen:

¥	1.	Heterotaxy syndrome	Temporality: Cannot rule out a possible association [1]
	2.	Right renal pelvic dilatation, resolved within one month	Temporality: Cannot rule out a possible association [1]
¥	3.	Polydactyly NOS – hand	Temporality: Cannot rule out a possible association [1]
¥	4.	Tricuspid atresia, tiny right ventricle, and Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
	5.	Polydactyly	Temporality: Cannot rule out a possible association [1]
	6.	Bilateral facial cleft, missing right globe, amniotic band	Temporality: Cannot rule out a possible association [1]
	7.	Incomplete formation of scalp tissue	Temporality: Cannot rule out a possible association [1]
	8.	Hypoplastic left ventricle, mitral valve hypoplasia, pulmonary valve hypoplasia, pulmonary valve stenosis	Temporality: Cannot rule out a possible association [1]
	9.	Patent ductus arteriosus (PDA), birthmark NOS	Temporality: Cannot rule out a possible association [1]
	10.	Cleft palate	Temporality: Cannot rule out a possible association [1]
	11.	Hip dysplasia/dislocation	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with First Trimester Exposure to NRTI(s) + NtRTI(s) + PI(s) Regimen:

	1.	Dilated right pyelum	Temporality: Cannot rule out a possible association [1]
	2.	Tetralogy of Fallot, Cleft palate, bilateral small kidneys, DiGeorge Syndrome, 22q11.2 deletion positive	Temporality: Cannot rule out a possible association [1]
¥	3.	Saccrococcygeal teratoma	Temporality: Cannot rule out a possible association [1]

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	4.	Tuberous sclerosis	Temporality: Cannot rule out a possible association [1]
	5.	Mild retromicrognathia	Temporality: Cannot rule out a possible association [1]
	6.	Polydactyly hand, polydactyly feet	Temporality: Cannot rule out a possible association [1]
	7.	Pallister-Killian Syndrome (induced abortion ≥20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
	8.	Congential hydronephrosis	Temporality: Cannot rule out a possible association [1]
	9.	Polydactyly 6th digit bilaterally	Temporality: Cannot rule out a possible association [1]
	10.	Absence of foot/toes	Temporality: Cannot rule out a possible association [1]
	11.	Polydactyly (toe)	Temporality: Cannot rule out a possible association [1]
	12.	Right multicystic Dysplastic kidney	Temporality: Cannot rule out a possible association [1]
	13.	Sacral meningocele	Temporality: Cannot rule out a possible association [1]
	14.	Patent Foramen Ovale (PFO), Patent Ductus Arteriosus (PDA), Bilateral Pyeliectasis	Temporality: Cannot rule out a possible association [1]
	15.	Left hydronephrosis, L hydroureter	Temporality: Cannot rule out a possible association [1]
	16.	Cysts of ovary	Temporality: Cannot rule out a possible association [1]
	17.	Neurofibromatosis	Temporality: Cannot rule out a possible association [1]
	18.	Cleft lip with/without cleft palate	Temporality: Cannot rule out a possible association [1]
	19.	Hydonephrosis, posterior urethral valves	Temporality: Cannot rule out a possible association [1]
	20.	Polydactyly postaxial hand	Temporality: Cannot rule out a possible association [1]
	21.	Omphalocele	Temporality: Cannot rule out a possible association [1]
	22.	Fetal Pyelectasis	Temporality: Cannot rule out a possible association [1]
	23.	Coarctation of aorta	Temporality: Cannot rule out a possible association [1]
	24.	Congenital heart defect, Gastrointestinal tract anomaly, Renal Agenesis / Potter's Syndrome	Temporality: Cannot rule out a possible association [1]
	25.	Ovarian cyst	Temporality: Cannot rule out a possible association [1]
	26.	Postaxial Polydactyly of Hands	Temporality: Cannot rule out a possible association [1]
	27.	Congenital Heart Disease Interventricular Communication	Temporality: Cannot rule out a possible association [1]
*	28.	Right ear did not form	Temporality: Cannot rule out a possible association [1]
*	29.	Positional calcaneovalgus foot	Temporality: Unable to assess [2]
	30.	Hydrocephalus, 2 vessel umbilical cord (induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
		Bilateral club foot	Temporality: Unable to assess [2]
	31.	Absent radii and thumbs bilaterally, Bilateral syndactyly toes 3/4/5, Cleft lip and palate, Imperforated anus, Left ear inferiorly set and rotated, Muscular Ventricular Septal Defect (VSD), Patent Foramen Ovale (PFO), Patent Ductus Arteriosus (PDA)	Temporality: Cannot rule out a possible association [1]
		Trisomy 18	Temporality: No temporal association [3]
	32.	Hydrops fetalis	Temporality: Cannot rule out a possible association [1]
		Congenital syphilis	Temporality: No temporal association [3]
	33.	Cleft leaflet of mitral valve, Endocardial cushion defect	Temporality: Cannot rule out a possible association [1]
		Trisomy 21	Temporality: No temporal association [3]
	34.	Enlarged clitoris, Enlarged labia majora, Epicanthal folds, Extra skin folds in neck, High arched palate, Micrognathia, Wide spaced nipples	Temporality: Cannot rule out a possible association [1]
		Down Syndrome	Temporality: No temporal association [3]
	35.	Tricuspid Regurgitation	Temporality: Cannot rule out a possible association [1]
		Down Syndrome	Temporality: No temporal association [3]
	36.	Bilateral Polydactyly on Ulnar Aspect of Hands	Temporality: Cannot rule out a possible association [1]
	37.	Polydactyly	Temporality: No temporal association [3]
	38.	Polydactyly	Temporality: No temporal association [3]
	39.	Tetralogy of Fallot, Digeorge Syndrome	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First Trimester Exposure to nnRTI(s) + NtRTI(s) + PI(s) Regimen:

	1.	Down syndrome	Temporality: No temporal association [3]

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[2] Insufficient data to assess temporality

[3] No temporal association

Birth Defects from Pregnancies with First Trimester Exposure to NRTI(s) + nnRTI(s) + NtRTI(s) + PI(s) Regimen:

	1.	Klinefelter, 47, XXY	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First Trimester Exposure to NRTI(s) + NtRTI(s) + InSTI(s) Regimen:

	1.	Median cleft lip	Temporality: Cannot rule out a possible association [1]
	2.	Atrial level shunt, Transposition of the Great Arteries	Temporality: Cannot rule out a possible association [1]
	3.	VSD	Temporality: Cannot rule out a possible association [1]
		Trisomy 18	Temporality: No temporal association [3]
	4.	Absent Bladder, Fetal dysplastic multicystic kidneys	Temporality: Cannot rule out a possible association [1]
	5.	Cleft palate	Temporality: Cannot rule out a possible association [1]
		Congenital heart defect	Temporality: Cannot rule out a possible association [1]
		Club feet	Temporality: Unable to assess [2]
	6.	Polydactyly on ulnar side bilaterally	Temporality: Cannot rule out a possible association [1]
		Syndactyly 2nd, 3rd, 4th fingers, Bilateral	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First Trimester Exposure to NRTI(s) + nnRTI(s) + NtRTI(s) Regimen:

	1.	Kyphosis, microcephaly, hydrops, 2 vessel cord	Temporality: Cannot rule out a possible association [1]
	2.	Sacral meningomyelocele+hydrocephalus, Fetal Alcohol Syndrome	Temporality: Cannot rule out a possible association [1]
	3.	Cardiac malformations (NOS)	Temporality: Cannot rule out a possible association [1]
	4.	Abnormal craniofacial appearance, craniosynostosis multisuture	Temporality: Cannot rule out a possible association [1]
	5.	Extra postaxial skin tag left lower extremity; extra postaxial skin tag left upper extremity	Temporality: Cannot rule out a possible association [1]
	6.	Polydactyly	Temporality: Cannot rule out a possible association [1]
*	7.	Tetralogy of fallot with absent pulmonary valve	Temporality: Cannot rule out a possible association [1]
*	8.	Atrial septal defect (ASD), micropenis, microtia, Emanuel syndrome	Temporality: Cannot rule out a possible association [1]
		Club foot	Temporality: Unable to assess [2]
	9.	AV Septal Defect	Temporality: Cannot rule out a possible association [1]
		Trisomy 21	Temporality: No temporal association [3]
	10.	Fetal CNS Anomaly	Temporality: Cannot rule out a possible association [1]
	11.	Pulmonary stenosis	Temporality: Cannot rule out a possible association [1]
		Immature hips (hip dysplasia)	Temporality: Unable to assess [2]
	12.	Bilateral club feet	Temporality: Unable to assess [2]
	13.	Postaxial Polydactyly (both hands)	Temporality: No temporal association [3]

Birth Defect from Pregnancies with First-Trimester Exposure to NRTI(s) + NtRTI(s) + InSTI(s) + PKE(s) Regimen:

	1.	Accessory digits on bilateral 5 digits of both hands	Temporality: Cannot rule out a possible association [1]
*		Hypoplastic aortic arch, hypoplastic aortic valve with stenosis, tricuspid atresia, ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) Only Regimen:

	2.	Pectus excavatum	Temporality: Cannot rule out a possible association [1]
	3.	Fetal Alcohol Syndrome	Temporality: Cannot rule out a possible association [1]
	4.	Down syndrome with facies, low-set ears, simian crease, trisomy 21	Temporality: Cannot rule out a possible association [1]
	5.	Bilateral polydactyly and feet anomalies, bilateral talipes equinovarus (TEV) positive	Temporality: Cannot rule out a possible association [1]
	6.	Patent ductus arteriosus (PDA), Patent Foramen Ovale (PFO), cardiomyopathy	Temporality: Cannot rule out a possible association [1]
	7.	Muscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	8.	Gastroschisis	Temporality: Cannot rule out a possible association [1]
	9.	Dacryocystocele	Temporality: Cannot rule out a possible association [1]
	10.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
	11.	Bilateral polydactyly	Temporality: Cannot rule out a possible association [1]

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[3] No temporal association

‡	12.	Premature synostosis of metopic suture	Temporality: Cannot rule out a possible association [1]
	13.	Down syndrome	Temporality: Cannot rule out a possible association [1]
	14.	Micrognathia	Temporality: Cannot rule out a possible association [1]
	15.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	16.	Congenital hydrocephalus	Temporality: Cannot rule out a possible association [1]
	17.	Multicystic left kidney	Temporality: Cannot rule out a possible association [1]
	18.	Enlarged, echogenic left kidney	Temporality: Cannot rule out a possible association [1]
	19.	Micrognathia	Temporality: Cannot rule out a possible association [1]
	20.	Atrial Fenestrations	Temporality: Cannot rule out a possible association [1]
‡	21.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association [1]
	22.	Plagiocephaly	Temporality: Cannot rule out a possible association [1]
‡	23.	Hydroureter	Temporality: Cannot rule out a possible association [1]
	24.	Inguinal hernia	Temporality: Cannot rule out a possible association [1]
‡	25.	Atrial septal defect (ASD)	Temporality: Cannot rule out a possible association [1]
	26.	Hydrocephalus of anterior lateral ventricle	Temporality: Unable to assess [2]
	27.	Right hip dislocation	Temporality: Unable to assess [2]
	28.	Subglottic stenosis	Temporality: Unable to assess [2]
‡	29.	Talipes calcaneovarus	Temporality: Unable to assess [2]
	30.	Hip dysplasia	Temporality: Unable to assess [2]
	31.	Down Syndrome, Ostium Secundum Atrial Septal Defect (ASD), Micropenis	Temporality: Cannot rule out a possible association [1]
		Congenital anomaly of face and neck, Congenital anomaly of upper limb	Temporality: Unable to assess [2]
	32.	Syndactyly fingers and toes	Temporality: Cannot rule out a possible association [1]
		Club feet, severe arthrogryposis	Temporality: Unable to assess [2]
	33.	Bilateral hydronephrosis	Temporality: Cannot rule out a possible association [1]
		Hypoplastic pubic bone, 2 vessel umbilical cord	Temporality: No temporal association [3]
	34.	Trisomy 13	Temporality: Cannot rule out a possible association [1]
		Dysmorphic eyes, patent ductus arteriosus (PDA), Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), duodenal atresia, rocker-bottom feet	Temporality: No temporal association [3]
‡	35.	Patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association [1]
		Umbilical hernia	Temporality: No temporal association [3]
	36.	Cardiac axis abnormality	Temporality: Unable to assess [2]
		Dandy Walker Malformation, ventriculomegaly	Temporality: No temporal association [3]
	37.	Atrial Septal Defect (ASD)	Temporality: No temporal association [3]
	38.	Micrognathia, left ear low-set pinna microtia, right ear malformation, small muscular Ventricular Septal Defect (VSD)	Temporality: No temporal association [3]
	39.	Microphthalmos of right eye with a possible coexistent cataract	Temporality: No temporal association [3]
	40.	Small cleft in front gum – very benign	Temporality: No temporal association [3]
	41.	Hand defect (missing digits)	Temporality: No temporal association [3]
	42.	Bicuspid aortic valve, abnormal pulmonic valve and possibly abnormal aorta but no gross aortic coarctation	Temporality: No temporal association [3]
	43.	Polydactyly	Temporality: No temporal association [3]
	44.	Syndactyly, right hand	Temporality: No temporal association [3]
	45.	Hypospadias, mild	Temporality: No temporal association [3]
	46.	Ventricular Septal Defect (VSD) - membranous; diagnosed at 2 months of age	Temporality: No temporal association [3]
	47.	Polydactyly (bilateral hands and feet, postaxial)	Temporality: No temporal association [3]

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	48.	Absence of mouth and esophagus, transversed organs	Temporality: No temporal association [3]
	49.	Cleft palate and lip	Temporality: No temporal association [3]
	50.	Hypospadias	Temporality: No temporal association [3]
	51.	Alobar holoprosencephaly (stillbirth), hypotelorism, proboscis	Temporality: No temporal association [3]
	52.	Polydactyly (bilateral)	Temporality: No temporal association [3]
	53.	Hypospadias	Temporality: No temporal association [3]
	54.	Cleft lip & palate	Temporality: No temporal association [3]
	55.	Sacrococcygeal teratoma	Temporality: No temporal association [3]
	56.	Cleft lip and palate	Temporality: No temporal association [3]
	57.	Choanal atresia	Temporality: No temporal association [3]
	58.	Cleft lip	Temporality: No temporal association [3]
	59.	Sacral tissue mass, tethered spinal cord	Temporality: No temporal association [3]
	60.	Cardiomegaly, Ebstein anomaly/dysplastic tricuspid valve, pulmonary atresia	Temporality: No temporal association [3]
	61.	Urethral stricture	Temporality: No temporal association [3]
	62.	Polydactyly	Temporality: No temporal association [3]
	63.	Bilateral cleft lip	Temporality: No temporal association [3]
	64.	Ectopic left kidney	Temporality: No temporal association [3]
	65.	Choanal atresia	Temporality: No temporal association [3]
	66.	Polydactyly left hand – postaxial	Temporality: No temporal association [3]
	67.	Polydactyly left hand – postaxial	Temporality: No temporal association [3]
	68.	Toes not well formed on both feet	Temporality: No temporal association [3]
	69.	Atrial septal defect (ASD), pulmonary insufficiency	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + PI(s) Regimen:

	1.	Bilateral talipes equinovarus	Temporality: Cannot rule out a possible association [1]
	2.	Ventriculomegaly	Temporality: Cannot rule out a possible association [1]
	3.	Neuroblastoma at 1 yr. old	Temporality: Cannot rule out a possible association [1]
	4.	Pulmonary regurgitation	Temporality: Cannot rule out a possible association [1]
	5.	Congenital toxoplasmosis	Temporality: Cannot rule out a possible association [1]
	6.	Myotonic dystrophy	Temporality: Cannot rule out a possible association [1]
	7.	Two mucosal cysts	Temporality: Cannot rule out a possible association [1]
	8.	Multiple intestinal atresias	Temporality: Cannot rule out a possible association [1]
	9.	Cataract	Temporality: Cannot rule out a possible association [1]
	10.	Secundum Atrial Septal Defect (ASD)/Stretched Patent Foramen Ovale (PFO)	Temporality: Cannot rule out a possible association [1]
	11.	Midmuscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	12.	Frontal Ventricular Septal Defect (VSD), hearing loss	Temporality: Cannot rule out a possible association [1]
	13.	Anomaly of Myocardium	Temporality: Cannot rule out a possible association [1]
	14.	Trisomy 18, Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	15.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
‡	16.	Mild bilateral renal pelviectasis	Temporality: Cannot rule out a possible association [1]
	17.	Cataracts, umbilical hernia	Temporality: Cannot rule out a possible association [1]
	18.	Trisomy 17	Temporality: Cannot rule out a possible association [1]
	19.	Arrhythmia	Temporality: Cannot rule out a possible association [1]
	20.	Congenital icthyosis	Temporality: Cannot rule out a possible association [1]
	21.	Bilateral hydronephrosis, Bilateral cystic kidneys, Grade 4 VUR on right	Temporality: Cannot rule out a possible association [1]
	22.	Pigmentary mosaicism	Temporality: Cannot rule out a possible association [1]
	23.	Abnormal face, low set ears, narrow eyes	Temporality: Cannot rule out a possible association [1]

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	24.	Small ventricular defect	Temporality: Cannot rule out a possible association [1]
	25.	Congenital CMV, microcephaly	Temporality: Cannot rule out a possible association [1]
	26.	L renal cyst	Temporality: Cannot rule out a possible association [1]
	27.	Vesicoureter junction obstruction, ASD, mild left pulmonary artery stenosis	Temporality: Cannot rule out a possible association [1]
	28.	Muscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	29.	Hydronephrosis and Ureteral meatal stenosis	Temporality: Cannot rule out a possible association [1]
‡	30.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]
	31.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]
	32.	Hydroureter	Temporality: Cannot rule out a possible association [1]
	33.	Atrial septal defect (ASD)	Temporality: Cannot rule out a possible association [1]
‡	34.	Atrial septal defect (ASD), ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]
	35.	Venticular septal defect	Temporality: Cannot rule out a possible association [1]
	36.	Right hydronephrosis	Temporality: Cannot rule out a possible association [1]
	37.	Microcephaly	Temporality: Cannot rule out a possible association [1]
	38.	Dysmorphic features Club foot	Temporality: Cannot rule out a possible association [1] Temporality: Unable to assess [2]
	39.	Hydrocephalus and Interventricular Communication Encephalic malformation	Temporality: Cannot rule out a possible association [1] Temporality: Unable to assess [2]
	40.	Trisomy 21, PDA AV Canal	Temporality: Cannot rule out a possible association [1] Temporality: No temporal association [3]
	41.	Ventricular septal defect (VSD) Bilateral cleft lip and palate, aortic stenosis, small aortic arch, persistent left SVC, translocation of chromosomes 21 and 22	Temporality: Cannot rule out a possible association [1] Temporality: No temporal association [3]
	42.	Right Cryptorchism Hypospadias	Temporality: Cannot rule out a possible association [1] Temporality: No temporal association [3]
	43.	Dysgenesis of the Corpus Callosum Neural Tube Defect, Chiari II Malformation	Temporality: Cannot rule out a possible association [1] Temporality: No temporal association [3]
	44.	Atrial septal defect (ASD) Tricuspid stenosis	Temporality: Cannot rule out a possible association [1] Temporality: No temporal association [3]
	45.	Bilateral temporal concavities and left kidney hydronephrotic Lumbo-sacral meningomyelocele, ventriculomegaly, abnormal cerebellum	Temporality: Cannot rule out a possible association [1] Temporality: No temporal association [3]
	46.	Ears mildly low-set (spontaneous abortion <20 weeks gestation) Ambiguous genitalia	Temporality: No temporal association [3] Temporality: Unable to assess [2]

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	47.	Polydactyly	Temporality: No temporal association [3]
	48.	Tethered cord, lipomeningocele, right kidney duplicated collecting system	Temporality: No temporal association [3]
	49.	Cleft palate, micrognathia	Temporality: No temporal association [3]
‡	50.	Other and unspecified polydactyly	Temporality: No temporal association [3]
	51.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
	52.	Congenital toxoplasmosis	Temporality: No temporal association [3]
	53.	Hydronephrosis of the left kidney with mild pelviectasis of the right collecting system	Temporality: No temporal association [3]
	54.	Gastroschisis	Temporality: No temporal association [3]
	55.	Omphalocele	Temporality: No temporal association [3]
	56.	Polydactyly (foot), long fingers, short ears with folded helices, low hairline front and posterior	Temporality: No temporal association [3]
	57.	Polydactyly (Extra digit left hand)	Temporality: No temporal association [3]
	58.	Polydactyly	Temporality: No temporal association [3]
	59.	Mild hypospadius	Temporality: No temporal association [3]
	60.	Diaphragmatic hernia	Temporality: No temporal association [3]
	61.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
	62.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
	63.	Cleft lip and palate	Temporality: No temporal association [3]
	64.	Cleft lip on the left	Temporality: No temporal association [3]
	65.	Hypospadias	Temporality: No temporal association [3]
	66.	Missing artery in heart	Temporality: No temporal association [3]
	67.	Branchial cleft cyst	Temporality: No temporal association [3]
	68.	Polydactyly	Temporality: No temporal association [3]
	69.	S1-2 hemivertebra	Temporality: No temporal association [3]
	70.	Small perimembranous Ventricular Septal Defect (VSD), mild tricuspid regurgitation	Temporality: No temporal association [3]
	71.	Undescended testes	Temporality Cannot rule out a possible association [1]
		Polydactyly (hand), Tetrology of Fallot	Temporality: No temporal association [3]
	72.	Cleft palate	Temporality: No temporal association [3]
	73.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
		Double outlet right ventricle	Temporality: No temporal association [3]
	74.	Patent Foramen Ovale (PFO), mild tricuspid regurgitation, peripheral pulmonary artery stenosis	Temporality: Cannot rule out a possible association [1]
		Ventricular Septal Defect (VSD)	Temporality: No temporal association [3]
	75.	Hydrocephalus NOS	Temporality: Cannot rule out a possible association [1]
		Dandy Walker	Temporality: No temporal association [3]
	76.	Down Syndrome, Facial features of Down Syndrome	Temporality: Cannot rule out a possible association [1]
		Cardiac abnormalities	Temporality: No temporal association [3]
	77.	Bilateral club feet	Temporality: Unable to assess [2]
	78.	Right club foot	Temporality: Unable to assess [2]
	79.	Umbilical cord anomaly	Temporality: Unable to assess [2]
	80.	Failed right ear hearing test	Temporality: Unable to assess [2]
	81.	Left club foot	Temporality: Unable to assess [2]
	82.	Congenital dislocated hips	Temporality: Unable to assess [2]
	83.	Hypoplastic kidneys	Temporality: Unable to assess [2]
	84.	Trisomy NOS	Temporality: Cannot rule out a possible association [1]

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	85.	Down Syndrome, Small Ventricular Septal Defect (VSD), Patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association [1]
		Down's facies, Small 5th finger	Temporality: No temporal association [3]
	86.	Trisomy 18, Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
		Overriding aorta	Temporality: No temporal association [3]
	87.	Agenesis of the Corpus Callosum, Feet Deep Plantar Creases, Short Neck	Temporality: Cannot rule out a possible association [1]
		Mosaic Trisomy 8, Ears have unusual Lobulation	Temporality: No temporal association [3]
	88.	Hay-Wells Syndrome, Lacrimal duct obstruction	Temporality: Cannot rule out a possible association [1]
		Bilateral cleft lip and palate, Supernumerary nipple (right)	Temporality: No temporal association [3]
	89.	Long thin fingers, long thin feet	Temporality: No temporal association [3]
		Toxoplasmosis, congenital absence of hair growth (right occipital area), obstructive hydrocephalus, hydrops fetalis/ascites	Temporality: Cannot rule out a possible association [1]
	90.	Transposition of major vessels	Temporality: No temporal association [3]
		Atrial septal defect (ASD)	Temporality: Cannot rule out a possible association [1]
	91.	Omphalocele, Sacral Agenesis, Fused lower extremities	Temporality: No temporal association [3]
		Dysmorphic features, Low set ears	Temporality: Cannot rule out a possible association [1]
	92.	Trisomy 18	Temporality: Unable to assess [2]
		Unspecified heart anomaly	Temporality: No temporal association [3]
	93.	Hirschprung's disease	Temporality: No temporal association [3]
	94.	Bilateral polydactyly – postaxial	Temporality: No temporal association [3]
	95.	Absence of hand/fingers	Temporality: No temporal association [3]
	96.	Dandy Walker Malformation	Temporality: No temporal association [3]
	97.	Trisomy 21	Temporality: No temporal association [3]
	98.	Pulmonary valve atresia/stenosis/hypoplasia with IVS	Temporality: No temporal association [3]
	99.	Syndacytly toes, 2nd thumb on right hand	Temporality: No temporal association [3]
	100.	Renal agenesis – left	Temporality: No temporal association [3]
	101.	Gastroschisis	Temporality: No temporal association [3]
	102.	Polydactyly (extra partial 5th finger on right)	Temporality: No temporal association [3]
	103.	Polydactyly	Temporality: No temporal association [3]
	104.	Polydactyly – preaxial	Temporality: No temporal association [3]
	105.	Vascular ring around trachea	Temporality: No temporal association [3]
	106.	Gastroschisis	Temporality: No temporal association [3]
	107.	Duplicated right renal collecting system	Temporality: No temporal association [3]
	108.	Other specified anomaly of nose	Temporality: No temporal association [3]
	109.	Polydactyly – postaxial Hand	Temporality: No temporal association [3]
	110.	Gastroschisis	Temporality: No temporal association [3]
	111.	Inlet Ventricular Septal Defect (VSD)	Temporality: No temporal association [3]
	112.	Ectopic kidney, Hirshsprung disease	Temporality: No temporal association [3]
‡	113.	Anencephaly	Temporality: No temporal association [3]
	114.	Myelomemingocele without hydrocephalus	Temporality: No temporal association [3]
	115.	Polydactyly – postaxial hand	Temporality: No temporal association [3]
	116.	Truncus arteriosus	Temporality: No temporal association [3]
	117.	Menkes syndrome	Temporality: No temporal association [3]
‡	118.	Polydactyly – postaxial hand	Temporality: No temporal association [3]
‡	119.	Umbilical hernia	Temporality: No temporal association [3]
		Fusion of vulva	Temporality: Unable to assess [2]
	120.	Aortic Coarctation	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + nnRTI(s) Regimen:

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[2] Insufficient data to assess temporality
[3] No temporal association

	1.	Hydronephrosis	Temporality: Cannot rule out a possible association [1]
	2.	Caudal thalamic notch cyst	Temporality: Cannot rule out a possible association [1]
	3.	Suspected hearing deficit	Temporality: Cannot rule out a possible association [1]
	4.	Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
	5.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
	6.	Fetal alcohol syndrome, moderate Patent Ductus Arteriosus (PDA), microcephaly	Temporality: Cannot rule out a possible association [1]
	7.	Fetal hydrops, cardiomyopathy, postnatal CMV	Temporality: Cannot rule out a possible association [1]
	8.	Hydrocephaly, microcephaly	Temporality: Cannot rule out a possible association [1]
	9.	Agenesis of the corpus callosum	Temporality: Cannot rule out a possible association [1]
	10.	Arrhythmia	Temporality: Cannot rule out a possible association [1]
	11.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]
	12.	Ependymal cysts	Temporality: Cannot rule out a possible association [1]
	13.	Hydrocele, inguinal hernia	Temporality: Cannot rule out a possible association [1]
	14.	Atrial septal defect (ASD)	Temporality: Cannot rule out a possible association [1]
‡	15.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]
	16.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]
	17.	Congenital heart disease	Temporality: Unable to assess [2]
	18.	Peripheral pulmonary artery stenosis	Temporality: Cannot rule out a possible association [1]
		Umbilical hernia	Temporality: No temporal association [3]
	19.	Flattened wide nasal ridge, wide set eyes, borderline low-set ears, short neck, and widespread nipples	Temporality: No temporal association [3]
	20.	Pulmonary valve stenosis	Temporality: No temporal association [3]
	21.	II/VI systolic murmur, polydactyly (bilateral hands)	Temporality: No temporal association [3]
	22.	Clubfoot	Temporality: No temporal association [3]
	23.	Cleft palate	Temporality: No temporal association [3]
	24.	Dysplastic toes	Temporality: No temporal association [3]
	25.	Renal agenesis, left	Temporality: No temporal association [3]
	26.	Polydactyly	Temporality: No temporal association [3]
	27.	Bilateral postaxial polydactyly	Temporality: No temporal association [3]
	28.	Anomaly of knee/patella	Temporality: No temporal association [3]
	29.	Hip dysplasia/dislocation	Temporality: No temporal association [3]
	30.	Polydactyly – postaxial hand	Temporality: No temporal association [3]
‡	31.	Cutis aplasia (scalp)	Temporality: No temporal association [3]
	32.	Cutis aplasia (scalp)	Temporality: No temporal association [3]
	33.	Polydactyly – preaxial hand	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + NtRTI(s) Regimen:

	1.	Truncus arteriosus	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + InSTI(s) Regimen:

*	2.	Down syndrome	Temporality: Cannot rule out a possible association [1]
		Brachydactyly, single palmar crease, upward slanting palpebral fissures	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + nnRTI(s) + PI(s) Regimen:

	1.	Down Syndrome, Patent Foramen Ovale (PFO) vs. secundum Atrial Septal Defect (ASD), patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association [1]
‡	2.	Microcephaly	Temporality: Cannot rule out a possible association [1]
	3.	Valgus malformation of foot	Temporality: Unable to assess [2]
	4.	Polydactyly (right hand)	Temporality: No temporal association [3]
	5.	Polydactyly	Temporality: No temporal association [3]

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‡	6.	Anophthalmia/microphlhalmia	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + NtRTI(s) + PI(s) Regimen:

	1.	Patent Foramen Ovale (PFO), trivial tricuspid regurgitation, mild mitral regurgitation, Wolff-Parkinson-White	Temporality: Cannot rule out a possible association [1]
	2.	Muscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	3.	Ventricular Septal Defect (VSD), Trisomy 21	Temporality: Cannot rule out a possible association [1]
	4.	Dermal melanocytosis	Temporality: Cannot rule out a possible association [1]
		Small macular hemangioma	Temporality: Unable to assess [2]
	5.	Pes equinovarus, bilateral	Temporality: Unable to assess [2]
	6.	Mongolian Spots	Temporality: Cannot rule out a possible association [1]
		Sacral Dimple	Temporality: No temporal association [3]
	7.	Skull ossification defect	Temporality: No temporal association [3]
	8.	Left hand 2nd & 3rd finger web	Temporality: No temporal association [3]
	9.	Bilateral Polydactyly, postaxial hand	Temporality: No temporal association [3]
	10.	Hypoplastic left heart	Temporality: No temporal association [3]
	11.	Syndactyly, absent middle phalanges 2-5 digit both hands, outlet VSD	Temporality: No temporal association [3]
	12.	Trisomy 7q, posteriorly rotated ears, high arched palate, Brachycephalic/Frontal bossing/tall forehead, small fontanelles, cleft above left eye, prominent nasal bridge/small narrow nose, underdeveloped left ear helix, vertical crease on soles	Temporality: Cannot rule out a possible association [1]
		Flat face	Temporality: Unable to assess [2]
		Wide spaced toes, widely spaced nipples, sacral dimple, clinodactyly pinky finger	Temporality: No temporal association [3]
	13.	Possible trisomy 13	Temporality: Cannot rule out a possible association [1]
		Holoprosencephaly (lobar) (induced abortion ≥20 weeks gestation), Polydactyly both hands, Cleft lip/palate bilateral, Hypotelorism	Temporality: No temporal association [3]
	14.	3rd Fontanel, Other specified anomaly of skull and/or face bones	Temporality: Cannot rule out a possible association [1]
		Skin tag anterior right ear	Temporality: No temporal association [3]
	15.	Mild Dysmorphism	Temporality: Cannot rule out a possible association [1]
		Inborn Error of metabolism NOS with dysmorphic features	Temporality: No temporal association [3]
	16.	Hypoglossia Hypodactylia Syndrome	Temporality: No temporal association [3]
	17.	Esophagus Atresia Type IIIB	Temporality: No temporal association [3]
	18.	Double outlet right ventricle with VSD	Temporality: No temporal association [3]
	19.	Encephalocele	Temporality: No temporal association [3]
*	20.	Cleft lip/cleft palate	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third- Trimester Exposure to NRTI(s) + NtRTI(s) + InSTI(s) Regimen:

	1.	Heart Valve Defect	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Second/Third- Trimester Exposure to NRTI(s) + PI(s) + InSTI(s) Regimen:

	1.	Trisomy 21, ASD	Temporality: Cannot rule out a possible association [1]
	2.	Hypospadias	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + nnRTI(s) + NtRTI(s) Regimen:

	1.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with Second/Third- Trimester Exposure to NRTI(s) + nnRTI(s) + InSTI(s) Regimen:

	1.	Bilateral cleft lip and palate	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third- Trimester Exposure to NRTI(s) + NtRTI(s) + PI(s) + InSTI(s) Regimen:

	1.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]
		Overriding aorta	Temporality: No temporal association [3]

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Birth Defects from Pregnancies with Unspecified Trimester Exposure to PI(s) only Regimen:

1.	Congenital adrenal hyperplasia	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) + nnRTI(s) Regimen:

1.	Scoliokyphosis	Temporality: Unable to assess [2]

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Retrospective Reports of Defects

List of reports of defects received after the outcome of the pregnancy was known.

Birth Defects from Pregnancies with First-Trimester Exposure to PI(s) Only Regimen:

1.	Cleft palate	Temporality: Cannot rule out a possible association [1]
2.	Small Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	Loud heart murmur	Temporality: No temporal association [3]
3.	Congenital genital malformation	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) Only Regimen:

1.	Multiple conditional abnormalities, including low-set ears posteriorly, superior helix of ear, retrognathia, epicanthal folds of eyes, hirsute, triangular face, blue sclera, long feet, palmar crease on index and middle fingers, hyperpigmented skin macules, prominent sacral dimple	Temporality: Cannot rule out a possible association [1]
2.	Pulmonary artery and aorta did not separate	Temporality: Cannot rule out a possible association [1]
3.	Total anomalous pulmonary venous return to coronary sinus with Atrial Septal Defect (ASD) on neonatal echo	Temporality: Cannot rule out a possible association [1]
4.	Imperforate anus	Temporality: Cannot rule out a possible association [1]
5.	Polymalformative syndrome: ventricular dilatation, duodenal atresia, single kidney, delayed development in utero, microgenitals and osseous abnormalities, possible triangular agenesis of the lower lip	Temporality: Cannot rule out a possible association [1]
6.	Vertebral defects: second lumbar vertebra consists of hemivertebrae and projects into spinal canal. First lumbar vertebra also displaced posteriorly	Temporality: Cannot rule out a possible association [1]
7.	Probable Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
8.	Congenital anomaly of brain, spinal cord, nervous system pachygyria/polymicrogyria, generalized mild hypotonia, cortical dysplasia, splenic agenesis of corpus callosum, asymmetric kidneys	Temporality: Cannot rule out a possible association [1]
9.	Ostium secundum type Atrial Septal Defect (ASD), mild right ventricular hypertrophy	Temporality: Cannot rule out a possible association [1]
10.	Panhypopituitarism, congenital anomalies of brain, musculoskeletal system, larynx, trachea & bronchus (cerebral dysgenesis, cartilaginous dysplasia)	Temporality: Cannot rule out a possible association [1]
11.	Polydactyly (bilateral hands).	Temporality: Cannot rule out a possible association [1]
12.	Polydactyly	Temporality: Cannot rule out a possible association [1]
13.	Malformation of external genitalia	Temporality: Cannot rule out a possible association [1]
14.	Bilateral club feet (equinovarus)	Temporality: Cannot rule out a possible association [1]
15.	Multiple rhabdomyomas in left ventrical and atrium, tuberosis sclerosis	Temporality: Cannot rule out a possible association [1]
16.	Congenital spine malformation	Temporality: Cannot rule out a possible association [1]
17.	Livedo reticularis, splenomegaly	Temporality: Cannot rule out a possible association [1]
18.	Holoprosencephaly, facial anomaly	Temporality: Cannot rule out a possible association [1]
19.	Pulmonary valve atresia/stenosis/hypoplasia	Temporality: Cannot rule out a possible association [1]
20.	Macula Abnormal	Temporality: Cannot rule out a possible association [1]
21.	Short neck, loose skin, bilateral club feet, contractures of hands/fingers, reduction of index finger left hand, possible arthrogryposis, lipodystrophy	Temporality: Cannot rule out a possible association [1]
22.	Ventricular Septal Defect (VSD), hepatosplenomegaly	Temporality: Cannot rule out a possible association [1]
23.	Inguinal hernia (resolved spontaneously at two months)	Temporality: Cannot rule out a possible association [1]
24.	Holoprosencephaly, cleft lip and palate, chromosome 18p deletion, cryptorchidism	Temporality: Cannot rule out a possible association [1]
25.	Strabismus, dysmorphic features of face and skull, atrophy of maculae and pigmental retinitis, cerebral atrophy	Temporality: Cannot rule out a possible association [1]
26.	Facial dysmorphism	Temporality: Cannot rule out a possible association [1]
27.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
28.	Alopecia, cavum septum pellucidum	Temporality: Cannot rule out a possible association [1]

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	29.	Hypospadias	Temporality: Cannot rule out a possible association [1]
	30.	Hydrocephalus	Temporality: Cannot rule out a possible association [1]
	31.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	32.	Congenital Ventricular Defect	Temporality: Cannot rule out a possible association [1]
	33.	Right Ventricular Hypertrophy	Temporality: Cannot rule out a possible association [1]
	1.	Pulmonary hypoplasia	Temporality: Cannot rule out a possible association [1]
	34.	Polycystic kidney	Temporality: Cannot rule out a possible association [1]
		Connective tissue disorder, arthropathy	Temporality: Unable to assess [2]
	35.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
		Cardiac murmur- Gr II-III/ VI	Temporality: No temporal association [3
	36.	Plagiocephaly	Temporality: Unable to assess [2]
	37.	Aortic coarctation, Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), hearing impairment	Temporality: Unable to assess [2]
	38.	Prognathism, genu valgum	Temporality: Unable to assess [2]
	39.	Agenesis of right nostril	Temporality: Unable to assess [2]
	40.	Ventricular Septal Defect (VSD) (induced abortion <20 weeks gestation), Multicystic dysplastic kidneys	Temporality: Unable to assess [2]
	41.	Atrioventricular septal defect, pulmonary artery atresia	Temporality: Unable to assess [2]
*	42.	Congenital hypertrophic pyloric stenosis	Temporality: Unable to assess [2]
	43.	Albinism	Temporality: No temporal association [3]
	44.	Hepatosplenomegaly, enlarged tongue, mongoloid appearance. Chromosomal evaluation showed no abnormalities	Temporality: No temporal association [3]
	45.	Cleft lip and palate	Temporality: No temporal association [3]
	46.	Large omphalocele including liver, spleen, and intestine (induced abortion <20 weeks gestation)	Temporality: No temporal association [3]
	47.	Congenital exomphalos	Temporality: No temporal association [3]
	48.	Dysmorphogenesis, bilateral deformity of feet, left hip dislocation, vertical talus of left foot	Temporality: No temporal association [3]
	49.	Transposition of great vessels	Temporality: No temporal association [3]
	50.	Bilateral vesicoureteral reflux, left cryptorchism, right hydrocele	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to nnRTI(s) Only Regimen:

ф	1.	Anomaly of foot	Temporality: Unable to assess [2]
	2.	Hearing impairment	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with First-Trimester Exposure to NtRTI(s) Only Regimen:

	1.	Cleft lip and palate	Temporality Cannot rule out a possible association [1]
	2.	Ventricular Septal Defect (VSD) (a heart murmur)	Temporality Cannot rule out a possible association [1]
	3.	Agenesis of 2nd/3rd phalanx on left hand	Temporality Cannot rule out a possible association [1]
	4.	Cleft lip and palate	Temporality: Cannot rule out a possible association [1]
	5.	Ventricular Septal Defect	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + nnRTI(s) Regimen:

	1.	Pulmonary valve stenosis	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + PI(s) Regimen:

	1.	Severe hypertrophic cardiomyopathy	Temporality: Cannot rule out a possible association [1]
	2.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
	3.	Cystic hygroma, congenital kyphosis; hemivertebra of L2 with partially dislocated spine (induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
	4.	Underdeveloped ribs, displaced hip, absence of chest muscle, abnormally placed kidney	Temporality: Cannot rule out a possible association [1]

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	5.	Hydrocephalus, cataracts, cardiac murmur	Temporality: Cannot rule out a possible association [1]
	6.	Facial nerve palsy (Bell's Palsy)	Temporality: Cannot rule out a possible association [1]
	7.	Right ear atresia. No external auditory canal visualized. Failed hearing screen in left ear. Bilateral hydronephrosis.	Temporality: Cannot rule out a possible association [1]
	8.	Bilateral choroid plexus cysts, microcephaly	Temporality: Cannot rule out a possible association [1]
	9.	Pyloric stenosis	Temporality: Cannot rule out a possible association [1]
	10.	Cleft lip/palate, precuricular skin tag, low-set left ear with no external auditory canal, Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	11.	Polydactyly (right hand)	Temporality: Cannot rule out a possible association [1]
	12.	Congenital glaucoma	Temporality: Cannot rule out a possible association [1]
	13.	Vertebral column anomaly, spine malformation, aortic coarctation, Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	14.	Severe cystic hygroma, chromosomal analysis normal, viral cultures negative. (induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
	15.	Skin rash over torso, face and head, bilateral talipes equinovarus, omphalocele	Temporality: Cannot rule out a possible association [1]
	16.	Extrahepatic biliary atresia, one month after birth	Temporality: Cannot rule out a possible association [1]
	17.	Tricuspid insufficiency, patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association [1]
	18.	CMV hepatitis	Temporality: Cannot rule out a possible association [1]
	19.	Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
	20.	At 19th month internal rotation of left lower limb, asymmetry between both hands: left smaller than right	Temporality: Cannot rule out a possible association [1]
	21.	Bilateral choroid plexus cysts	Temporality: Cannot rule out a possible association [1]
	22.	Ascites, left ventricular dilatation	Temporality: Cannot rule out a possible association [1]
	23.	Retraction of eyelid, pulmonary valvular stenosis	Temporality: Cannot rule out a possible association [1]
	24.	Polycystic dysplasia of right kidney	Temporality: Cannot rule out a possible association [1]
	25.	Hydrocephalus, strabismus	Temporality: Cannot rule out a possible association [1]
	26.	Cardiomegaly, tricuspid insufficiency, and hepatomegaly	Temporality: Cannot rule out a possible association [1]
	27.	Meconium peritonitis, ascites	Temporality: Cannot rule out a possible association [1]
	28.	Absent Fingers/Phalanges L Hand	Temporality: Cannot rule out a possible association [1]
	29.	One kidney	Temporality: Cannot rule out a possible association [1]
¥	30.	Mild hydronephrosis, hypospadias (3rd degree)	Temporality: Cannot rule out a possible association [1]
	31.	Myelomeningocele, Arnold-Chiari Malformation, membranous Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
	32.	Polydactyly (right hand)	Temporality: Cannot rule out a possible association [1]
	33.	Klinefelter syndrome XXY	Temporality: Cannot rule out a possible association [1]
	34.	Coarctation of the aorta, Ventricular Septal Defect (VSD), Patent Ductus Arteriosus (PDA), complete heart block	Temporality: Cannot rule out a possible association [1]
	35.	Pulmonary atresia, tricuspid insufficiency	Temporality: Cannot rule out a possible association [1]
	36.	Double outlet right ventricle, Transposition of the great vessels, Inlet Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	37.	Microcephaly, Cardiac Rhythm Abnormalities, Encephalopathy	Temporality: Cannot rule out a possible association [1]
	38.	Cardiac Hypertrophy, Encephalopathy	Temporality: Cannot rule out a possible association [1]
	39.	Congenital diaphragmatic hernia	Temporality: Cannot rule out a possible association [1]
	40.	Facial dysmorphism	Temporality: Cannot rule out a possible association [1]
	41.	Interventricular communication (VSD), Foramen ovale patent (PFO)	Temporality: Cannot rule out a possible association [1]
	42.	Muscular Ventricular Septal Defect (VSD), Patent foramen ovale (PFO), Patent Ductus Arteriosus (PDA)	Temporality: Cannot rule out a possible association [1]
	43.	Volvulus malrotation of intestine	Temporality: Cannot rule out a possible association [1]
	44.	Congenital hand malformation, Microdactyly	Temporality: Cannot rule out a possible association [1]
	45.	Ventricular septal defect (VSD): apical muscular	Temporality: Cannot rule out a possible association [1]
	46.	Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]

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[2] Insufficient data to assess temporality
[3] No temporal association

47.	Facial dysmorphia	Temporality: Cannot rule out a possible association [1]
48.	Double aortic arch / vascular ring	Temporality: Cannot rule out a possible association [1]
49.	Congenital heart malformation	Temporality: Cannot rule out a possible association [1]
	Suspected Trisomy 18	Temporality: Unable to assess [2]
50.	Metatarsus varus on right foot at 6.5 months	Temporality: Cannot rule out a possible association [1]
	Genu valgum developed at 3 years 8 months	Temporality: Unable to assess [2]
51.	Aorta hypoplasia	Temporality: Cannot rule out a possible association [1]
	Congenital malformation of fetus	Temporality: Unable to assess [2]
52.	Craniostenosis	Temporality: Cannot rule out a possible association [1]
	Congenital talipes (talus valgus)	Temporality: Unable to assess [2]
53.	Abdominal hernia, cryptorchism	Temporality: Cannot rule out a possible association [1]
	Murmur	Temporality: Unable to assess [2]
54.	Meningomyelocele (induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
	Talipes (induced abortion <20 weeks gestation)	Temporality: Unable to assess [2]
55.	Anomalous Coronary Artery, Multiple VSDs, Small, low lying left kidney, Soft Cleft Palate	Temporality: Cannot rule out a possible association [1]
	Small Perimembraneous VSD	Temporality: No temporal association [3]
56.	Talus Valgus, craniostenosis	Temporality: Unable to assess [2]
57.	Trisomy 18	Temporality: Unable to assess [2]
58.	Hypochromic Skin Around Right Eye and Mouth/Hanartomatous	Temporality: Unable to assess [2]
59.	Bilateral club feet	Temporality: Unable to assess [2]
60.	Unspecified heart anomaly	Temporality: Unable to assess [2]
61.	Congenital anomaly, abdominal hernia	Temporality: Unable to assess [2]
	Cryptorchism	Temporality: Cannot rule out a possible association [1]
62.	Triploidy	Temporality: Cannot rule out a possible association [1]
63.	Cardiomyopathy Neonatal	Temporality: Cannot rule out a possible association [1]
	Aortic Stenosis	Temporality: No temporal association [3]
64.	Absent 5th digits each hand, high arched palate, short phallus, long sacral dimple	Temporality: Cannot rule out a possible association [1]
	Skeletal dysplasia	Temporality: No temporal association [3]
65.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association [1]
	Down syndrome	Temporality: No temporal association [3]
66.	Hypospadias	Temporality: No temporal association [3]
67.	Congenital toxoplasmosis (spontaneous abortion ≥ 20 weeks gestation)	Temporality: No temporal association [3]
68.	Arthrogryposis, sloping forehead and ventricular cavities dilation	Temporality: Cannot rule out a possible association [1]
	Curved feet and short ankles	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + nnRTI(s) Regimen:

2.	Fetal malformation. Hydrocephalus, ventriculomegaly, Arnold-Chiari malformation, sacral spina bifida, lumbo-sacral meningomyelocele (induced abortion ≥ 20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
3.	Retrognathia	Temporality: Cannot rule out a possible association [1]
4.	Polycystic right kidney	Temporality: Cannot rule out a possible association [1]
5.	Pulmonary abnormalities, bone abnormalities (induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
6.	Left kidney oligohydramnios (severe), abnormally enlarged with pyelectasis	Temporality: Cannot rule out a possible association [1]
7.	Single ventricle, pulmonary atresia, discontinuous pulmonary arteries, dextrocardia, asplenia, situs inversus, heterotaxia syndrome	Temporality: Cannot rule out a possible association [1]
8.	Extended lumbosacral meningomyelocele	Temporality: Cannot rule out a possible association [1]
9.	Hydrocephalic, patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association [1]
10.	Congenital torticollis	Temporality: Cannot rule out a possible association [1]

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	11.	Trisomy 21 (questionable, induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
	12.	Frontal osteoma, deviated right 3-4 fingers, asymmetric feet	Temporality: Cannot rule out a possible association [1]
	13.	Bilateral absent kidney, dysplastic kidney	Temporality: Cannot rule out a possible association [1]
	14.	Ependymal cyst	Temporality: Cannot rule out a possible association [1]
	15.	Atrioventricular Septal Defect with double outlet right ventricle, transposition of great arteries, coarctation of aorta, ventriculomegaly of brain, situs inversus (liver and spleen)	Temporality: Cannot rule out a possible association [1]
	16.	Defective hearing in one ear	Temporality: Cannot rule out a possible association [1]
	17.	Dandy Walker malformation, cystic hygroma/ nuchal edema (spontaneous abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
	18.	Cleft palate	Temporality: Cannot rule out a possible association [1]
	19.	Bilateral clubfeet, hydrocephalus, lumbosacral meningomyelocele with Arnold-Chiari malformation (induced abortion ≥ 20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
	20.	Abnormal right auditory evoked potentials were evidenced at 22 months	Temporality: Cannot rule out a possible association [1]
	21.	Central cleft palate	Temporality: Cannot rule out a possible association [1]
	22.	Congenital hernia, Ventricular Septal Defect (VSD), labial fissure	Temporality: Cannot rule out a possible association [1]
	23.	Interventricular Septal Defect (VSD), persistent ductus botalli	Temporality: Cannot rule out a possible association [1]
	24.	Agenesis of the corpus callosum	Temporality: Cannot rule out a possible association [1]
	25.	Septo-optic dysplasia, hypoplasia of cerebellum	Temporality: Cannot rule out a possible association [1]
	26.	Possible spinal defect	Temporality: Cannot rule out a possible association [1]
	27.	Omphalocele	Temporality: Cannot rule out a possible association [1]
	28.	Left eye ptosis, left hydrocele	Temporality: Cannot rule out a possible association [1]
	29.	Abnormal urethral meatus	Temporality: Cannot rule out a possible association [1]
	30.	Agenesis of left hand below wrist	Temporality: Cannot rule out a possible association [1]
ф	31.	Dandy Walker variant, mild ventriculomegaly	Temporality: Cannot rule out a possible association [1]
¥	32.	Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
¥	33.	Slightly flattened bridge of nose, bifid femur	Temporality: Cannot rule out a possible association [1]
	34.	Hydrocephalus NOS	Temporality: Cannot rule out a possible association [1]
	35.	Spina Bifida/Chiari	Temporality: Cannot rule out a possible association [1]
	36.	Pulmonary artery atresia, pulmonary insufficiency and tricuspid insufficiency	Temporality: Cannot rule out a possible association [1]
	37.	Flat Midface, Low set ears, Sandal gap toes	Temporality: Cannot rule out a possible association [1]
		Down Syndrome	Temporality: No temporal association [3]
	38.	Patent ductus arteriosus (PDA), Patent Foramen Ovale (PFO), mild mitral valve atresia, mild tricuspid valve atresia	Temporality: Cannot rule out a possible association [1]
		Heart murmur	Temporality: Unable to assess [2]
	39.	Posterior cervical hygroma, hydrops (induced abortion <20 weeks gestation), bilateral club feet	Temporality: Unable to assess [2]
	40.	Omphalocele	Temporality: Unable to assess [2]
	41.	No brain stem (spontaneous abortion <20 weeks gestation)	Temporality: Unable to assess [2]
ф	42.	Patent Foramen Ovale	Temporality: Unable to assess [2]
	43.	Craniostenosis	Temporality: Unable to assess [2]
	44.	Atrioventricular canal, singular artery of umbilicus, symmetrical skeletal malformation: mesomelic dysplasia with short ulnae (left and right). Deviation to ulnar side for both hands	Temporality: No temporal association [3]
ф	45.	Mitral valve stenosis, Pulmonary valve stenosis	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + NtRTI(s) Regimen:

	1.	Hydrocephalus	Temporality: Cannot rule out a possible association [1]
	2.	Bone Deformations	Temporality: Cannot rule out a possible association [1]
*	3.	Anal atresia	Temporality: Cannot rule out a possible association [1]

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*	4.	Cleft lip, interventricular communication, multiple congenital malformations, trisomy 18	Temporality: Cannot rule out a possible association [1]
	5.	Pulmonary atresia with intact ventricular septum	Temporality: Unable to assess [2]
	6.	Hypospadias – angled penis	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + nnRTI(s) + PI(s) Regimen:

	1.	Ambiguous genitalia	Temporality: Cannot rule out a possible association [1]
	2.	Cystic adenomatoid malformation of lung	Temporality: Cannot rule out a possible association [1]
	3.	Down syndrome, polydactyly (2 thumbs right hand)	Temporality: Cannot rule out a possible association [1]
	4.	Right diaphragmatic hernia, Omphalocele, Microcephaly	Temporality: Cannot rule out a possible association [1]
	5.	Reduction defect of lower limb, Anal atresia, Malformation cloaca, Spinal malformation, Hypoplasia corpur callosum, Only one Kidney, Absent uterus	Temporality: Cannot rule out a possible association [1]
	6.	Spina Bifida With Cerebellar Engagement	Temporality: Cannot rule out a possible association [1]
	7.	Angioma	Temporality: Unable to assess [2]
ф	8.	Talipes Equinovarus	Temporality: Unable to assess [2]
ф	9.	Plydactyly – postaxial hand	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + NtRTI(s) + PI(s) Regimen:

¥	1.	Trisomy 8	Temporality: Cannot rule out a possible association [1]
	2.	Ocular abnormality	Temporality: Cannot rule out a possible association [1]
	3.	Light hydronephrosis at both sides	Temporality: Cannot rule out a possible association [1]
	4.	Partial trisomy 15	Temporality: Cannot rule out a possible association [1]
	5.	Distinctive hernia diaphragmatica	Temporality: Cannot rule out a possible association [1]
	6.	Bilateral arthrogryposis plus arthrogryposis multiplex congenital, bilateral club feet	Temporality: Cannot rule out a possible association [1]
	7.	Hydrocephalus, cardiac anomaly	Temporality: Cannot rule out a possible association [1]
	8.	Renal dysplasia, Posterior urethral valves	Temporality: Cannot rule out a possible association [1]
	9.	Tracheal Atresia	Temporality: Cannot rule out a possible association [1]
	10.	Omphalocele, Anal Atresia, Bladder Agenesis, Cloacal Exstrophy, Congenital Genital Malformation	Temporality: Cannot rule out a possible association [1]
	11.	Myelomeingocele with hydrocephalus/Arnold-Chiari malformation	Temporality: Cannot rule out a possible association [1]
	12.	Holoprosencephaly, abnormal shape of head-no craniosynostosis, Anophthalmia/microphthalmia, structural defect of CND – other specified, Microghathia/retrognathia, hydrocephalus NOS, hypertelorism, other specified anomaly of nose, other specified anomaly of ear, other specified anomaly of eye	Temporality: Cannot rule out a possible association [1]
	13.	Anomaly in cardiac rhythm	Temporality: Cannot rule out a possible association [1]
	14.	Anomaly of cardiac rhythm, anomaly of myocardium	Temporality: Cannot rule out a possible association [1]
	15.	VSD	Temporality: Cannot rule out a possible association [1]
	16.	Erb Palsy	Temporality: Cannot rule out a possible association [1]
	17.	Acrania with exencephaly (induced abortion >20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
	18.	Renal agenesis, imperforate anus, anomaly of intestinal rotation, prunebelly syndrome, mega bladder	Temporality: Cannot rule out a possible association [1]
	19.	Gastroschisis	Temporality: Cannot rule out a possible association [1]
	20.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
	21.	Perimembraneous VSD, Secundum ASD	Temporality: Cannot rule out a possible association [1]
	22.	Bud attached to 5th left toe, Chondroma of right ear pinna, Flesh buds attached to 5th fingers	Temporality: Cannot rule out a possible association [1]
	23.	Congenital anomaly of the Central Nervous System	Temporality: Cannot rule out a possible association [1]
	24.	Patent ductus Arteriosus (PDA), Patent foramen ovale (PFO) / Atrial septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
	25.	Atrio-septal defect; Down Syndrome	Temporality: Cannot rule out a possible association [1]
	26.	Osteogenesis Imperfecta or Campomelic Dysplasia	Temporality: Cannot rule out a possible association [1]

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	27.	Frontal bossing of the head, Lumbosacral Spina Bifida/Bilateral Ventriculomegaly	Temporality: Cannot rule out a possible association [1]
*	28.	Trisomy 18	Temporality: Cannot rule out a possible association [1]
*	29.	Myelomeningocele and hydrocephalus	Temporality: Cannot rule out a possible association [1]
*	30.	Right ear microtia/no ear canal	Temporality: Cannot rule out a possible association [1]
	31.	Unspecified heart anomaly	Temporality: Unable to assess [2]
	32.	Left superior vena cava	Temporality: Unable to assess [2]
	33.	Esophageal Atresia/tracheoesophageal fistula, vertebral malformation	Temporality: Unable to assess [2]
	34.	Left club foot	Temporality: Unable to assess [2]
	35.	Hemangiomas	Temporality: Unable to assess [2]
	36.	Polydactyly	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to EI(s) + PI(s) Regimen:

	1.	Heart malformation, Renal agenesis	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + NtRTI(s) + nnRTI(s) Regimen:

	1.	Epidermolysis bullosa	Temporality: Cannot rule out a possible association [1]
	2.	Myelomeningocele	Temporality: Cannot rule out a possible association [1]
	3.	Dandy Walker Syndrome, 2 vessel cord, multiple fetal malformations	Temporality: Cannot rule out a possible association [1]
	4.	Anencephaly (spontaneous abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
	5.	Cleft palate	Temporality: Cannot rule out a possible association [1]
	6.	Hypoplastic Right Ventricle, Tricuspid Atresia	Temporality: Cannot rule out a possible association [1]
	7.	Cardiac malformation, Facial dysmorphy	Temporality: Cannot rule out a possible association [1]
	8.	Left ulnar polydactyly	Temporality: Cannot rule out a possible association [1]
	9.	Bilateral Hydronephrosis, posterior urethral valves	Temporality: Cannot rule out a possible association [1]
	10.	Anencephaly	Temporality: Cannot rule out a possible association [1]
	11.	Atrial septal defect (ASD), epicanthal folds, low set ears, trisomy 21	Temporality: Cannot rule out a possible association [1]
*	12.	Bilateral cleft lip and palate	Temporality: Cannot rule out a possible association [1]
*	13.	Bilateral multicystic dysplastic kidneys	Temporality: Cannot rule out a possible association [1]
	1.	Patent Ductus Arteriosus (PDA), Patent Foramen Ovale (PFO), Tetralogy of Fallot	Temporality: Cannot rule out a possible association [1]
		22Q11.2 Deletion, Digeorge Syndrome	Temporality: No temporal association [3]
	2.	Varus (inward) anomaly of foot	Temporality: Unable to assess [2]
ф	3.	Gastroschisis	Temporality: Unable to assess [2]
	4.	Spina bifida	Temporality: Unable to assess [2]
ф	5.	Spina bifida	Temporality: Unable to assess [2]
ф	6.	Spina bifida	Temporality: Unable to assess [2]
	7.	Anterior Anus, Bilateral cryptotia and preauricular pits, Broad thumbs, Chin dimple, Cleft soft palate, Duplicate distal phalanges of index fingers, High nasal bridge, Hypertelorism, Hypoplastic labia minora and urovaginal opening, Lumpy gum, Radial deviation of thumbs, Robinow syndrome, Small mandible, Tetralogy of Fallot, Wide mouth	Temporality: Cannot rule out a possible association [1]
		Wide nipples	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s)+ NtRTI(s) + InSTI(s) Regimen:

	1.	VSD, Duodenal atresia	Temporality: Cannot rule out a possible association [1]
	2.	Myelomeningocele with Hydrocephalus	Temporality: Cannot rule out a possible association [1]
	3.	Club Foot	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s)+ NtRTI(s) + InSTI(s) + PI(s) Regimen:

	1.	Esophageal atresia, butterfly vertebra, hemivertebra	Temporality: Cannot rule out a possible association [1]

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	1.	Encephalocele	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s)+ nnRTI + NtRTI(s) + PI(s) Regimen:

	1.	Right pelvic kidney	Temporality: Cannot rule out a possible association [1]
	2.	Hydrocephalus NOS	Temporality: Cannot rule out a possible association [1]
	3.	Grade 2 VSD	Temporality: Cannot rule out a possible association [1]
	4.	Microcephalus	Temporality: Cannot rule out a possible association [1]
	5.	Congential teratoma	Temporality: Cannot rule out a possible association [1]
	6.	Broncho-pulmonary dysplasia, Congenital anomaly of adrenal gland, Facial dysmorphism, Hydrocephalus	Temporality: Cannot rule out a possible association [1]
	7.	Familial polydactyly	Temporality: Cannot rule out a possible association [1]
	8.	Lung malformation (CCAM or Sequestration)	Temporality: Cannot rule out a possible association [1]
	9.	Bilateral Postaxial Polydactyly Hands	Temporality: Cannot rule out a possible association [1]
	10.	Diaphragmatic Hernia	Temporality: Cannot rule out a possible association [1]
ф¥	11.	Plagiocephaly	Temporality: Unable to assess [2]
	12.	Hyperextension of the lower left limb, Reducible Recurvatum	Temporality: Unable to assess [2]
	13.	Wolf-Hirschhorn phenotype	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s)+ NtRTI(s) + InSTI(s) + PKE(s) Regimen:

*	1.	Hypoplastic left heart syndrome	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) Only Regimen:

	1.	Left hydronephrosis and ureteropelvic junction (UPJ) obstruction	Temporality: Cannot rule out a possible association [1]
	2.	Spastic torticollis of left sternocleidomastoid muscle	Temporality: Cannot rule out a possible association [1]
	3.	Talipes (right)	Temporality: Cannot rule out a possible association [1]
	4.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
	5.	Ureteral pelvic junction obstruction	Temporality: Cannot rule out a possible association [1]
		Fetal cardiac defect, epicanthus	Temporality: No temporal association [3]
	6.	Cardiomyopathy	Temporality: Cannot rule out a possible association [1]
		Septal defect (NOS)	Temporality: No temporal association [3]
	7.	Down syndrome	Temporality: Cannot rule out a possible association [1]
		A-V Canal	Temporality: No temporal association [3]
	8.	Bilateral genu recurvatum	Temporality: Cannot rule out a possible association [1]
	9.	Congenital hydronephrosis (left kidney)	Temporality: Cannot rule out a possible association [1]
	10.	Hypoplastic toes (left foot)	Temporality: Cannot rule out a possible association [1]
	11.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	12.	Down syndrome	Temporality: Cannot rule out a possible association [1]
		Ventricular Septal Defect (VSD), ostium secundum type Atrial Septal Defect (ASD)	Temporality: No temporal association [3]
	13.	Functional, undiagnosed cardiac murmurs (I, II/VI SEM)	Temporality: Cannot rule out a possible association [1]
	14.	Small Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
	15.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	16.	Fetal arrhythmia	Temporality: Cannot rule out a possible association [1]
	17.	Congenital anomalies of heart (hypertrophic cardiomyopathy)	Temporality: Cannot rule out a possible association [1]
	18.	Abnormal fetal heart rate/rhythm	Temporality: Cannot rule out a possible association [1]
	19.	Congenital obstructive defects of renal pelvis and ureter, cardiac murmur	Temporality: Cannot rule out a possible association [1]
	20.	Right ureteral pelvic junction obstruction	Temporality: Cannot rule out a possible association [1]
	21.	Microcephalus	Temporality: Cannot rule out a possible association [1]

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22.	Polydactyly	Temporality: Cannot rule out a possible association [1]
23.	Congenital talipes equinovarus	Temporality: Cannot rule out a possible association [1]
24.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
25.	Macroglossia, oblique palpebral fissures	Temporality: Cannot rule out a possible association [1]
26.	Hypertrophic cardiomyopathy	Temporality: Cannot rule out a possible association [1]
27.	Hepatosplenomegaly	Temporality: Cannot rule out a possible association [1]
28.	Hernia (left ovary)	Temporality: Cannot rule out a possible association [1]
29.	Macrocephaly	Temporality: Cannot rule out a possible association [1]
30.	Cardiac arrhythmia	Temporality: Cannot rule out a possible association [1]
31.	Hepatomegaly, cardiac rhythm disorder	Temporality: Cannot rule out a possible association [1]
32.	Convergent strabismus, torticollis, pedipes valgus	Temporality: Cannot rule out a possible association [1]
33.	Hollow feet, twisted right foot	Temporality: Cannot rule out a possible association [1]
34.	Albinism, nystagmus	Temporality: Cannot rule out a possible association [1]
35.	Multiple exostosis	Temporality: Cannot rule out a possible association [1]
36.	Inguinal hernia, hydrocele, strabismus	Temporality: Cannot rule out a possible association [1]
37.	Hepatosplenomegaly	Temporality: Cannot rule out a possible association [1]
	Umbilical hernia	Temporality: No temporal association [3]
38.	Renal dilatation (left)	Temporality: Cannot rule out a possible association [1]
39.	Skeletal dysplasia (with bowed femurs)	Temporality: Cannot rule out a possible association [1]
40.	Patent Foramen Ovale (PFO)	Temporality: Cannot rule out a possible association [1]
41.	Hypertrophic cardiomyopathy	Temporality: Unable to assess [2]
42.	Genu valgum	Temporality: Unable to assess [2]
43.	Ventricular Septal Defect (VSD)	Temporality: Unable to assess [2]
44.	Right club foot	Temporality: Unable to assess [2]
45.	Left ventricular hypertrophy	Temporality: Unable to assess [2]
	Scaphocephaly	Temporality: No temporal association [3]
46.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
47.	Asymptomatic Ventricular Septal Defect (VSD)	Temporality: No temporal association [3]
48.	Diaphragmatic hernia	Temporality: No temporal association [3]
49.	Two-vessel cord, hypoplastic left heart and mitral atresia	Temporality: No temporal association [3]
50.	Mitral valve atresia	Temporality: No temporal association [3]
51.	Robert Syndrome: cleft palate with cleft lip, bilateral, incomplete; congenital anomalies of skull and face bones; absent clitoris and labia minora; phocomelia (upper and lower extremities); right ectopic kidney, nevus flammeus forehead, hypertelorism, malformed ears, fusion of left humerus and radius, marked widening of symphysis pubis, absent fibulas, hips fused	Temporality: No temporal association [3]
52.	Ventricular Septal Defect (VSD), diaphragmatic hernia	Temporality: No temporal association [3]
53.	Polydactyly (left hand)	Temporality: No temporal association [3]
54.	Enlarged penis (>97 percentile)	Temporality: No temporal association [3]
55.	Double-outlet right ventricle and Ventricular Septal Defect (VSD)	Temporality: No temporal association [3]
56.	Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD)	Temporality: No temporal association [3]
57.	Cleft palate	Temporality: No temporal association [3]
58.	Acrania, sacral neural tube defect, bilateral cleft upper palate, contracted lower limbs	Temporality: No temporal association [3]
59.	Atrial septal defect (ASD)	Temporality: No temporal association [3]
60.	Hypospadias	Temporality: No temporal association [3]
61.	Missing/depressed right angularis muscle and absent orbicularis muscle, small patent ductus arteriosus (PDA)	Temporality: No temporal association [3]
62.	Congenital obstructive defect of renal pelvis and ureter	Temporality: No temporal association [3]
63.	Congenital subluxation of hip (unilateral)	Temporality: No temporal association [3]

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64.	Abnormality of chorion and amnion, cephalhematoma, caput succedaneum, chignon/massive epicranial hemorrhage, erythema toxicum, urticaria neonatorum, congenital anomaly of breast	Temporality: No temporal association [3]
65.	Congenital anomalies of larynx, trachea, and bronchus (congenital anterior subglottis web)	Temporality: No temporal association [3]
66.	Cardiac murmurs, congenital anomalies of brain (right choroid plexus cyst)	Temporality: No temporal association [3]
67.	Congenital musculoskeletal deformities of skull, face and jaw. Microcephalus seizures	Temporality: No temporal association [3]
68.	Polydactyly (left foot)	Temporality: No temporal association [3]
69.	Polydactyly (left hand)	Temporality: No temporal association [3]
70.	Nonspecific abnormality of skull/head, questionable click of left hip	Temporality: No temporal association [3]
71.	Congenital heart disease (biventricular hypertrophy), cardiomegaly	Temporality: No temporal association [3]
72.	Cardiac murmurs	Temporality: No temporal association [3]
73.	Cardiac murmur	Temporality: No temporal association [3]
74.	Cardiac murmur	Temporality: No temporal association [3]
75.	Potter's syndrome	Temporality: No temporal association [3]
76.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
77.	Congenital anomaly of genital organs (ambiguous genitalia)	Temporality: No temporal association [3]
78.	Atrial septal defect (ASD)	Temporality: No temporal association [3]
79.	Polydactyly (hand)	Temporality: No temporal association [3]
80.	Congenital subluxation of hip (unilateral), toxic erythema	Temporality: No temporal association [3]
81.	Polydactyly (hand)	Temporality: No temporal association [3]
82.	Hypospadias, epispadias	Temporality: No temporal association [3]
83.	Abnormal left ventricle	Temporality: No temporal association [3]
84.	Atrial septal defect (ASD)	Temporality: No temporal association [3]
85.	Hypospadias, microphallus	Temporality: No temporal association [3]
86.	Microcephalus	Temporality: No temporal association [3]
87.	Congenital stenosis of pulmonary valve, congenital anomaly of biliary tract	Temporality: No temporal association [3]
88.	Amniotic band syndrome right ankle	Temporality: No temporal association [3]
89.	Polydactyly (left hand)	Temporality: No temporal association [3]
90.	Hypoplastic left ventricle/atresic aortic arch	Temporality: No temporal association [3]
91.	Finger tag, heart murmur	Temporality: No temporal association [3]
92.	Vater/vacterl. Bilateral radial abnormalities, deformed thumbs, imperforate anus, single testes, mild hypospadias, hemivertebrae S1-2-3, small Ventricular Septal Defect (VSD) and patent ductus arteriosus (PDA)	Temporality: No temporal association [3]
93.	Talipes varus	Temporality: No temporal association [3]
94.	Fetal hydronephrosis	Temporality: No temporal association [3]
95.	Hypospadias	Temporality: No temporal association [3]
96.	Congenital megacolon	Temporality: No temporal association [3]
97.	Congenital megacolon	Temporality: No temporal association [3]
98.	Complex heart disease, aortic outflow obstruction	Temporality: No temporal association [3]
99.	Syndactyly of right 3-4 fingers, syndactyly of left 3-4 toes, left cleft lip	Temporality: No temporal association [3]
100.	Left chonal atresia, possible flattened facies, possible positional plagiocephaly	Temporality: No temporal association [3]
101.	Congenital dislocated hip (left)	Temporality: No temporal association [3]
102.	Duodenal atresia, cardiac malformation	Temporality: No temporal association [3]
103.	Mild strabismus, abnormal left ear	Temporality: No temporal association [3]
104.	Pulmonary atresia	Temporality: No temporal association [3]
105.	Microcephaly, dilated left cerebral ventricle	Temporality: No temporal association [3]
106.	Malrotation of small intestine	Temporality: No temporal association [3]
107.	Cleft lip and palate	Temporality: No temporal association [3]

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	108.	Right Ventricular Hypoplasia	Temporality: No temporal association [3]
	109.	Polydactyly NOS - Hand	Temporality: No temporal association [3]
	110.	Cleft lip	Temporality: No temporal association [3]
ф	111.	Mitochondriopathy	Temporality: Cannot rule out [1]
		White matter degeneration	Temporality: Unable to assess [2]
		Corpus callosum hypoplasia	Temporality: No temporal association [3]
	112.	Trisomy 21, Dawn phenomenon	Temporality: Cannot rule out a possible association [1]
		Congenital anomaly NOS	Temporality: Unable to assess [2]
		Dysmorphism	Temporality: No temporal association [3]
	113.	Congenital anomaly NOS	Temporality: Unable to assess [2]
		Single umbilical artery	Temporality: No temporal association [3]
	114.	Pulmonary stenosis, umbilical hernia, brown nevus	Temporality: Cannot rule out a possible association [1]
		Supernumerary nipple	Temporality: No temporal association [3]
	115.	Angioma (nape of neck)	Temporality: Cannot rule out a possible association [1]
		Umbilical hernia	Temporality: No temporal association [3]
	116.	Ptosis, strabismus, nystagmus	Temporality: Cannot rule out a possible association [1]
		Epicanthal folds	Temporality: No temporal association [3]
	117.	Left eye defect	Temporality: Unable to assess [2]
		Left cleft lip and soft palate	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NtRTI(s) only Regimen:

	1.	Hydronephrosis	Temporality: Cannot rule out a possible association [1]
		Multicystic dysplastic right kidney, ectopic right kidney	Temporality: No temporal association [3]
	2.	Deaf in one ear	Temporality: Unable to assess [2]
	3.	Agenesis of Clavicles, Agenesis of Parietal Bones	Temporality: Unable to assess [2]
		Cleidocranial Dysplasia	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + PI(s) Regimen:

	1.	Trisomy 21, renal anomalies, bilateral hydroureter to the bladder, mild left hydronephrosis, patent ductus arteriosis (PDA)	Temporality: Cannot rule out a possible association [1]
	2.	Clubfeet, bilateral	Temporality: Cannot rule out a possible association [1]
	3.	Cystic hygroma	Temporality: Cannot rule out a possible association [1]
	4.	Down syndrome	Temporality: Cannot rule out a possible association [1]
	5.	Poor growth, short stature, chromosomal or dwarfism	Temporality: Cannot rule out a possible association [1]
	6.	Ventricular dilatation and hydrocephalus– external, possible cerebral atrophy, beta Thalassemia	Temporality: Cannot rule out a possible association [1]
	7.	Angiomas (2), facial asymmetry, valgus foot	Temporality: Cannot rule out a possible association [1]
	8.	Eyelid retraction	Temporality: Cannot rule out a possible association [1]
	9.	Varus feet at 4 ½ months	Temporality: Cannot rule out a possible association [1]
	10.	Right hydronephrosis	Temporality: Cannot rule out a possible association [1]
	11.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association [1]
	12.	Micrognathia, myotonic dystrophy	Temporality: Cannot rule out a possible association [1]
	13.	Down syndrome	Temporality: Cannot rule out a possible association [1]
	14.	Atrial septal defect secundum (ASD)	Temporality: Cannot rule out a possible association [1]
	15.	Left hydronephrosis	Temporality: Cannot rule out a possible association [1]
	16.	Anomaly in cardiac rhythm, anomaly of myocardium	Temporality: Cannot rule out a possible association [1]
	17.	Down Syndrome	Temporality: Cannot rule out a possible association [1]
	18.	Pulmonary artery enlarged, small heart, club foot	Temporality: Cannot rule out a possible association [1]
		Dandy Walker Syndrome, aortic stenosis	Temporality: Unable to assess [2]

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19.	Trisomy 18, Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]
	Congenity gastric anomaly (“small stomach”), esophageal atresia, Ventricular Septal Defect (VSD)	Temporality: Unable to assess [2]
	Esophageal atresia	Temporality: No temporal association [3]
20.	Craniosynostosis	Temporality: Unable to assess [2]
21.	Left Sided Neck Mass	Temporality: Unable to assess [2]
22.	Hip dysplasia/dislocation	Temporality: Unable to assess [2]
23.	Congenital anomaly NOS	Temporality: Unable to assess [2]
24.	Bronchogenic cyst	Temporality: Unable to assess [2]
25.	Congenital myopathy	Temporality: Unable to assess [2]
26.	Down Syndrome, patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association [1]
	AV canal	Temporality: No temporal association [3]
27.	Sickle cell disease	Temporality: Cannot rule out a possible association [1]
	Polydactyly (hand)	Temporality: No temporal association [3]
28.	Pulmonary valve aatresia/Stenosis/hypoplasia, anomaly of myocardium	Temporality: Cannot rule out a possible association [1]
	Dysplastic aortic valve	Temporality: No temporal association [3]
29.	Hydrocephalus	Temporality: Cannot rule out a possible association [1]
	Dandy Walker	Temporality: No temporal association [3]
30.	Microcephaly	Temporality: Cannot rule out a possible association [1]
	Congenital toxoplasmosis, CMV infection	Temporality: No temporal association [3]
31.	Hydronephrosis	Temporality: Cannot rule out a possible association [1]
	Fetal Ventriculomegaly	Temporality: No temporal association [3]
32.	Unilateral deafness	Temporality: Unable to assess [2]
	Glaucoma (right eye), café au lait spots: Recklinghausen disease	Temporality: No temporal association [3]
33.	Omphalocele with bowel gangrene	Temporality: No temporal association [3]
34.	Hypoplastic left heart ventricle	Temporality: No temporal association [3]
35.	Coarctation of the aorta and patent ductus arteriosus (PDA)	Temporality: No temporal association [3]
36.	Polycystic kidney, hypoplastic lungs	Temporality: No temporal association [3]
37.	Prognathism	Temporality: No temporal association [3]
38.	Anencephaly (induced abortion <20 weeks gestation)	Temporality: No temporal association [3]
39.	Polydactyly (bilateral hands), accessory auricle left ear	Temporality: No temporal association [3]
40.	Trisomy 21, atrioventricular canal defect	Temporality: No temporal association [3]
41.	Polydactyly both hands	Temporality: No temporal association [3]
42.	Polydactyly postaxial hand and foot	Temporality: No temporal association [3]
43.	Laryngeal atresia	Temporality: No temporal association [3]
44.	Polydactyly postaxial hands, polydactyly postaxial feet	Temporality: No temporal association [3]
45.	Ebstein’s Anomaly	Temporality: No temporal association [3]
46.	Gastroschisis	Temporality: No temporal association [3]
47.	Unspecified heart anomalies	Temporality: No temporal association [3]
48.	Esophageal atresia	Temporality: No temporal association [3]
49.	Right kidney low and probably fused with midline left kidney	Temporality: No temporal association [3]
50.	Omphalocele	Temporality: No temporal association [3]
51.	Glandular hypospadia	Temporality: No temporal association [3]
52.	Cleft Lip	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + nnRTI(s) Regimen:

1.	Congenital diaphragmatic hernia, dysmorphic features, clinodactyly, long forehead, long ears, Zellweger syndrome	Temporality: Cannot rule out a possible association [1]
2.	Down syndrome	Temporality: Cannot rule out a possible association [1]

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3.	Microcephaly	Temporality: Cannot rule out a possible association [1]
4.	Occipital plagiocephaly	Temporality: Unable to assess [2]
5.	Undescended testicles	Temporality: Unable to assess [2]
	Maxillolabial cleft	Temporality: No temporal association [3]
6.	Turner syndrome	Temporality: No temporal association [3]
7.	Syndactyly of both hands	Temporality: No temporal association [3]
8.	Partial midline cleft palate	Temporality: No temporal association [3]
9.	Polydactyly	Temporality: No temporal association [3]
10.	Large fontanelle anterior and posterior, large glabellar crease, multicystic dysplastic left kidney	Temporality: No temporal association [3]
11.	Tetralogy of Fallot	Temporality: No temporal association [3]
12.	Mild dysmorphic features including cleft soft palate, long fingers, toes, low-set ears, simple philtrum, wide nipples, flat nasal bridge	Temporality: No temporal association [3]
13.	No fingers and toes, hypoplastic mandible, long right femur, and long right radius and ulna (bilateral)	Temporality: No temporal association [3]
14.	Imperforate rectum, cleft palate / cleft lip (double), absent corpus callosum, patent ductus arteriosus (PDA), no external ears, ambiguous genitals, hypoplastic pulmonary artery	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to EI(s)+ InSTI(s) Regimen:

1.	Polydactyly NOS - hand	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s)+ nnRTI + PI(s) Regimen:

1.	Umbilical hernia, hepatomegaly, strabismus	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s)+ NtRTI(s) + PI(s) Regimen:

1.	Macroglossia, patent ductus arteriosus (PDA), Patent Foramen Ovale (PFO)	Temporality: Cannot rule out a possible association [1]
2.	VSD, PDA, Patent Foramen Ovale (PFO), Pulmonary valve stenosis	Temporality: Cannot rule out a possible association [1]
3.	Pyelectasis, Down syndrome	Temporality: Cannot rule out a possible association [1]
	Tetralogy of Fallot	Temporality: No temporal association [3]
4.	Bilateral Extranumerary Digits – Postaxial Hand	Temporality: Unable to assess [2]
5.	Ventricular Septal Defect (VSD)	Temporality: Unable to assess [2]
6.	Equinovarus deformity bilateral	Temporality: Unable to assess [2]
7.	Hypospadias	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s)+ InSTI(s) + PI(s) Regimen:

1.	Left eyelid lag, Ventriculomegaly	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s)+ nnRTI(s) + NtRTI(s) Regimen:

1.	Equinas of R & L Feet	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + NtRTI(s) + InSTI(s) Regimen:

1.	Genetic Defect (Unspecified)	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s)+ NtRTI(s) + PI(s) + InSTI(s) Regimen:

1.	Left multicystic dysplastic kidney	Temporality Cannot rule out a possible association [1]
2.	Mitral insufficiency	Temporality Cannot rule out a possible association [1]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) only Regimen:

1.	Glycogenosis type II (Pompe's disease)	Temporality: Cannot rule out a possible association [1]
2.	Dysmorphia	Temporality: Cannot rule out a possible association [1]

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3.	Fetal Alcohol Syndrome Microcephaly, posterior segment anomaly, dysmorphic facies, other specified anomaly of the eye	Temporality: Cannot rule out a possible association [1] Temporality: Unable to assess [2]
4.	Umbilical hernia, strabismus	Temporality: Unable to assess [2]
5.	Dysmelia of right hand	Temporality: Unable to assess [2]
6.	Hypospadias (presumed male)	Temporality: Unable to assess [2]
7.	Short segment Hirschsprung's Disease, bilateral supernumary nipples	Temporality: Unable to assess [2]
8.	Microcephaly	Temporality: Unable to assess [2]
9.	Intestinal atresia	Temporality: Unable to assess [2]
10.	Biventricular hypertrophy, tricuspid regurgitation, Patent Foramen Ovale (PFO), patent ductus arteriousus (PDA)	Temporality: Unable to assess [2]
11.	Imperforate anus – no fistula, 2 vessel umbilical cord, minimal dilation of the cerebral ventricles, small Ventricular Septal Defect (VSD), moderate bilateral hydronephrosis, urogenital sinus malformation	Temporality: Unable to assess [2]
12.	Polydactyly (bilateral hands, left foot)	Temporality: Unable to assess [2]
13.	Communicating hydrocephalus, Ex vacuo ventriculomegaly	Temporality: Unable to assess [2]
14.	Talipes valgus	Temporality: Unable to assess [2]
15.	Potter's sequence	Temporality: Unable to assess [2]
16.	Cardiac malformation	Temporality: Unable to assess [2]
17.	Epicanthus, flat root of nose, high arched palate, hypertelorism, large earlobes, lowset ears, microcephaly	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to PI(s) only Regimen:

1.	Gastrointestinal malformation, Tetralogy of Fallot	Temporality: Unable to assess [2]
2.	Slight Malformation (Congenital Malformation)	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified-Trimester Exposure to NtRTI only Regimen:

1.	Birth Defect was noted	Temporality: Unable to assess [2]
	No fetal heart	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to EI(s) + NRTI(s) + PI(s) Regimen:

1.	Cutaneous Depigmentation	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) + InSTI(s) + PI(s) Regimen:

1.	Ventricular enlargement	Temporality: Cannot rule out a possible association [1]
2.	Congenital anomaly	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) + PI(s) Regimen:

1.	Bilateral glaucoma, Corneal opacity	Temporality: Cannot rule out a possible association [1]
2.	Retrognathia, posterior cleft palate, moderate ventriculomegaly, mega cisterna magna	Temporality: Cannot rule out a possible association [1]
3.	Talipes equines (bilateral)	Temporality: Unable to assess [2]
4.	Malrotation, incomplete obstruction of intestines	Temporality: Unable to assess [2]
5.	Patent Foramen Ovale (PFO), Patent Ductus Arteriosus (PDA), mild TI, apical muscular Ventricular Septal Defect (VSD)	Temporality: Unable to assess [2]
6.	Hepatomegaly, hypertrophic cardiomyopathy	Temporality: Unable to assess [2]
7.	Multiple congenital anomalies	Temporality: Unable to assess [2]
8.	Congenital club foot	Temporality: Unable to assess [2]
9.	Unspecified fetal abnormalities	Temporality: Unable to assess [2]
10.	Congenital cataract	Temporality: Unable to assess [2]
11.	Syndactyly, congenital jaw malformation, congenital club foot, cleft lip and palate	Temporality: Unable to assess [2]
12.	Pulmonary stenosis	Temporality: Unable to assess [2]

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	13.	Right-sided aortic arch/double aortic arch/vascular ring, anomaly of trachea	Temporality: Unable to assess [2]
	14.	Coarctation of aorta	Temporality: Unable to assess [2]
	15.	Club foot	Temporality: Unable to assess [2]
	16.	Facial dysmorphism, Osseous abnormalities	Temporality: Unable to assess [2]
	17.	Congenital central nervous system anomaly, Congenital intestinal malformation, hydrocephalus	Temporality: Unable to assess [2]
	18.	Café au lait spots multiple, Glaucoma, Neurofibromatosis / Recklinghausen's Disease	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to InSTI(s) + PI(s) Regimen:

	1.	Syndactyly	Temporality: Unable to assess [2]
	2.	Cervical butterfly vertebrae; costal snostosis on both sides; esophageal atresia; hydrocephalus/aqueductal stenosis; lumbar hemivertibrae; malformed right ear with no auditory canal	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NtRTI(s) + nnRTI(s) + PI(s) Regimen:

	1.	Varus of Left Foot	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) + NtRTI(s) + PI(s) Regimen:

	1.	Tetralogy of Fallot	Temporality: Unable to assess [2]
	2.	Clinodactyly, short fingers	Temporality: Unable to assess [2]
	2.	Hydrocephalus	Temporality: Unable to assess [2]
	3.	Cardiomegaly, coarctation of the aorta, mitral valve incompetence, PDA, tricuspid valve incompetence	Temporality: Unable to assess [2]
	4.	Hemangioma	Temporality: Unable to assess [2]
	5.	Ventricular Septal Defect (VSD)	Temporality: Unable to assess [2]
	6.	Micrognathia	Temporality: Unable to assess [2]
*	7.	Tetralogy of fallot	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to nnRTI(s) Only Regimen:

	1.	Congenital deafness	Temporality: Unable to assess [2]
	2.	Truncus Arteriosus	Temporality: Unable to assess [2]
ф	3.	Pachygyria	Temporality: Unable to assess [2]
ф	4.	Corpus callosum agenesis	Temporality: Unable to assess [2]
ф	5.	Hydrocephaly	Temporality: Unable to assess [2]
ф	6.	Cerebral cyst	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) + nnRTI(s) Regimen:

	1.	Bilateral renal dilation	Temporality: Unable to assess [2]
ф	2.	Bilateral inguinal hernia, hydronephrosis, UJP obstruction, right ureter dilation, nasal piriform aperture stenosis, and single midline incisor	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) + InSTI(s) Regimen:

	1.	Plagiocephaly	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) + EI(s) + InSTI(s) Regimen:

ф	1.	Plagiocephaly	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to EI(s) + InSTI(s) + PI(s) Regimen:

	1.	Abnormal bladder base, Unilateral multicystic kidney, Vesicoureteric reflux	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) + NtRTI(s) + InSTI(s) + PI(s) Regimen:

	1.	Down Syndrome	Temporality: Cannot rule out a possible association [1]

Note: Some affected cases are twins, triplets, etc., who had normal co-twins, co-triplets, etc., or in which more than one fetus had a defect. This portion of the cases is small, which puts confidentiality at risk for those families. The multiple gestation indicator is temporarily removed from the report until the sample is of adequate size not to compromise the mother's privacy.

Note: The temporality rating is assigned only once per case and represents a single assessment based on the earliest exposure to any antiretroviral. Individual drugs may be introduced at times which are not temporally related, however all drugs will carry the case temporality assignment.

* New, **Updated reports this period, ¥ didanosine first trimester defects (Table 5), ‡ didanosine second/third trimester defects (Table 5), † didanosine unknown trimester of exposure (Table 5), ф literature report

[1] The development of this defect and the timing of the exposure to antiretroviral drug therapy cannot rule out a possible association
[2] Insufficient data to assess temporality
[3] No temporal association

	2.	Congenital aortic anomaly, Pulmonary hypoplasia, Ventricular septal defect (VSD)	Temporality: Unable to assess [2]
	3.	Right Hexadactylia Grade II Left Hexadactylia	Temporality: Unable to assess [2]
	4.	Congenital heart defect	Temporality: Unable to assess [2]
	5.	Club foot	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) + nnRTI(s) + NtRTI(s) Regimen:

ф	1.	Bilateral pyelocaliceal dilation	Temporality: Cannot rule out a possible association [1]
	2.	Cerebral developmental disorder, hygroma coli, hypoplasia of whole spinal cord, hypoplasia of auricular buds, retrognathia, small opening of the mouth	Temporality: Unable to assess [2]
	3.	Polydactyly	Temporality: Unable to assess [2]
	4.	Six fingers each hand	Temporality: Unable to assess [2]
		Six toes each foot	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to NRTI(s) + PI(s) + nnRTI(s) + NtRTI(s) + InSTI(s) Regimen:

	1.	Ambiguous genitalia, bladder agenesis, cloacal exstrophy, gastrointestinal malformation, lipodystrophy, meningomyelocele, spine malformation, tethered cord, umbilical cord abnormality	Temporality: Unable to assess [2]
	2.	Abnormal umbilical cord, ambiguous genitalia, bladder agenesis, caudal regression, cloacal exstrophy, exomphalos, lipodystrophy, meningomyelocele, tethered cord	Temporality: Unable to assess [2]

Birth Defects from Pregnancies with Unspecified Trimester Exposure to PI(s) + NtRTI(s) Regimen:

	1.	Ventricular Septal Defect (VSD)	Temporality: Unable to assess [2]

Note: Some affected cases are twins, triplets, etc., who had normal co-twins, co-triplets, etc., or in which more than one fetus had a defect. This portion of the cases is small, which puts confidentiality at risk for those families. The multiple gestation indicator is temporarily removed from the report until the sample is of adequate size not to compromise the mother's privacy.

Note: The temporality rating is assigned only once per case and represents a single assessment based on the earliest exposure to any antiretroviral. Individual drugs may be introduced at times which are not temporally related, however all drugs will carry the case temporality assignment.

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[2] Insufficient data to assess temporality

[3] No temporal association

Reports from Clinical Studies in Pregnancy

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) Only Regimen:

	1.	Trisomy 21 (Down Syndrome)	Temporality: Cannot rule out a possible association [1]
	2.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	3.	Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
	4.	Small muscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	5.	Partial fusion proximal radius, ulna; Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	6.	Membranous Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	7.	Left costal margin birthmark, pilonidal dimple, grade II/IV systolic murmur	Temporality: Cannot rule out a possible association [1]
	8.	Deformed right ear, skin tags, facial asymmetry (hemiofacial microsomia)	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + PI(s) Only Regimen:

	1.	Small muscular Ventricular Septal Defect (VSD) with L-R shunting; moderate peripheral pulmonary artery stenosis	Temporality: Cannot rule out a possible association [1]
	2.	Polydactyly (right foot)	Temporality: Cannot rule out a possible association [1]
	3.	Atrial septal defect (ASD)	Temporality: Cannot rule out a possible association [1]
	4.	Patent Ductus Arteriosus (PDA), atrial septal defect (ASD)	Temporality: Cannot rule out a possible association [1]
	5.	Hypospadias	Temporality: Cannot rule out a possible association [1]
	6.	Ventricular Septal Defect (VSD)	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + nnRTI(s) Regimen:

	1.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	2.	Patent Ductus Arteriosus (PDA), Patent Foramen Ovale (PFO)	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + nnRTI(s) + PI(s) Regimen:

	1.	Hypospadias	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + NtRTI(s) + PI(s) Regimen:

*	2.	Atrial septal defect (ASD), cleft palate, down syndrome	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + nnRTI(s) + NtRTI(s) Regimen:

	1.	Hydronephrosis	Temporality: Cannot rule out a possible association [1]
	2.	Congenital Peyronie's Disease	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to PI + nnRTI + InSTI Regimen:

	1.	Bilateral hydroureter, right hydronephrosis	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with First-Trimester Exposure to NRTI(s) + NtRTI(s) + InSTI +PKE(s) Regimen:

*	1.	Patent foramen ovale, undescended right testicle	Temporality: Cannot rule out a possible association [1]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) Only Regimen:

	1.	Cystic lesions of head	Temporality: Cannot rule out a possible association [1]
	2.	Peripheral pulmonic stenosis, Patent Foramen Ovale (PFO)	Temporality: Cannot rule out a possible association [1]
	3.	Umbilical hernia	Temporality: Cannot rule out a possible association [1]
		Polydactyly	Temporality: No temporal association [3]
	4.	Clitoromegaly with hyperkalemia	Temporality: Cannot rule out a possible association [1]
		Polydactyly, syndactyly (both big toes)	Temporality: No temporal association [3]
	5.	Pectus excavatum	Temporality: Cannot rule out a possible association [1]
	6.	Down Syndrome	Temporality: Cannot rule out a possible association [1]

Note: Some affected cases are twins, triplets, etc., who had normal co-twins, co-triplets, etc., or in which more than one fetus had a defect. This portion of the cases is small, which puts confidentiality at risk for those families. The multiple gestation indicator is temporarily removed from the report until the sample is of adequate size not to compromise the mother's privacy.

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[2] Insufficient data to assess temporality
[3] No temporal association

	7.	Clubfoot	Temporality: Cannot rule out a possible association [1]
	8.	Myocardial hypertrophy, enlarged adrenals, pulmonary hypoplasia, ascites	Temporality: Cannot rule out a possible association [1]
	9.	Bilateral club feet, Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association [1]
		Cleft lip and palate	Temporality: No temporal association [3]
	10.	Talipes equinovarus both lower limbs	Temporality: Cannot rule out a possible association [1]
	11.	Syndactyly (fingers without fusion of bone)	Temporality: No temporal association [3]
	12.	Hemivertibra (S2-S3)	Temporality: No temporal association [3]
	13.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
	14.	Venticular Septal Defect (VSD)	Temporality: No temporal association [3]
	15.	Hypospadias	Temporality: No temporal association [3]
	16.	Polydactyly	Temporality: No temporal association [3]
	17.	Polydactyly (bilateral)	Temporality: No temporal association [3]
	18.	Polydactyly (bilateral)	Temporality: No temporal association [3]
	19.	Polydactyly (bilateral)	Temporality: No temporal association [3]
	20.	Thyroglossal cysts	Temporality: No temporal association [3]
	21.	Atrial septal defect (ASD)	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + PI(s) Regimen:

	1.	Patent Ductus Arteriosus (PDA)Ventricular Septal Defect (VSD), Perimembranous	Temporality: Cannot rule out a possible association [1]
			Temporality: No temporal association [3]
	2.	Ventricular Septal Defect (VSD) Membranous	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + nnRTI(s) Regimen:

	1.	Ventricular Septal Defect (VSD), Patent Foramen Ovale (PFO)	Temporality: Cannot rule out a possible association [1]
	2.	Inguinal herniation (right)	Temporality: Cannot rule out a possible association [1]
		Herniation of umbilicus	Temporality: No temporal association [3]
	3.	Hydrocele	Temporality: Cannot rule out a possible association [1]
		Umbilical Hernia	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + InSTI(s) Regimen:

	1.	Cryptorchidism	Temporality: Cannot rule out a possible association [1]
*	2.	Atrial communication	Temporality: Cannot rule out a possible association [1]
*	3.	Interatrial communication	Temporality: Cannot rule out a possible association [1]
	4.	Total Anomalous Pulmonary Venous Return	Temporality: No temporal association [3]
	5.	Polydactyly, Postaxial	Temporality: No temporal association [3]

Birth Defects from Pregnancies with Second/Third-Trimester Exposure to NRTI(s) + nnRTI(s) + NtRTI(s) Regimen:

*	1.	Umbilical hernia, infant treated for syphilis after delivery	Temporality: Cannot rule out a possible association [1]
	2.	Polydactyly	Temporality: No temporal association [3]

Note: Some affected cases are twins, triplets, etc., who had normal co-twins, co-triplets, etc., or in which more than one fetus had a defect. This portion of the cases is small, which puts confidentiality at risk for those families. The multiple gestation indicator is temporarily removed from the report until the sample is of adequate size not to compromise the mother's privacy.

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[3] No temporal association

Appendix D: Index

Appendix E: Brief Descriptions of Antiretroviral Drugs Included in the Registry

This appendix includes a synopsis of safety data relative to pregnancy for each drug included in the Registry. To provide consistent, relevant information to health care providers on the use and safety of the Registry drugs during pregnancy, the drug descriptions in this appendix include the following sections from the US package insert, which are derived from the FDA's final rule on Requirements on Content and Format of Labeling for Human Prescription Drug and Biologic Products (Federal Register, January 24, 2006, Vol 71, No. 15, p. 3987):

Indications and usage
Pregnancy
Labor and Delivery
Nursing Mothers
Pediatric use
Carcinogenesis, mutagenesis, impairment of fertility
Patient Counseling Information (to be included only if it relates to pregnancy)

For complete safety data, please consult the appropriate drug label and relevant published literature.

Generic products are available for didanosine, efavirenz, lamivudine, nevirapine, stavudine and zidovudine. The safety information for generic drugs is, by law, identical to the parent drug for drugs approved in the US.

WHO continues to coordinate efforts to assure that information about adverse events are disseminated rapidly in "data poor" environments. There is a WHO web site which is focused on patient safety, www.who.int/patientsafety/en and which is continually updated. Further, there is a section on that WHO web site dealing with reporting strategies for adverse events.

Abacavir (ZIAGEN®, ABC)

ZIAGEN® is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside analogue with inhibitory activity against HIV-1.

Pregnancy: Abacavir is assigned FDA Pregnancy Category C status. Reproduction studies were performed in rats and rabbits at orally administered doses up to 1,000 mg/kg per day and 700 mg/kg per day, respectively. These doses in rats and rabbits achieved approximately 35 and 8.5 times, respectively, the exposure associated with the recommended human dose. Developmental toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed when rats were treated with abacavir at doses of 1000 mg/kg during organogenesis. This dose produced 33 times the human exposure, based on AUC.

The offspring of female rats treated with abacavir at 500 mg/kg (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations at doses up to 700 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC). In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations.

There are no adequate and well-controlled studies in pregnant women. Abacavir should be used during pregnancy only if the potential benefits outweigh the risk.

Pharmacokinetics and Transmission: Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peripartum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports on developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peripartum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Fertility: Abacavir had no adverse effects on the mating performance or fertility of male and female rats at doses of up to 500 mg/kg per day, a dose expected to produce exposures approximately eight-fold higher than that in humans at the therapeutic dose based on body surface area comparisons, a dose that was toxic to the parental generation. Evidence of toxicity to the developing embryo and fetus (increased resorption, decreased fetal body weight) occurred only at 500 mg/kg per day.

Carcinogenicity: Abacavir was administered orally at three dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenesis: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. At systemic exposures approximately nine times higher than that in humans at the therapeutic dose, abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

(Last reviewed October 2014)

Adefovir dipivoxil (HEPSERA®, ADV)

Adefovir dipivoxil (HEPSERA®) is an oral prodrug of adefovir, an acyclic nucleotide phosphonate analogue of adenosine monophosphate, which is actively transported into mammalian cells where it is converted by host enzymes to adefovir diphosphate. Adefovir diphosphate inhibits HBV polymerase by competing for direct binding with the natural substrate (deoxyadenosine triphosphate) and, after incorporation into viral DNA, causes DNA chain termination.

HEPSERA® is indicated for the treatment of chronic hepatitis B in patients 12 years of age and older.

HEPSERA® is assigned FDA Pregnancy Category C status. There are no adequate and well-controlled studies on the use of HEPSERA® in pregnant women. HEPSERA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reproduction studies with oral administration of adefovir dipivoxil to pregnant rats and rabbits showed no evidence of embryotoxicity or teratogenicity at systemic exposures equivalent to 23 times (rats) and 40 times (rabbits) that achieved in humans at the therapeutic dose. However, embryotoxicity and an increased incidence of fetal malformations (anasarca, depressed eye bulge, umbilical hernia and kinked tail) occurred when adefovir was administered intravenously to pregnant rats at 38 times the human therapeutic exposure. These adverse reproductive effects did not occur following an intravenous dose where exposure was 12 times the human therapeutic exposure.

There are no studies in pregnant women and no data on the effect of HEPSERA® on transmission of hepatitis B virus from mother to infant. Therefore, appropriate infant immunizations should be used to prevent neonatal acquisition of hepatitis B virus.

It is not known whether adefovir is excreted in human milk. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from HEPSERA®, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

The safety, efficacy, and pharmacokinetics of HEPSERA® in pediatric patients (aged 12 to less than 18 years) were evaluated in a double-blind, randomized, placebo-controlled study (GS-US-103-0518) in 83 pediatric patients with chronic hepatitis B and compensated liver disease. The proportion of patients treated with HEPSERA® who achieved the primary efficacy endpoint of serum HBV DNA less than 1,000 copies/mL and normal ALT levels at the end of 48 weeks blinded treatment was significantly greater (23%) when compared to placebo-treated patients (0%). Patients 2 to less than 12 years of age were also evaluated. The efficacy of adefovir dipivoxil was not significantly different from placebo in patients less than 12 years of age. HEPSERA® is not recommended for use in children below 12 years of age.

In long-term carcinogenicity studies in rats and mice with adefovir dipivoxil, no treatment-related increase in tumor incidence was found in mice or rats (systemic exposures approximately 10 and 4 times those achieved in humans at the therapeutic dose of 10 mg/day, respectively).

Adefovir dipivoxil was mutagenic in the in vitro mouse lymphoma cell assay (with or without metabolic activation). Adefovir induced chromosomal aberrations in the *in vitro* human peripheral blood lymphocyte assay without metabolic activation. Adefovir dipivoxil was not clastogenic in the in vivo mouse micronucleus assay and adefovir was not mutagenic in microbial mutagenicity assays involving *Salmonella typhimurium* (Ames) and *Escherichia coli* in the presence and absence of metabolic activation. In reproductive toxicology studies, no evidence of impaired fertility was seen in male or female rats at systemic exposure approximately 19 times that achieved in humans at the therapeutic dose.

(Last reviewed April 2016)

Amprenavir (AGENERASE®, APV) – No longer manufactured

Amprenavir (AGENERASE®) is an inhibitor of the human immunodeficiency virus (HIV) protease. AGENERASE® is assigned FDA Pregnancy Category C. Embryo/fetal development studies were conducted in rats (dosed from 15 days before pairing to day 17 of gestation) and rabbits (dosed from day 8 to day 20 of gestation). In pregnant rabbits, amprenavir administration was associated with abortions and an increased incidence of three minor skeletal variations resulting from deficient ossification of the femur, humerus trochlea, and humerus. Systemic exposure at the highest tested dose was approximately one-twentieth of the exposure seen at the recommended human dose. In rat fetuses, thymic elongation and incomplete ossification of bones were attributed to amprenavir. Both findings were

seen at systemic exposures that were one half of that associated with the recommended human dose. Pre- and post-natal developmental studies were performed in rats dosed from day 7 of gestation to day 22 of lactation. Reduced body weights (10% to 20%) were observed in the offspring. The systemic exposure associated with this finding was approximately twice the exposure in humans following administration of the recommended human dose. The subsequent development of these offspring, including fertility and reproductive performance, was not affected by the maternal administration of amprenavir. There are no adequate and well-controlled studies in pregnant women. Amprenavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atazanavir (REYATAZ®, ATV)

Atazanavir is an antiviral agent that is an inhibitor of HIV-1 protease. Atazanavir selectively inhibits the virus specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to REYATAZ during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Atazanavir has been evaluated in a limited number of women during pregnancy. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate [see Data]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. No treatmentrelated malformations were observed in rats and rabbits, for which the atazanavir exposures were 0.7-1.2 times of those at the human clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir). When atazanavir was administered to rats during pregnancy and throughout lactation, reversible neonatal growth retardation was observed.

Clinical Considerations

Dose Adjustments during Pregnancy and the Postpartum Period

- REYATAZ must be administered with ritonavir in pregnant women.
- For pregnant patients, no dosage adjustment is required for REYATAZ with the following exceptions:
    - For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is coadministered with either an H2-receptor antagonist or tenofovir disoproxil fumarate, REYATAZ 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a REYATAZ dose for use with both an H2-receptor antagonist and tenofovir disoproxil fumarate in treatment-experienced pregnant women. No dosage adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery.

Maternal Adverse Reactions

Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have occurred in pregnant women using REYATAZ in combination with nucleoside analogues, which are associated with an increased risk of lactic acidosis syndrome.

Hyperbilirubinemia occurs frequently in patients who take REYATAZ, including pregnant women.

Advise pregnant women of the potential risks of lactic acidosis syndrome and hyperbilirubinemia.

Fetal/Neonatal Adverse Reactions
All infants, including neonates exposed to REYATAZ in utero, should be monitored for the development of severe hyperbilirubinemia during the first few days of life [see Data].

Data

Human Data
In clinical trial AI424-182, REYATAZ/ritonavir (300/100 mg or 400/100 mg) in combination with zidovudine/lamivudine was administered to 41 HIV-infected pregnant women during the second or third trimester. Among the 39 women who completed the study, 38 women achieved an HIV RNA less than 50 copies/mL at time of delivery. Six of 20 (30%) women on REYATAZ/ritonavir 300/100 mg and 13 of 21 (62%) women on REYATAZ/ritonavir 400/100 mg experienced hyperbilirubinemia (total bilirubin greater than or equal to 2.6 times ULN). There were no cases of lactic acidosis observed in clinical trial AI424-182.
Atazanavir drug concentrations in fetal umbilical cord blood were approximately 12% to 19% of maternal concentrations. Among the 40 infants born to 40 HIV-infected pregnant women, all had test results that were negative for HIV-1 DNA at the time of delivery and/or during the first 6 months postpartum. All 40 infants received antiretroviral prophylactic treatment containing zidovudine. No evidence of severe hyperbilirubinemia (total bilirubin levels greater than 20 mg/dL) or acute or chronic bilirubin encephalopathy was observed among neonates in this study. However, 10/36 (28%) infants (6 greater than or equal to 38 weeks gestation and 4 less than 38 weeks gestation) had bilirubin levels of 4 mg/dL or greater within the first day of life.

Lack of ethnic diversity was a study limitation. In the study population, 33/40 (83%) infants were Black/African American, who have a lower incidence of neonatal hyperbilirubinemia than Caucasians and Asians. In addition, women with Rh incompatibility were excluded, as well as women who had a previous infant who developed hemolytic disease and/or had neonatal pathologic jaundice (requiring phototherapy).

Additionally, of the 38 infants who had glucose samples collected in the first day of life, 3 had adequately collected serum glucose samples with values of less than 40 mg/dL that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis.

Based on prospective reports from the APR of approximately 1600 live births following exposure to atazanavir-containing regimens (including 1037 live births in infants exposed in the first trimester and 569 exposed in second/third trimesters), there was no difference between atazanavir and overall birth defects compared with the background birth defect rate. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2-4%.

Animal Data
In animal reproduction studies, there was no evidence of mortality or teratogenicity in offspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir). In pre- and postnatal development studies in the rat, atazanavir caused neonatal growth retardation during lactation that reversed after weaning. Maternal drug exposure at this dose was 1.3 times the human exposure at the recommended clinical exposure. Minimal maternal toxicity occurred at this exposure level.

Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Atazanavir has been detected in human milk. No data are available regarding atazanavir effects on milk production. Atazanavir was present in the milk of lactating rats and was associated with neonatal growth retardation that reversed after weaning.

Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed.

(Last reviewed November 2015)

Cobicistat (TYBOST®, COBI)

Cobicistat is a mechanism-based inhibitor of cytochrome P-450 (CYP) enzymes of the CYP3A family which belongs to the class of drugs called pharmacokinetic enhancers and is used to increase systemic exposure of atazanavir or darunavir in combination with other antiretroviral agents to treat HIV-1 infection. Cobicistat is also one of the components of the single tablet regimens, Stribild® (150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate) and Genvoya® (150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide). Please refer to the local prescribing information for Tybost, Stribild, and Genvoya.

Studies of cobicistat in animals have shown no evidence of teratogenicity and some effect on maternal reproductive function at the highest experimental dose. In offspring from rat and rabbit dams treated with cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 1.4 and 3.3 times higher than the exposure in humans at the recommended daily dose of 150 mg. When administered orally to pregnant rats at doses of 0, 25, 50, and 125 mg/kg/day on gestation day 6 to 17, maternal toxicity (adverse clinical signs, decreased body weight and food consumption) was noted at 125 mg/kg/day and was associated with increases in post-implantation loss and decreased fetal weights. No malformations were noted at doses up to 125 mg/kg/day. Systemic exposures (AUC) at 50 mg/kg/day in pregnant females was 1.4-fold higher than the exposures at the MRHD. There are, however, no adequate and well-controlled studies in pregnant women. Cobicistat should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There is no information regarding the presence of cobicistat in human milk, the effects on the breastfed infant, or the effects on milk production. Because of both the potential for HIV-1 transmission and the unknown potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving cobicistat.

Safety and effectiveness of cobicistat in children less than 18 years of age have not been established.

In a long-term carcinogenicity study in mice, no drug-related increases in tumor incidence were observed at doses up to 50 and 100 mg/kg/day (males and females, respectively). Cobicistat exposures at these doses were approximately 7 (male) and 16 (females) times, respectively, the human systemic exposure at the therapeutic daily dose. In a long-term carcinogenicity study of cobicistat in rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses of 25 and 50 mg/kg/day in males, and at 30 mg/kg/day in females. The follicular cell findings are considered to be rat-specific, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not relevant for humans. At the highest doses tested in the rat carcinogenicity study, systemic exposures were approximately 2 times the human systemic exposure at the therapeutic daily dose.

Cobicistat was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays and did not affect fertility in male or female rats at daily exposures (AUC) approximately 3-fold higher than human exposures at the recommended 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately similar than human exposures at the recommended 150 mg daily dose.

(Last reviewed April 2017)

Darunavir (PREZISTA®, DRV)

Darunavir (Prezista®, DRV) is an inhibitor of the human immunodeficiency virus (HIV) protease.
Indications and usage: PREZISTA is a human immunodeficiency virus (HIV-1) protease inhibitor indicated for the treatment of HIV infection in adult patients. PREZISTA is also indicated for the treatment of HIV infection in pediatric patients 3 years of age and older. PREZISTA must be co-administered with ritonavir (PREZISTA/ritonavir) and with other antiretroviral agents.

Pregnancy: Pregnancy Category C: PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk.

No adequate and well-controlled studies have been conducted in pregnant women. Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice, rats and rabbits. However, due to limited bioavailability and/or dosing limitations, animal exposures (based on AUC) were only 50% (mice and rats) and 5% (rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility and mating performance of offspring were not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the juvenile toxicity study where rats were directly dosed with darunavir, deaths occurred from post-natal day 5 through 11 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) of 0.1 of the human plasma exposure levels.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known whether darunavir is secreted in human milk, darunavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving PREZISTA®**.

Pediatric Use: Do not administer PREZISTA/ritonavir in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age. PREZISTA should be taken with ritonavir twice daily and with food.

The safety, pharmacokinetic profile, and virologic and immunologic responses of PREZISTA/ritonavir were evaluated in treatment-experienced HIV-1-infected pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg. These subjects were evaluated in clinical trials TMC114-C212 (80 subjects, 6 to less than 18 years of age) and TMC114-228 (21 subjects, 3 to less than 6 years of age). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults. Please see product label for twice-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

In clinical trial TMC114-C230, the safety, pharmacokinetic profile and virologic and immunologic responses of PREZISTA/ritonavir administered once daily were evaluated in treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age (12 subjects). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults. Once daily dosing recommendations for pediatric patients 3 to less than 12 years of age were derived using population pharmacokinetic modeling and simulation. Although a PREZISTA/ritonavir once daily dosing pediatric trial was not conducted in children less than 12 years of age, there is sufficient clinical safety data to support the predicted PREZISTA exposures for the dosing recommendations in this age group. Please see Dosage and Administration (2.2) for once-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

Carcinogenesis, mutagenesis, impairment of fertility:

Carcinogenesis and Mutagenesis
Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas were observed in males and females of both species as well as an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on AUC) were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg once daily).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reserve mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

Impairment of Fertility
No effects on fertility or early embryonic development were observed with darunavir in rats and darunavir has shown no teratogenic potential in mice (in the presence or absence of ritonavir), rats and rabbits.

(Last reviewed April 2015)

Delavirdine mesylate (RESCRIPTOR®, DLV)

Delavirdine mesylate (RESCRIPTOR®) is a non-nucleoside reverse transcriptase inhibitor of HIV-1.

Pregnancy: Delavirdine is assigned FDA Pregnancy Category C status. Delavirdine has been shown to be teratogenic in rats. Delavirdine caused ventricular septal defects in rats at doses of 50, 100, and 200 mg/kg/day when administered during the period of organogenesis. The lowest dose of delavirdine that caused malformations produced systemic exposures in pregnant rats equal to or lower than the expected human exposure to delavirdine (Cmin 15 µM) at the recommended dose. Because exposure in rats was approximately 5-fold higher than the expected human exposure, results were marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival. Additionally, reduced pup survival on postpartum day 0 occurred at an exposure (mean Cmin) approximately equal to the expected human exposure. Delavirdine was excreted in the milk of lactating rats at a concentration three to five times that of rat plasma.

Delavirdine at doses of 200 and 400 mg/kg/day administered during the period of organogenesis caused maternal toxicity, embryotoxicity and abortions in rabbits. The lowest dose of delavirdine that resulted in these toxic effects produced systemic exposures in pregnant rabbits approximately 6-fold higher than the expected human exposure to delavirdine (Cmin 15 µM) at the recommended dose. The no-observed-adverse-effect dose in the pregnant rabbit was 100 mg/kg/day. Various malformations were observed at this dose, but the incidence of such malformations was not statistically significantly different from those in the control group. Systemic exposures in pregnant rabbits at 100 mg/kg/day were lower than those expected in humans at the recommended clinical dose. Malformations were not apparent at 200 and 400 mg/kg/day; however, only a limited number of fetuses were available for examination as a result of maternal and embryo death.

No adequate and well-controlled studies in pregnant women have been conducted. Delavirdine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Of nine pregnancies reported in premarketing clinical studies and post marketing experience, a total of ten infants were born (including one set of twins). Eight of the infants were born healthy. One infant was born HIV-positive but was otherwise healthy and with no congenital abnormalities detected, and one infant was born prematurely (34 to 35 weeks) with a small muscular ventricular septal defect that spontaneously resolved. The patient received approximately six weeks of treatment with delavirdine and zidovudine early in the course of the pregnancy.

Fertility: Delavirdine at doses of 20, 100, and 200 mg/kg/day did not cause impairment of fertility in rats when males were treated for 70 days and females were treated for 14 days prior to mating.

Carcinogenicity: Lifetime carcinogenicity studies were conducted in rats at doses of 10, 32, and 100 mg/kg/day and in mice at doses of 62.5, 250, and 500 mg/kg/day for males and 62.5, 125, and 250 mg/kg/day for females. In rats, delavirdine was noncarcinogenetic at maximally tolerated doses that produced exposures (AUC) up to 12 (male rats) and 9 (female rats) times human exposure at the recommended clinical dose. In mice, delavirdine produced significant increases in the incidence of hepatocellular adenoma/adenocarcinoma in both males and females, hepatocellular adenoma in females, and mesenchymal urinary bladder tumors in males. The systemic drug exposures (AUC) in female mice were 0.5- to 3-fold and in male mice 0.2- to 4-fold of those in humans at the recommended clinical dose.

Mutagenesis: Delavirdine was negative in a battery of genetic toxicology tests which included an Ames assay, an *in vitro* rat hepatocyte unscheduled DNA synthesis assay, an *in vitro* chromosome aberration assay in human peripheral lymphocytes, an *in vitro* mutation assay in Chinese hamster ovary cells, and an *in vivo* micronucleus test in mice.

Given the lack of genotoxic activity of delavirdine, the relevance of urinary bladder and hepatocellular neoplasm in delavirdine-treated mice to humans is not known.

(Last reviewed October 2014)

Didanosine (VIDEX®, VIDEX® EC, ddI®)

Didanosine in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxyadenosine in which the 3'-hydroxyl group is replaced by hydrogen. Intracellularly, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5'-triphosphate. Dideoxyadenosine 5'-triphosphate inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate, deoxyadenosine 5'-triphosphate, and by its incorporation into viral DNA causing termination of viral DNA chain.

Evidence of a dose-limiting skeletal muscle toxicity has been observed in mice and rats (but not in dogs) following long-term (greater than 90 days) dosing with didanosine at doses that were approximately 1.2 to 12 times the estimated human exposure. The relationship of this finding to the potential of didanosine to cause myopathy in humans is unclear. However, human myopathy has been associated with administration of other nucleoside analogues.

Lifetime carcinogenicity studies were conducted in mice and rats for 22 and 24 months, respectively. In the mouse study, initial doses of 120, 800, and 1200 mg/kg/day for each sex, were lowered after 8 months to 120, 210, and 210 mg/kg/day for females and 120, 300, and 600 mg/kg/day for males. The two higher doses exceeded the maximally tolerated doses in females and the high dose exceeded the maximally tolerated doses in males. The low dose in females represented 0.68-fold maximum human exposure and the intermediate dose in males represented 1.7-fold maximum human exposure. In the rat study, initial doses were 100, 250, and 1000 mg/kg/day, and the high dose was lowered to 500 mg/k/day after 18 months. The upper dose in male and female rats represented 3-fold maximum human exposure. Didanosine induced no significant increase in neoplastic lesions in mice or rats at maximally tolerated doses.
Didanosine was positive in the following toxicology assays: 1) the *Escherichia Coli* tester strain WP2 uvrA bacterial mutagenicity assay; 2) the L5178Y/TK+/- mouse lymphoma mammalian cell gene mutation assay; 3) the *in vitro* chromosomal aberrations assay in cultured human peripheral lymphocytes; 4) the *in vitro* chromosomal aberrations assay in Chinese Hamster Lung cells; and 5) the BALB/c 3T3 *in vitro* transformation assay. No evidence of mutagenicity was observed in an AMES *Salmonella* bacterial mutagenicity assay or in rat and mouse *in vivo* micronucleus assay.

Didanosine is assigned FDA Pregnancy Category B status. Reproduction studies have been performed in rats and rabbits at doses up to 12 and 14.2 times the estimated human exposure (based upon plasma levels), respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to didanosine. At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains but the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation. A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of didanosine in pregnant women. Didanosine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic

acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues. **The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Healthcare providers caring for HIV-infected pregnant women receiving didanosine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

(Last reviewed March 2016)

Dolutegravir (TIVICAY®, DTG)

TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg.

Pregnancy: Dolutegravir is assigned FDA Pregnancy Category B status. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and dolutegravir was shown to cross the placenta in animal studies, this drug should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats and rabbits at doses up to 27 times the human dose of 50 mg twice daily and have revealed no evidence of impaired fertility or harm to the fetus due to TIVICAY. Oral administration of dolutegravir to pregnant rats at doses up to 1,000 mg/kg daily, approximately 27 times the 50-mg twice-daily human clinical exposure based on AUC, from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity, or teratogenicity. Oral administration of dolutegravir to pregnant rabbits at doses up to 1,000 mg/kg daily, approximately 0.4 times the 50-mg twice-daily human clinical exposure based on AUC, from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreased food consumption, scant/no feces/urine, suppressed body weight gain) was observed at 1,000 mg/kg.

Nursing mothers: Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving TIVICAY.

Pediatric use: Treatment-Naïve or Treatment-Experienced INSTI-Naïve: The recommended dose of TIVICAY in pediatric patients aged 12 years and older and weighing at least 40 kg is 50 mg administered orally once daily. If efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin are coadministered, the recommended dose of TIVICAY is 50 mg twice daily. Safety and efficacy of TIVICAY have not been established in pediatric patients younger than 12 years or weighing less than 40 kg, or in pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir).

Carcinogenesis: Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg/kg, and rats were administered doses of up to 50 mg/kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 14-fold higher than those in humans at the recommended dose of 50 mg twice daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10-fold and 15-fold higher in males and females, respectively, than those in human at the recommended dose of 50 mg twice daily.

Mutagenesis: Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

Impairment of fertility: In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg/kg/day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at the recommended dose of 50 mg twice daily.

(Last reviewed October 2014)

Efavirenz (SUSTIVA®, STOCRIN®, EFV)

SUSTIVA® (efavirenz) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on two clinical trials of at least one year duration that demonstrated prolonged suppression of HIV RNA.

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SUSTIVA during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263.

Risk Summary

There are retrospective case reports of neural tube defects in infants whose mothers were exposed to efavirenz containing regimens in the first trimester of pregnancy. Prospective pregnancy data from the Antiretroviral Pregnancy Registry are not sufficient to adequately assess this risk. Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Although a causal relationship has not been established between exposure to efavirenz in the first trimester and neural tube defects, similar malformations have been observed in studies conducted in monkeys at doses similar to the human dose. In addition, fetal and embryonic toxicities occurred in rats, at a dose ten times less than the human exposure at recommended clinical dose. Because of the potential risk of neural tube defects, efavirenz should not be used in the first trimester of pregnancy. Advise pregnant women of the potential risk to a fetus.

Data

Human Data
There are retrospective postmarketing reports of findings consistent with neural tube defects, including meningomyelocele, all in infants of mothers exposed to efavirenz-containing regimens in the first trimester.

Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of approximately 1000 live births following exposure to efavirenz containing regimens (including over 800 live births exposed in the first trimester), there was no difference between efavirenz and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program. As of the interim APR report issued December 2014, the prevalence of birth defects following first-trimester exposure was 2.3% (95% CI: 1.4%-3.6%). One of these prospectively reported defects with firsttrimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported. This case also included severe oblique facial clefts and amniotic banding, which have a known association with anophthalmia.

Animal Data

Effects of efavirenz on embryo-fetal development have been studied in three nonclinical species (cynomolgus monkeys, rats, and rabbits). In monkeys, efavirenz 60 mg/kg/day was administered 20 to pregnant females throughout pregnancy (gestation days 20 through 150). The maternal systemic drug exposures (AUC) were 1.3 times the exposure in humans at the recommended clinical dose (600 mg/day), with fetal umbilical venous drug concentrations approximately 0.7 times the maternal values. Three of 20 fetuses/infants had one or more malformations; there were no malformed fetuses or infants from placebo-treated mothers. The malformations that occurred in these three monkey fetuses included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in a second, and cleft palate in the third. There was no NOAEL (no observable adverse effect level) established for this study because only one dosage was evaluated. In rats, efavirenz was administered either during organogenesis (gestation days 7 to 18) or from gestation day 7 through lactation day 21 at 50, 100, or 200 mg/kg/day. Administration of 200 mg/kg/day in rats was associated with increase in the incidence of early resorptions; and doses 100 mg/kg/day and greater were associated with early neonatal mortality. The AUC at the NOAEL (50 mg/kg/day) in this rat study was 0.1 times that in humans at the recommended clinical dose. Drug concentrations in the milk on lactation day 10 were approximately 8 times higher than those in maternal plasma. In pregnant rabbits, efavirenz was neither embryo lethal nor teratogenic when administered at doses of 25, 50, and 75 mg/kg/day over the period of organogenesis (gestation days 6 through 18). The AUC at the NOAEL (75 mg/kg/day) in rabbits was 0.4 times that in humans at the recommended clinical dose.

Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Because of the potential for HIV transmission in breastfed infants, advise women not to breastfeed.

Females and Males of Reproductive Potential

Because of potential teratogenic effects, pregnancy should be avoided in women receiving SUSTIVA.

Pregnancy Testing

Females of reproductive potential should undergo pregnancy testing before initiation of SUSTIVA.

Contraception

Females of reproductive potential should use effective contraception during treatment with SUSTIVA and for 12 weeks after discontinuing SUSTIVA due to the long half-life of efavirenz. Barrier contraception should always be used in combination with other methods of contraception. Hormonal methods that contain progesterone may have decreased effectiveness

(Last reviewed November 2015)

Elvitegravir (VITEKTA®, EVG)

Elvitegravir is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor used in combination with an HIV protease inhibitor coadministered with ritonavir and with other antiretroviral drug(s) for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults. Elvitegravir is also one of the components of the single tablet regimens, Stribild® (150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate) and Genvoya® (150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide). Please refer to the local prescribing information for Vitekta,Stribild, and Genvoya.

Studies of elvitegravir in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with elvitegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 23 and 0.2 times higher than the exposure in humans at the recommended daily dose of 150 mg. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Vitekta® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Studies in rats have demonstrated that elvitegravir is secreted in milk. It is not known whether elvitegravir is excreted in human milk. It is recommended that mothers being treated with elvitegravir do not breast-feed their infants.

Safety and effectiveness of elvitegravir in children less than 18 years of age have not been established.

In long-term carcinogenicity studies of elvitegravir, no drug-related increases in tumor incidence were found in mice at doses up to 2000 mg/kg/day alone or in combination with 25 mg/kg/day ritonavir (3-and 14 times, respectively, the human systemic exposure at the therapeutic 150 mg daily dose), or in rats at doses up to 2000 mg/kg/day (12- to 27-times, respectively in male and female, the human systemic exposure at the therapeutic daily dose).

Elvitegravir was not genotoxic in the reverse mutation bacterial test (Ames test) and the rat micronucleus assay. In an in vitro chromosomal aberration test, elvitegravir was negative with metabolic activation; however, an equivocal response was observed without activation.

Elvitegravir did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures (AUC), respectively, than in humans at the therapeutic 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 18-fold higher than human exposures at the recommended 150 mg daily dose.

(Last reviewed April 2017)

Emtricitabine (EMTRIVA®, FTC)

EMTRIVA® is the brand name of emtricitabine. Emtricitabine is a nucleoside analog of and is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate, which competitively inhibits human immunodeficiency virus type-1 (HIV-1) reverse transcriptase, resulting in DNA chain termination.

EMTRIVA® is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

EMTRIVA® is assigned Pregnancy Category B status. Reproductive studies were conducted in rats, mice, and rabbits. Animal studies (performed at 60 to 120-fold higher than human exposures at the recommended daily dose)) did not indicate harmful effects of emtricitabine with respect to fertility, pregnancy, fetal development, parturition or postnatal development. There are, however, no adequate and well-controlled trials in pregnant women. Because animal reproduction studies are not always predictive of human response,

EMTRIVA® should be used during pregnancy only if clearly needed.

Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving EMTRIVA. Therefore, it is recommended that mothers being treated with EMTRIVA® do not breast-feed their infants.

Long-term carcinogenicity studies of emtricitabine in rats and mice did not show any carcinogenicity potential. No drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose). Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended daily dose.

(Last reviewed April 2016)

Enfuvirtide (FUZEON®, T-20)

Enfuvirtide (FUZEON®) is an inhibitor of the fusion of HIV-1 with CD4 cells. Enfuvirtide in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of FUZEON® of 48 weeks duration. Subjects enrolled were treatment-experienced adults; many had advanced disease. There are no studies of FUZEON® in antiretroviral naive patients.

Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

Enfuvirtide was neither mutagenic nor clastogenic in a series of in vivo and in vitro assays including the Ames bacterial reverse mutation assay, a mammalian cell forward gene mutation assay in AS52 Chinese Hamster ovary cells or an in vivo mouse micronucleus assay.

Enfuvirtide produced no adverse effects on fertility in male or female rats at enfuvirtide doses 0.7, 2.5, and 8.3 times the maximum recommended adult human daily does on a mg/kg basis administered by subcutaneous injection (or 1.6 times the maximum recommended adult human daily dose on a m2 basis).

Enfuvirtide is assigned FDA Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 27 times and 3.2 times the adult human dose on a m2 basis. The animal studies revealed no evidence of harm to the fetus from enfuvirtide. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

(References: FUZEON Core Data Sheet version 3.0 November 10, 2007; FUZEON USPI Revised: February 2010)

(Last Reviewed February 2016)

Entecavir (BARACLUDE®, ETV)

Entecavir (BARACLUDE®, ETV) is a guanosine nucleoside analogue with activity against hepatitis B virus (HBV) reverse transcriptase. Entecavir is efficiently phosphorylated to the active triphosphate form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine triphosphate, entecavir triphosphate functionally inhibits all three activities of the HBV polymerase (reverse transcriptase, rt): 1) base priming, 2) reverse transcription of the negative strand from the pregenomic messenger RNA, and 3) synthesis of the positive strand of HBV DNA. Entecavir triphosphate has an inhibition constant (Ki) for HBV DNA polymerase of 0.0012 µM. Entecavir triphosphate is a weak inhibitor of cellular DNA polymerases α, ß, and δ and mitochondrial DNA polymerase γ with Ki values ranging from 18 > 160 µM.

Entecavir is indicated for the treatment of chronic hepatitis B virus infection in adults and children at least 2 years of age with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

In adults, this indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment- naïve and lamivudine resistant patients with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease. Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease. Virologic, biochemical, serologic, and safety data are available for a limited number of adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy. In pediatric patients 2 years of age and older, this indication is based on clinical trial data in nucleoside-treatment-naive and in a limited number of lamivudine-experienced subjects with HBeAg-positive chronic HBV infection and compensated liver disease.

Long-term oral carcinogenicity studies of entecavir in mice and rats were carried out at exposures up to approximately 42 times (mice) and 35 times (rats) those observed in humans at the highest recommended dose of 1 mg/day. In mouse and rat studies, entecavir was positive for carcinogenic findings.

In mice, lung adenomas were increased in males and females at exposures 3 and 40 times those in humans. Lung carcinomas in both male and female mice were increased at exposures 40 times those in humans. Combined lung adenomas and carcinomas were increased in male mice at exposures 3 times and in female mice at exposures 40 times those in humans. Tumor development was preceded by pneumocyte proliferation in the lung, which was not observed in rats, dogs, or monkeys, administered entecavir, supporting the conclusion that lung tumors in mice may be a species-specific event. Hepatocellular carcinomas were increased in males and combined liver adenomas and carcinomas were also increased at exposures 42 times those in humans. Vascular tumors in female mice (hemangiomata of ovaries and uterus and hemangiosarcomas of spleen) were increased at exposures 40 times those in humans; hepatocellular adenomas and combined adenomas and carcinomas were increased in females at exposures 24 times those in humans. Brain gliomas were induced in both males and females at exposures 35 and 24 times those in humans. Skin fibromas were induced in females at exposures 4 times those in humans.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Entecavir was clastogenic to human lymphocyte cultures. Entecavir was not mutagenic in the Ames bacterial reverse mutation assay using S. typhimurium and E. Coli strains in the presence or absence of metabolic activation, a mammalian-cell gene mutation assay, and transformation assay with Syrian hamster embryo cells. Entecavir was also negative in an oral micronucleus study and an oral DNA repair study in rats. In reproductive toxicology studies, in which animals were administered entecavir at up to 30 mg/kg for up to four weeks, no evidence of impaired fertility was seen in male or female rats at systemic exposures > 90 times those achieved in humans. No testicular changes were evident in monkeys. In rodent and dog toxicology studies, seminiferous tubular degeneration was observed at exposures 35 times or greater than those achieved in humans. No testicular changes were evident in monkeys.

Entecavir is labeled Pregnancy Category C. Developmental toxicity studies were performed in rats and rabbits. There were no signs of embryofetal or maternal toxicity when pregnant animals received oral entecavir at approximately 28 (rat) and 212 (rabbit) times the human exposure achieved at the highest recommended human dose of 1mg/kg. In rats, maternal toxicity, embryo-fetal toxicity (resorptions), lower fetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternebrea, and phalanges), and extra lumbar vertebrae and ribs were observed at exposures 3100 times those in humans. In rabbits, embryo-fetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed at exposures 883 times those in humans. In a peri-post-natal study, no adverse effects on offspring were seen with entecavir administered orally to rats at exposures > 94 times those in humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, entecavir should be used during pregnancy only if clearly needed and after consideration of the risks and benefits.

(Last reviewed March 2016)

Etravirine (INTELENCE®, ETR)

INTELENCE® is a human immunodeficiency virus type 1 (HIV-1) non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated, in combination with other antiretroviral agents, for treatment of HIV-1 infection in antiretroviral treatment-experienced patients 6 years of age and older with viral strains resistant to an NNRTI and other antiretroviral agents.

The indication for adult use is based on Week 48 analyses from 2 randomized, double-blind, placebo-controlled trials of INTELENCE®. Both studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, N[t]RTI, PI) treatment-experienced adults. The indication for pediatric use is based on 24-week analyses of a single-arm, Phase 2 trial in antiretroviral treatment-experienced pediatric subjects 6 years to less than 18 years of age.

In treatment-experienced adult and pediatric patients, the following points should be considered when initiating therapy with INTELENCE®:

- Treatment history and resistance testing should guide the use of INTELENCE® due to concerns for potential cross-resistance.
- In patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE® in combination with only N[t]RTIs.
- The use of other active antiretroviral agents with INTELENCE® is associated with an increased likelihood of treatment response.
- The safety and efficacy of INTELENCE® have not been established in pediatric patients less than 6 years of age or in treatment-naïve adult or pediatric patients.

The safety and efficacy of INTELENCE® have not been established in treatment-naïve adult patients.

Pregnancy: Pregnancy Category B

No adequate and well-controlled studies of INTELENCE® use in pregnant women have been conducted. In addition, no pharmacokinetic studies have been conducted in pregnant patients. INTELENCE® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reproductive and developmental toxicity studies were performed in rabbits (at oral doses up to 375 mg per kg per day) and rats (at oral doses up to 1000 mg per kg per day). In both species, no treatment-related embryo-fetal effects including malformations were observed. In addition, no treatment-related effects were observed in a separate pre- and postnatal study performed in rats at oral doses up to 500 mg per kg per day. The systemic drug exposures achieved in these animal studies were equivalent to those at the recommended human dose (400 mg per day).

Nursing mothers: **The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.** It is not known whether etravirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving INTELENCE®.**

Pediatric Use: Treatment with INTELENCE® is not recommended in children less than 6 years of age. The pharmacokinetics, safety, tolerability, and efficacy of INTELENCE® in children less than 6 years age have not been established.

The safety, pharmacokinetic profile, and virologic and immunologic responses of INTELENCE® were evaluated in treatment-experienced HIV-1-infected pediatric subjects 6 years to less than 18 years of age and weighing at least 16 kg. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults, except for rash. Please see Dosage and Administration (2.2) for dosing recommendations for pediatric subjects 6 years to less than 18 years of age and weighing at least 16 kg.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis and Mutagenesis
Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to approximately 104 weeks. Daily doses of 50, 200 and 400 mg/kg were administered to mice and doses of 70, 200 and 600 mg/kg were administered to rats in the initial period of approximately 41-52 weeks. The high and middle doses were subsequently adjusted due to tolerability and reduced by 50% in mice and by 50-66% in rats to allow for completion of the studies. In the mouse study, statistically significant increases in the incidences of hepatocellular carcinoma and incidences of hepatocellular adenomas or carcinomas combined were observed in treated females. In the rat study, no statistically significant increases in tumor findings were observed in either sex. The relevance of these liver tumor findings in mice to humans is not known. Because of tolerability of the formulation in these rodent studies, maximum systemic drug exposures achieved at the doses tested were lower than those in humans at the clinical dose (400 mg/day), with animal vs. human AUC ratios being 0.6-fold (mice) and 0.2-0.7-fold (rats).

Etravirine tested negative in the *in vitro* Ames reverse mutation assay, *in vitro* chromosomal aberration assay in human lymphocyte, and *in vitro* clastogenicity mouse lymphoma assay, tested in the absence

and presence of a metabolic activation system. Etravirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

Impairment of Fertility
No effects on fertility and early embryonic development were observed when etravirine was tested in rats at maternal doses up to 500 mg/kg/day, resulting in systemic drug exposure up to the recommended human dose (400 mg/day).

(Last reviewed April 2015)

Fosamprenavir calcium (LEXIVA®, FOS)

LEXIVA® is the brand name for fosamprenavir calcium, a prodrug of amprenavir, an inhibitor of HIV protease.

Pregnancy: Fosamprenavir is assigned FDA Pregnancy Category C status. Embryo/fetal development studies were conducted in rats (dosed from day 6 to day 17 of gestation) and rabbits (dosed from day 7 to day 20 of gestation). Administration of fosamprenavir to pregnant rats and rabbits produced no major effects on embryo-fetal development; however, the incidence of abortion was increased in rabbits that were administered fosamprenavir. Systemic exposures ($AUC_{0\text{-}24\ hr}$) to amprenavir at these dosages were 0.8 (rabbits) to 2 (rats) times the exposures in humans following administration of the MRHD of fosamprenavir alone or 0.3 (rabbits) to 0.7 (rats) times the exposures in humans following administration of the MRHD of fosamprenavir in combination with ritonavir. In contrast, administration of amprenavir was associated with abortions and an increased incidence of minor skeletal variations resulting from deficient ossification of the femur, humerus, and trochlea, in pregnant rabbits at the tested dose; approximately one-twentieth the exposure seen at the recommended human dose.

There are no adequate and well-controlled studies in pregnant women. Fosamprenavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fertility: The mating and fertility of the F_1 generation born to female rats given fosamprenavir was no different from control animals; however, fosamprenavir did cause a reduction in both pup survival and body weights. Surviving F_1 female rats showed an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared with control animals. Systemic exposure ($AUC_{0\text{-}24\ hr}$) to amprenavir in the F_0 pregnant rats was approximately 2 times higher than exposures in humans following administration of the MRHD of fosamprenavir alone or approximately the same as those seen in humans following administration of the MRHD of fosamprenavir calcium in combination with ritonavir.

Carcinogenicity: In long-term carcinogenicity studies, fosamprenavir was administered orally for up to 104 weeks at doses of 250, 400, or 600 mg/kg/day in mice and at doses of 300, 825, or 2,250 mg/kg/day in rats. Exposures at these doses were 0.3- to 0.7-fold (mice) and 0.7- to 1.4-fold (rats) those in humans given 1,400 mg twice daily of fosamprenavir alone, and 0.2- to 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1,400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily. Exposures in the carcinogenicity studies were 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily. There was an increase in hepatocellular adenomas and hepatocellular carcinomas at all doses in male mice and at 600 mg/kg/day in female mice, and in hepatocellular adenomas and thyroid follicular cell adenomas at all doses in male rats, and at 835 mg/kg/day and 2,250 mg/kg/day in female rats. The relevance of the hepatocellular findings in the rodents for humans is uncertain. Repeat dose studies with fosamprenavir in rats produced effects consistent with

enzyme induction, which predisposes rats, but not humans, to thyroid neoplasms. In addition, in rats only there was an increase in interstitial cell hyperplasia at 825 mg/kg/day and 2,250 mg/kg/day, and an increase in uterine endometrial adenocarcinoma at 2,250 mg/kg/day. The incidence of endometrial findings was slightly increased over concurrent controls, but was within background range for female rats. The relevance of the uterine endometrial adenocarcinoma findings in rats for humans is uncertain.

Mutagenesis: Fosamprenavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays. These assays included bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus and chromosome aberrations in human lymphocytes. The effects of fosamprenavir on fertility and general reproductive performance were investigated in male (treated for 4 weeks before mating) and female rats (treated for 2 weeks before mating through postpartum day 6). Systemic exposures ($AUC_{0\text{-}24\ hr}$) to amprenavir in these studies were 3 (males) to 4 (females) times higher than exposures in humans following administration of the maximum recommended human dose (MRHD) of fosamprenavir alone or similar to those seen in humans following administration of fosamprenavir in combination with ritonavir. Fosamprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats.

(Last reviewed October 2014)

Indinavir (CRIXIVAN®, IDV)

Indinavir (CRIXIVAN®, IDV) is an inhibitor of the human immunodeficiency virus protease.

Indications and usage: CRIXIVAN in combination with antiretroviral agents is indicated for the treatment of HIV infection. This indication is based on two clinical trials of approximately 1 year duration that demonstrated: 1) a reduction in the risk of AIDS-defining illnesses or death; 2) a prolonged suppression.

Pregnancy: Pregnancy Category C: Developmental toxicity studies were performed in rabbits (at doses up to 240 mg/kg/day), dogs (at doses up to 80 mg/kg/day), and rats (at doses up to 640 mg/kg/day). The highest doses in these studies produced systemic exposures in these species comparable to or slightly greater than human exposure. No treatment-related external, visceral, or skeletal changes were observed in rabbits or dogs. No treatment-related external or visceral changes were observed in rats. Treatment-related increases over controls in the incidence of supernumerary ribs (at exposures at or below those in humans) and of cervical ribs (at exposures comparable to or slightly greater than those in humans) were seen in rats. In all three species, no treatment-related effects on embryonic/fetal survival or fetal weights were observed.

In rabbits, at a maternal dose of 240 mg/kg/day, no drug was detected in fetal plasma 1 hour after dosing. Fetal plasma drug levels 2 hours after dosing were approximately 3% of maternal plasma drug levels. In dogs, at a maternal dose of 80 mg/kg/day, fetal plasma drug levels were approximately 50% of maternal plasma drug levels both 1 and 2 hours after dosing. In rats, at maternal doses of 40 and 640 mg/kg/day, fetal plasma drug levels were approximately 10 to 15% and 10 to 20% of maternal plasma drug levels 1 and 2 hours after dosing, respectively.

Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately fourfold above controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after in utero

exposure to indinavir during the third trimester of pregnancy. In Rhesus monkeys, fetal plasma drug evels were approximately 1 to 2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

Hyperbilirubinemia has occurred during treatment with CRIXIVAN (see PRECAUTIONS and ADVERSE REACTIONS). It is unknown whether CRIXIVAN administered to the mother in the perinatal period will exacerbate physiologic hyperbilirubinemia in neonates.

There are no adequate and well-controlled studies in pregnant patients. CRIXIVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

A CRIXIVAN dose of 800 mg every 8 hours (with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day) has been studied in 16 HIV-infected pregnant patients at 14 to 28 weeks of gestation at enrollment (study PACTG 358). Given the substantially lower antepartum exposures observed and the limited data in this patient population, indinavir use is not recommended in HIV-infected pregnant patients (see CLINICAL PHARMACOLOGY, Pregnant Patients).

Nursing Mothers: Studies in lactating rats have demonstrated that indinavir is excreted in milk. Although it is not known whether CRIXIVAN is excreted in human milk, there exists the potential for adverse effects from indinavir in nursing infants. Mothers should be instructed to discontinue nursing if they are receiving CRIXIVAN. This is consistent with the recommendation by the U.S. Public Health Service Centers for Disease Control and Prevention that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

Pediatric use: The optimal dosing regimen for use of indinavir in pediatric patients has not been established. A dose of 500 mg/m2 every eight hours has been studied in uncontrolled studies of 70 children, 3 to 18 years of age. The pharmacokinetic profiles of indinavir at this dose were not comparable to profiles previously observed in adults receiving the recommended dose (see CLINICAL PHARMACOLOGY, Pediatric). Although viral suppression was observed in some of the 32 children who were followed on this regimen through 24 weeks, a substantially higher rate of nephrolithiasis was reported when compared to adult historical data (see WARNINGS, Nephrolithiasis/Urolithiasis). Physicians considering the use of indinavir in pediatric patients without other protease inhibitor options should be aware of the limited data available in this population and the increased risk of nephrolithiasis.

Carcinogenesis, mutagenesis, impairment of fertility: Carcinogenicity studies were conducted in mice and rats. In mice, no increased incidence of any tumor type was observed. The highest dose tested in rats was 640 mg/kg/day; at this dose a statistically significant increased incidence of thyroid adenomas was seen only in male rats. At that dose, daily systemic exposure in rats was approximately 1.3 times higher than daily systemic exposure in humans. No evidence of mutagenicity or genotoxicity was observed in in vitro microbial mutagenesis (Ames) tests, in vitro alkaline elution assays for DNA breakage, in vitro and in vivo chromosomal aberration studies, and in vitro mammalian cell mutagenesis assays. No treatment-related effects on mating, fertility, or embryo survival were seen in female rats and no treatment-related effects on mating performance were seen in male rats at doses providing systemic exposure comparable to or slightly higher than that with the clinical dose. In addition, no treatment-related effects were observed in fecundity or fertility of untreated females mated to treated males.

(Last reviewed April 2017)

Lamivudine (EPIVIR®, 3TC)

EPIVIR® (formerly known as 3TC) is the brand name for lamivudine, a synthetic nucleoside analogue with activity against HIV-1 and HBV.

Pregnancy: Lamivudine is assigned FDA Pregnancy Category C status. Reproduction studies have been performed in rats and rabbits at orally administered doses up to approximately 130 and 60 times, respectively, the usual adult dose and have revealed no evidence of teratogenicity due to lamivudine. Reproduction studies have also been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans. Some evidence of early embryolethality was seen in the rabbit at doses similar to those produced by the usual adult dose and higher, but there was no indication of this effect in the rat at orally administered doses up to 35 times the usual adult dose. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. However, there are no adequate and well-controlled studies in pregnant women.
Animal reproduction studies in rats and rabbits revealed no evidence of teratogenicity. Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans. Lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

Pharmacokinetics and Transmission: Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies conducted in South Africa. The study assessed pharmacokinetics in: 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, lamivudine amniotic fluid specimens were collected following natural rupture of membranes. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily). It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients.

Carcinogenicity: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection. In a study of reproductive performance, lamivudine, administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Mutagenesis: Limited short-term safety information is available from two small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at Week 38 or 36 of gestation. Selected adverse reactions reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances,

hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, and sepsis; three neonates died (one from gastroenteritis with acidosis and convulsions, one from traumatic injury, and one from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including one with convulsions; one infant had transient renal insufficiency associated with dehydration. The absence of control groups limits assessments of causality, but it should be assumed that perinatally exposed infants may be at risk for adverse reactions comparable to those reported in pediatric and adult HIV-1-infected patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

(Last reviewed October 2014)

Lopinavir/ritonavir (KALETRA®, ALUVIA®, LPV/r)

Lopinavir/ritonavir (KALETRA®, ALUVIA®, LPV/r) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in KALETRA®, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir. Lopinavir/ritonavir has been tested extensively for its ability to inhibit the HIV-1 protease enzyme and HIV viral replication in cell culture. HIV-1 protease is the virus-encoded enzyme necessary for the processing of the viral Gag-Pol polyprotein. Inhibition of this enzyme yields noninfectious, immature virions.

Lopinavir/ritonavir, as a co-formulation, has a broad spectrum of activity against HIV type 1, including resistant strains of HIV, in a variety of transformed and primary human cell lines. Clinical trials with lopinavir/ritonavir at 400/100 mg twice daily, alone or in combination with reverse transcriptase inhibitors demonstrated profound reductions in viral RNA levels and substantial increases in CD4 cell counts among patients across a wide spectrum of HIV disease. Lopinavir/ritonavir is labeled for use in combination with other antiretroviral agents for the treatment of HIV infection in the adult and pediatric (>14 days and older) populations.

Lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6-2.2 times (mice) and 0.5 times (rats) the human exposure (based on AUC0-24hr measurement) at the recommended dose of 400/100 mg LPV/r twice daily. Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg LPV/r twice daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. There were no carcinogenic effects in rats. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg LPV/r twice daily regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known.

Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of in vitro or in vivo assays including the Ames bacterial reverse mutation assay using S. typhimurium and E. coli, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg twice daily).

Pregnancy

Risk Summary

Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits; however embryonic and fetal developmental toxicities occurred in rats administered maternally toxic doses.

Clinical Considerations

Dose Adjustments During Pregnancy and the Postpartum Period

Administer 400/100 mg of LPV/r twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions. There are insufficient data to recommend LPV/r dosing for pregnant patients with any documented lopinavir-associated resistance substitutions. No dose adjustment of LPV/r is required for patients during the postpartum period. Once daily LPV/r dosing is not recommended in pregnancy. Avoid use of KALETRA oral solution during pregnancy due to the alcohol content. KALETRA oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v).

Human Data: LPV/r was evaluated in 12 HIV-infected pregnant women in an open-label pharmacokinetic trial. No new trends in the safety profile were identified in pregnant women dosed with LPV/r compared to the safety described in non-pregnant adults, based on the review of these limited data.

Antiretroviral Pregnancy Registry Data: Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of over 3,000 exposures to lopinavir containing regimens (including over 1,000 exposed in the first trimester), there was no difference between lopinavir and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program. Based on prospective reports from the APR of over 5,000 exposures to ritonavir containing regimens (including over 2,000 exposures in the first trimester) there was no difference between ritonavir and overall birth defects compared with the U.S. background rate (MACDP). For both lopinavir and ritonavir, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5 fold increase in risk of overall birth defects and a 2 fold increase in risk of birth defects in the cardiovascular and genitourinary systems.

Animal Data: Embryonic developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations or skeletal ossification delays) occurred in rats receiving a maternally toxic dosage that produced drug exposures (AUCs) that are approximately 0.7 times the lopinavir and 1.8 times the ritonavir exposures in humans at the recommended therapeutic dose of 400/100 mg BID. No embryonic or fetal developmental toxicities were observed in rabbits at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at this maternally toxic dosage were approximately 0.6 times the lopinavir and 1.0-fold for ritonavir exposures in humans at the recommended therapeutic dose of 400/100 mg BID. Lopinavir in combination with ritonavir produced no effects on fertility in female or male rats at the dosage tested. There are no adequate and well-controlled studies in pregnant women. Since animal studies are not always predictive of human response, lopinavir/ritonavir should be used during pregnancy only when benefits outweigh the risks.

(Last reviewed April 2015)

Maraviroc (CELSENTRI®, SELZENTRY®, MVC)

Maraviroc (SELZENTRY) is a CCR5 co-receptor antagonist indicated for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1.

In vitro pharmacology studies have shown that maraviroc is a slowly reversible and selective antagonist of the human chemokines receptor CCR5 and inhibits its binding to endogenous chemokine ligands. Antiviral activity occurs against a range of CCR5-tropic isolates from various sub-types or clades and against virus derived from antiretroviral-naïve or -experienced isolates, and inhibition of viral replication is CCR5-dependent and occurs in the absence of effects on cell growth.

Pregnancy: Maraviroc is assigned FDA Pregnancy Category B status. Embryofetal development studies were conducted in rats and rabbits at doses up to 39 and 34-fold the estimated free clinical AUC for a 300 mg twice daily dose. In an oral embryo-fetal development study in rats at daily doses of 100, 300, and 1000 mg/kg, the high dose was slightly toxic to the pregnant females (decreased body weight and food consumption). There was no effect on reproductive parameters and on embryo or fetal development and growth at any dose tested. The incidences of fetal variations and malformations in rats were not increased in embryofetal toxicity studies performed with maraviroc at exposures (AUC) approximately 20-fold higher than humans (up to 1000 mg/kg/day). In rats, the NOAEL was 300 mg/kg for pregnant females and 1000mg/kg for the fetuses. In an oral embryo-fetal development study in rabbits at daily doses of 30, 75, and 200 mg/kg, death was observed at the high dose. The incidences of fetal variations and malformations in rabbits were not increased in embryofetal toxicity studies performed with maraviroc at exposures (AUC) approximately 5-fold higher than humans (up to 75 mg/kg/day). There were no associated clinical signs or macroscopic findings. Treatment with maraviroc had no effect on reproductive parameters. An increased incidence of external anomalies was observed at the high dose. Thus, the NOAEL was 75 mg/kg (approximately 7-fold higher than seen at the therapeutic dose) for the pregnant females and fetuses. Pre- and post-natal developmental studies were performed in rats at doses up to 27-fold the estimated free clinical AUC for a 300 mg twice daily dose. The only effect in the offspring was a slight increase in motor activity in male offspring rats at both weaning and as adults at the high dose, while no effects were seen in female offspring. The subsequent development of these offspring, including fertility and reproductive performance, was not affected by the maternal administration of maraviroc.

However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SELZENTRY should be used during pregnancy only if clearly needed.

Fertility: A fertility study was conducted to evaluate the effects of maraviroc on mating performance, the fertility of adult male and female rats and the development of the embryos during the pre- and post-implantation stages. Maraviroc did not impair mating or fertility of male or female rats and did not affect sperm of treated male rats at approximately 20-fold higher exposures (AUC) than in humans given the recommended 300 mg twice daily dose. The NOAEL for adult male and female rats was 300 mg/kg. There were no effects on fertility up to 1000 mg/kg in rats of either sex.

Carcinogenicity: Carcinogenic potential was assessed in a 6-month study with Tg (rasH2) hemizygous mice and in a 24-month study using Sprague-Dawley rats. In Tg(rasH2) mice, daily doses of 200, 800 and 1500 mg/kg did not produce hyperplastic, neoplastic inflammatory or degenerative changes. The free plasma AUC exposure in Tg mice at 1500 mg/kg was 54-times higher than that found at the human therapeutic dose. In rats, daily doses of 50, 100, 500 and 900 mg/kg were administered to males for 104 weeks and to females for 96 weeks (due to high mortality in female control rats). There was no adverse

treatment effect on survival. Maraviroc produced a toxicologically significant decrease in mean body weight in the males at 500 and 900 mg/kg and in females at 900 mg/kg. In mice, maraviroc did not cause a statistically significant increase in the incidence of any tumor type at systemic exposures in the range 7- to 39-times the human exposure (based on unbound area under the plasma concentration-time curve from 0 to 24 hours (AUC (0-24) hr measurement) at the maximum recommended dose of 300 mg twice daily. In rats an increased incidence of follicular cell adenoma of the thyroid associated with adaptive liver changes was observed in both males and females of the high dose group (900 mg/kg); 21 times higher than that found at the human therapeutic dose of 300 mg bid). A rare tumor, cholangiocarcinoma, was observed in the liver of 2 male rats at 900 mg/kg. The incidence was slightly higher than that observed in a large database of control animals (3/1850) and in the control group of a concurrent study (1/65).

Mutagenesis: Maraviroc is not considered to be genotoxic based on *In Vitro* (bacterial mutation, chromosome aberration in human lymphocytes) and *In Vivo* (mouse bone marrow micronucleus) tests.

(Last reviewed October 2014)

Nelfinavir (VIRACEPT®, NFV)

Nelfinavir mesylate is an inhibitor of the human immunodeficiency virus (HIV) protease. Inhibition of the viral protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, non-infectious virus.

Nelfinavir was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* tests including microbial mutagenesis (Ames), mouse lymphoma, chromosome aberrations in human lymphocytes, and an *in vivo* mouse micronucleus assay. Carcinogenicity studies in animals have not yet been completed. Nelfinavir is assigned FDA Pregnancy Category B status. Nelfinavir produced no effects on either male or female mating and fertility or embryo survival in rat studies at exposures (based on the steady-state area under the plasma concentration time curve) comparable to human therapeutic exposure. There were also no effects on fetal development or maternal toxicity when nelfinavir was administered to pregnant rats at systemic exposures comparable to human exposure. Administration of nelfinavir to pregnant rabbits resulted in no fetal development effects up to a dose at which a slight decrease in maternal body weight was observed; however, even at the highest dose evaluated, systemic exposure in rabbits was significantly lower than human exposure. Additional studies in rats indicated that exposure to nelfinavir in females from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Subsequent reproductive performance of these offspring was also not affected by maternal exposure to nelfinavir. However, there are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response; nelfinavir should be used during pregnancy with caution.

(References: VIRACEPT International Standard Prescribing Information version 5.0 19-Nov-2008; VIRACEPT (nelfinavir) USPI Revised 05/2009)

(Last reviewed September 2015)

Nevirapine (VIRAMUNE®, VIRAMUNE XR®, NVP)

Pregnancy: Nevirapine is assigned to the FDA Pregnancy Category B. No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. The maternal and developmental no-observable-effect level dosages produced systemic exposures approximately

equivalent to or approximately 50% higher in rats and rabbits, respectively, than those seen at the recommended daily human dose (based on AUC). In rats, decreased fetal body weights were observed due to administration of a maternally toxic dose (exposures approximately 50% higher than that seen at the recommended human clinical dose).

There are no adequate and well-controlled studies of VIRAMUNE® in pregnant women. The Antiretroviral Pregnancy Registry, which has been surveying pregnancy outcomes since January 1989, has not found an increased risk of birth defects following first trimester exposures to nevirapine. The prevalence of birth defects after any trimester exposure to nevirapine is comparable to the prevalence observed in the general population.

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with CD4+ cell counts greater than 250 cells/mm^3 should not initiate nevirapine unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women.

VIRAMUNE XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Nevirapine is excreted in breast milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving VIRAMUNE.

VIRAMUNE® (nevirapine) is marketed in the United States with a black box warning. The specific warning reads:

HEPATOTOXICITY:

Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with VIRAMUNE. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher $CD4^+$ cell counts at initiation of therapy place patients at increased risk; women with $CD4^+$ cell counts greater than 250 cells/mm^3, including pregnant women receiving VIRAMUNE in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk. However, hepatotoxicity associated with VIRAMUNE use can occur in both genders, all $CD4^+$ cell counts and at any time during treatment. Hepatic failure has also been reported in patients without HIV taking VIRAMUNE for post-exposure prophylaxis (PEP). Use of VIRAMUNE for occupational and non-occupational PEP is contraindicated. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue VIRAMUNE and seek medical evaluation immediately.

SKIN REACTIONS:

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue VIRAMUNE and seek medical evaluation immediately. Transaminase levels should be checked immediately for all patients who develop a rash in the

first 18 weeks of treatment. The 14-day lead-in period with VIRAMUNE 200 mg daily dosing has been observed to decrease the incidence of rash and must be followed.

MONITORING:

Patients must be monitored intensively during the first 18 weeks of therapy with VIRAMUNE to detect potentially life-threatening hepatotoxicity or skin reactions. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart VIRAMUNE following severe hepatic, skin or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment.

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases α, ß, γ, or δ) are not inhibited by nevirapine**.**

Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (Vdss) of nevirapine was 1.21 +/- 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 µg/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% (±5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein. In the multinational 2NN study, a population pharmacokinetic substudy of 1077 patients was performed that included 391 females. Female patients showed a 13.8% lower clearance of nevirapine than did men. Since neither body weight nor Body Mass Index (BMI) had an influence on the clearance of nevirapine, the effect of gender cannot solely be explained by body size.

Long**-**term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, 375 or 750 mg/kg/day for two years. Hepatocellular adenomas and carcinomas were increased at all doses in males and at the two high doses in females. In studies in which rats were administered nevirapine at doses of 0, 3.5, 17.5 or 35 mg/kg/day for two years, an increase in hepatocellular adenomas was seen in males at all doses and in females at the high dose. The systemic exposure (based on AUCs) at all doses in the two animal studies was lower than that measured in humans at the 200 mg BID dose. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included microbial assays for gene mutation (Ames: Salmonella strains and *E. coli*), mammalian cell gene mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is not known. In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of VIRAMUNE.

(Last reviewed April 2016)

Raltegravir (ISENTRESS®, RAL)

Raltegravir (ISENTRESS®, RAL) is a human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI).

Indications and usage: ISENTRESS® is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in patients 4 weeks of age and older.

Pregnancy: Pregnancy Category C: ISENTRESS® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. In addition, there have been no pharmacokinetic studies conducted in pregnant patients.

Developmental toxicity studies were performed in rabbits (at oral doses up to 1000 mg/kg/day) and rats (at oral doses up to 600 mg/kg/day). The reproductive toxicity study in rats was performed with pre-, peri, and postnatal evaluation. The highest doses in these studies produced systemic exposures in these species approximately 3- to 4-fold the exposure at the recommended human dose. In both rabbits and rats, no treatment-related effects on embryonic/fetal survival or fetal weights were observed. In addition, no treatment-related external, visceral, or skeletal changes were observed in rabbits. However, treatment-related increases over controls in the incidence of supernumerary ribs were seen in rats at 600 mg/kg/day (exposures 3-fold the exposure at the recommended human dose).

Placenta transfer of drug was demonstrated in both rats and rabbits. At a maternal dose of 600 mg/kg/day in rats, mean drug concentrations in fetal plasma were approximately 1.5- to 2.5-fold greater than in maternal plasma at 1 hour and 24 hours postdose, respectively. Mean drug concentrations in fetal plasma were approximately 2% of the mean maternal concentration at both 1 and 24 hours postdose at a maternal dose of 1000 mg/kg/day in rabbits.

Nursing Mothers: Breastfeeding is not recommended while taking ISENTRESS. In addition, it is recommended that HIV- 1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1.

It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. Mean drug concentrations in milk were approximately 3-fold greater than those in maternal plasma at a maternal dose of 600 mg/kg/day in rats. There were no effects in rat offspring attributable to exposure of ISENTRESS through the milk.

Pediatric use: The safety, tolerability, pharmacokinetic profile, and efficacy of ISENTRESS were evaluated in HIV-1 infected infants, children and adolescents 4 weeks to 18 years of age in an open-label, multicenter clinical trial, IMPAACT P1066 *[see Clinical Pharmacology (12.3)* and *Clinical Studies (14.3)]*. The safety profile was comparable to that observed in adults *[see Adverse Reactions (6.1)]*. See Dosage and Administration (2.3) for dosing recommendations for children 4 weeks of age and older. The safety and dosing information for ISENTRESS have not been established in infants less than 4 weeks of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies of raltegravir in mice did not show any carcinogenic potential. At the highest dose levels, 400 mg/kg/day in females and 250 mg/kg/day in males, systemic exposure was 1.8-fold (females) or 1.2-fold (males) greater than the AUC (54 μM●hr) at the 400-mg twice daily human dose. Treatment-related squamous cell carcinoma of nose/nasopharynx was observed in female rats dosed with 600 mg/kg/day raltegravir for 104 weeks. These tumors were possibly the result of local irritation and inflammation due to local deposition and/or aspiration of drug in the mucosa of the nose/nasopharynx during dosing. No tumors of the nose/nasopharynx were observed in rats dosed with 150 mg/kg/day (males) and 50 mg/kg/day (females) and the systemic exposure in rats was 1.7-fold (males) to 1.4-fold (females) greater than the AUC (54 μM●hr) at the 400-mg twice daily human dose.

No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage and *in vitro* and *in vivo* chromosomal aberration studies.

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in a 3-fold exposure above the exposure at the recommended human dose.

(Last reviewed April 2017)

Rilpivirine (EDURANT®, RPV)

EDURANT® (rilpivirine), in combination with other antiretroviral agents, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

The following points should be considered when initiating therapy with EDURANT®:

- More EDURANT®-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥50 copies/mL) compared to EDURANT®-treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL
- Regardless of HIV-1 RNA at the start of therapy, more EDURANT®-treated subjects with CD4+ cell count less than 200 cells/mm3 experienced virologic failure compared to EDURANT®-treated subjects with CD4+ cell count greater than or equal to 200 cells/mm3
- The observed virologic failure rate in EDURANT®-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz
- More subjects treated with EDURANT® developed tenofovir disoproxil fumarate and lamivudine/emtricitabine-associated resistance compared to efavirenz. EDURANT® is not recommended for patients less than 12 years of age.
- The observed virologic failure rate in EDURANT®-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz

Pregnancy: Pregnancy Category B

No adequate and well-controlled or pharmacokinetic studies of EDURANT® use in pregnant women have been conducted. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. In offspring from rats and rabbits treated with rilpivirine during pregnancy and lactation, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily. EDURANT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats and their offspring indicate that rilpivirine was present in rat milk. It is not known whether rilpivirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving EDURANT®.

Pediatric Use: The safety, efficacy and pharmacokinetics of EDURANT were evaluated in a single arm, open-label, Phase 2 trial that enrolled 36 antiretroviral treatmentnaïve, HIV-1 infected pediatric subjects 12 to less than 18 years of age and weighing at least 32 kg.

Safety and effectiveness in pediatric patients less than 12 years of age have not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis and Mutagenesis

Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1500 mg/kg/day were administered to rats. In rats, there were no drug related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg q.d.).

Rilpivirine has tested negative in the absence and presence of a metabolic activation system in the in vitro Ames reverse mutation assay and the in vitro clastogenicity mouse lymphoma assay. Rilpivirine did not induce chromosomal damage in the in vivo micronucleus test in mice.

Impairment of Fertility

No human data on the effect of rilpivirine on fertility are available. In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg/kg/day, a dose of rilpivirine that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily.

Patient Counseling Information

Before taking EDURANT®, tell your doctor if you are:

- Pregnant or planning to become pregnant. It is not known if EDURANT® will harm your unborn baby. Pregnancy Registry: There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.
- Breastfeeding or plan to breastfeed. You should not breastfeed if you have HIV because of the risk of passing HIV to your baby. Do not breastfeed if you take EDURANT®. We do not know if EDURANT® can be passed to your baby in your breast milk and whether it could harm your baby. Talk with your doctor about the best way to feed your baby

(Last reviewed May 2017)

Ritonavir (NORVIR®, RTV)

Ritonavir (NORVIR®) is an HIV protease inhibitor that has been tested extensively for its ability to inhibit the HIV-1 protease enzyme and HIV viral replication in cell culture. HIV-1 protease is the virus-encoded enzyme necessary for the processing of the viral gagpol polyprotein. Inhibition of this enzyme yields noninfectious immature virions.

The activity of ritonavir was assessed in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. The concentration of drug that inhibits 50% (EC50) value of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC50 value for low passage clinical isolates was 22 nM (n = 13). In MT4 cells, ritonavir demonstrated additive effects against HIV-1 in combination with either didanosine (ddI) or zidovudine (ZDV). Studies which measured cytotoxicity of ritonavir on several cell lines showed that greater than 20 µM was required to inhibit cellular growth by 50% resulting in a cell culture therapeutic index of at least 1000.

Ritonavir is labeled for use in combination with other antiretroviral agents for the treatment of HIV-infection.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg per kg per day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 0.3-fold for males that of the exposure in humans with the recommended therapeutic dose (600 mg twice-daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 0.6-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg per kg per day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 6% that of the exposure in humans with the recommended therapeutic dose. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known.

Ritonavir was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames) using S. Typhimurium and E. coli, mouse lymphoma, mouse micronucleus, and chromosome aberrations in human lymphocytes.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 40% (male) and 60% (female) of that achieved with the proposed therapeutic dose. Higher dosages were not feasible due to hepatic toxicity.

Pregnancy
Ritonavir is labeled Pregnancy Category B.

Human Data
There are no adequate and well-controlled studies in pregnant women. NORVIR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: As of January 2012, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 3860 exposures to ritonavir containing regimens (1567 exposed in the first trimester and 2293 exposed in the second and third trimester). Birth defects occurred in 35 of the 1567 (2.2%) live births (first trimester exposure) and 59 of the 2293 (2.6%) live births (second/third trimester exposure).

Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between ritonavir and overall birth defects observed in the APR.

Animal Data
No treatment related malformations were observed when ritonavir was administered to pregnant rats or rabbits. Developmental toxicity observed in rats (early resorptions, decreased fetal body weight and ossification delays and developmental variations) occurred at a maternally toxic dosage at an exposure equivalent to approximately 30% of that achieved with the proposed therapeutic dose. A slight increase in the incidence of cryptorchidism was also noted in rats at an exposure approximately 22% of that achieved with the proposed therapeutic dose. Developmental toxicity observed in rabbits (resorptions, decreased litter size and decreased fetal weights) also occurred at a maternally toxic dosage equivalent to 1.8 times the proposed therapeutic dose based on a body surface area conversion factor.

(Last reviewed April 2015)

Saquinavir mesylate (INVIRASE®, SQV-HGC), saquinavir (FORTOVASE®, SQV-SGC)

(FORTOVASE® no longer manufactured as of 6 July 2006)

Saquinavir is an inhibitor of HIV protease. HIV protease is an enzyme required for the proteolytic cleavage of viral polyprotein precursors into individual functional proteins found in HIV-1 particles. Saquinavir is a peptide-like substrate analogue that binds to the protease active site and inhibits the activity of the enzyme. Saquinavir inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature noninfectious viral particles.

In cell culture, saquinavir demonstrated additive to synergistic effects against HIV-1 in combination with reverse transcriptase inhibitors (didanosine, lamivudine, nevirapine, stavudine, zalcitabine and zidovudine) without enhanced cytotoxicity. Saquinavir in combination with the protease inhibitors amprenavir, atazanavir, or lopinavir resulted in synergistic antiviral activity.

Carcinogenicity studies found no carcinogenic activity in rats and mice administered saquinavir for approximately 2 years. Because of limited bioavailability of saquinavir in animals, the plasma exposures (AUC values) in the respective species were approximately 29% (using rat) and 65% (using mouse) of those obtained in humans at the recommended clinical dose boosted with ritonavir.

Mutagenicity and genotoxicity studies, with and without metabolic activation where appropriate, have shown that saquinavir has no mutagenic activity in vitro in either bacterial (Ames test) or mammalian cells (Chinese hamster lung V79/HPRT test). Saquinavir does not induce chromosomal damage in vivo in the mouse micronucleus assay or in vitro in human peripheral blood lymphocytes, and does not induce primary DNA damage in vitro in the unscheduled DNA synthesis test.

No adverse effects were reported in fertility and reproductive performance study conducted in rats. Because of limited bioavailability of saquinavir in animals, the maximal plasma exposures achieved in rats were approximately 26% of those obtained in humans at the recommended clinical dose boosted with ritonavir.
Saquinavir is assigned FDA Pregnancy Category B status. Reproduction studies conducted with saquinavir have shown no embryotoxicity or teratogenicity in both rats and rabbits. Because of limited bioavailability of saquinavir in animals and/or dosing limitations, the plasma exposures (AUC values) in the respective species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir. Clinical experience in pregnant women is limited. Saquinavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

(References: INVIRASE Core Data Sheet Version 11.0 Approved 16-Nov-2009; INVIRASE USPI Revised: March 2010)

(Last reviewed October 2014)

Stavudine (ZERIT®, d4T)

Stavudine, a nucleoside analogue of thymidine is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate thymidine triphosphate (K - 0.0083 to 0.032

μM); and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases β and γ and markedly reduces the synthesis of mitochondrial DNA.

In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses, which produced exposures (AUC) 39 and 168 times, respectively, human exposure at the recommended clinical dose. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred at levels of exposure, 250 (mice) and 732 (rats) time human exposure at the recommended clinical dose.

Stavudine was not mutagenic in the Ames *E. coli* reverse mutation or the CHO/HGPRT mammalian cell forward gene mutation assays with and without metabolic activation. Stavudine produced positive results in the *in vitro* human lymphocyte clastogenesis and mouse fibroblast assays and in the *in vivo* mouse micronucleus test. In the *in vitro* assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25 to 250 μg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 μg/mL, with and without metabolic activation). In the *in vivo* micronucleus assay, stavudine was clastogenic in bone marrow cells following oral stavudine administration to mice at dosages of 600 to 2000 mg/kg/day for three days.
No evidence of impaired fertility was seen in rats with exposures based on C_{max} up to 216 times that observed following a clinical dosage of 1 mg/kg/day.

Stavudine is assigned FDA Pregnancy Category C status. Reproduction studies have been performed in rats and rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence of fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, while no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to four days of age) occurred at 399 times the human exposure, while survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies in pregnant women. Stavudine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is not known if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues. **The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Health care providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

(Last reviewed March 2016)

Telbivudine (SEBIVO®, TYZEKA®, LdT)

TYZEKA® is indicated for the treatment of chronic hepatitis B (CHB) in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

This indication is based on virologic, serologic, biochemical and histologic responses after one year of treatment in nucleoside treatment-naïve adult patients with HbeAg-positive and HbeAg-negative CHB with compensated liver disease.

Telbivudine has shown no carcinogenic potential. Long term oral carcinogenicity studies with telbivudine were negative in mice and rats at exposures up to 14 times those observed in humans at the therapeutic dose of 600 mg/day.

There was no evidence of genotoxicity based on *in vitro* or *in vivo* tests. Telbivudine was not mutagenic in the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli* strains with or without metabolic activation. Telbivudine was not clastogenic in mammalian-cell gene mutation assays, including human lymphocyte cultures and an assay with Chinese hamster ovary cells with or without metabolic activation. Furthermore, telbivudine showed no effect in an *in vivo* micronucleus study in mice.
In reproductive toxicology studies, no evidence of impaired fertility was seen in male or female rats at systemic exposures approximately 14 times that achieved in humans at the therapeutic dose.

Telbivudine is assigned FDA Pregnancy Category B status. Telbivudine is not teratogenic and has shown no adverse effects in developing embryos and fetuses in preclinical studies. Studies in pregnant rats and rabbits showed that telbivudine crosses the placenta. Developmental toxicity studies revealed no evidence of harm to the fetus in rats and rabbits at doses up to 1000 mg/kg/day, providing exposure levels 6- and 37-times higher, respectively, than those observed with the 600 mg/day dose in humans.

There are no adequate and well-controlled studies of telbivudine in pregnant women. Because animal reproductive toxicity studies are not always predictive of human response, telbivudine should be used during pregnancy only if potential benefits outweigh the risks.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals.

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including TYZEKA®. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

(Last reviewed February 2014)

Tenofovir alafenamide (VEMLIDY®, TAF)

VEMLIDY® is the brand name of tenofovir alafenamide. Tenofovir alafenamide, a hepatitis B virus (HBV) and HIV-1 nucleoside analog reverse transcriptase inhibitor, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. VEMLIDY is indicated for the treatment of chronic HBV infection in adults with compensated liver disease.

There are no human data on the use of VEMLIDY in pregnant women to inform drug-associated risks of adverse fetal developmental outcomes. Embryonic fetal development studies performed in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. The embryo-fetal NOAELs (no observed adverse effect level) in rats and rabbits occurred at tenofovir alafenamide exposures similar to and 51 times higher than, respectively, the exposure in humans at the recommended daily dose. Tenofovir alafenamide is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 54 (rats) and 85 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Tenofovir alafenamide was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed when tenofovir alafenamide was administered during the period of organogenesis at exposures equal to or 51 times (rats and rabbits, respectively) the tenofovir alafenamide exposure at the recommended daily dose of VEMLIDY in humans.

It is not known whether VEMLIDY and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. It is not known if tenofovir alafenamide can be present in animal milk. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF (tenofovir disoproxil fumarate), another prodrug for tenofovir administration. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 12 times the exposure at the recommended daily dosage of VEMLIDY. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VEMLIDY and any potential adverse effects on the breastfed infant from VEMLIDY or from the underlying maternal condition.

Safety and effectiveness of VEMLIDY in HBV-infected pediatric patients less than 18 years of age have not been established.

Since tenofovir alafenamide is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after tenofovir alafenamide administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of TDF for chronic hepatitis B. The tenofovir exposure in these studies was approximately 151 times (mice) and 50 times (rat) those observed in humans after administration of VEMLIDY treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times those observed after VEMLIDY administration in humans. In rats, the study was negative for carcinogenic findings.

Tenofovir alafenamide was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

(Last reviewed April 2017)

Tenofovir disoproxil fumarate (VIREAD®, TDF)

VIREAD® is the brand name for tenofovir disoproxil fumarate, an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV polymerase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination.

VIREAD® is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and in pediatric patients ≥ 2 years of age. It is also indicated for the treatment of chronic hepatitis B in adults and in pediatric patients ≥12 years of age.

Reproductive studies were conducted in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil fumarate with respect to pregnancy, fetal development, parturition or postnatal development. There were no effects on mating or fertility parameters. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk. The impact of this exposure in breastfed infants is unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving VIREAD.

The safety of VIREAD in pediatric patients aged 2 to less than 18 years is supported by data from two randomized trials in which VIREAD was administered to HIV-1 infected treatment-experienced subjects. In addition, the pharmacokinetic profile of tenofovir in patients aged 2 to less than 18 years of age at the recommended doses was similar to that found to be safe and effective in adult clinical trials. The safety of VIREAD in pediatric patients younger than 2 years of age with HIV-1 infection, nor in those 12 years of age or less than 35 kg with chronic hepatitis B, has not been established.

Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times of that in humans. In rats, tenofovir disoproxil fumarate did not show any carcinogenic potential at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative at doses up to 2000 mg/kg when administered to male mice.

(Last reviewed April 2017)

Tipranavir (APTIVUS®, TPV)

Pregnancy: Tipranavir is assigned to the FDA Pregnancy Category C: No teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits up to dose levels of 1000 mg/kg/day and 150

mg/kg/day tipranavir, respectively, at exposure levels approximately 1.1-fold and 0.1-fold human exposure. At 400 mg/kg/day and above in rats, fetal toxicity (decreased sternebrae ossification and body weights) was observed, corresponding to an AUC of 1310 µM·h or approximately 0.8-fold human exposure at the recommended dose. In rats and rabbits, fetal toxicity was not noted at 40 mg/kg/day and 150 mg/kg/day, respectively, corresponding accordingly to Cmax/AUC0-24h levels of 30.4 µM/340 µM·h and 8.4 µM/120 µM·h. These exposure levels (AUC) are approximately 0.2-fold and 0.1-fold the exposure in humans at the recommended dose. In pre- and post-development studies in rats, tipranavir showed no adverse effects at 40 mg/kg/day (~0.2-fold human exposure), but caused growth inhibition in pups and maternal toxicity at dose levels of 400 mg/kg/day (~0.8-fold human exposure). No post-weaning functions were affected at any dose level. There are no adequate and well-controlled studies in pregnant women for the treatment of HIV-1infection. APTIVUS® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. With respect to the potential for HIV transmission and any possible adverse effects of tipranavir, mothers should be instructed not to breastfeed if they are receiving APTIVUS®.

APTIVUS® (tipranavir) is marketed in the United States with a black box warning. The specific warning reads:

WARNING: HEPATOTOXICITY and INTRACRANIAL HEMORRHAGE

Hepatotoxicity: Clinical hepatitis and hepatic decompensation, including some fatalities, have been reported. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.

Intracranial Hemorrhage: Both fatal and non-fatal intracranial hemorrhage have been reported

Tipranavir (APTIVUS®, TPV) is a non-peptidic HIV-1 protease inhibitor that inhibits the virus-specific processing of the viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.
APTIVUS®, co-administered with ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*:** Long-term carcinogenicity studies in mice and rats have been conducted with tipranavir. Mice were administered 30, 150 or 300 mg/kg/day tipranavir, 150/40 mg/kg/day tipranavir/ritonavir in combination, or 40 mg/kg/day ritonavir. The incidences of benign hepatocellular adenomas and combined adenomas/carcinomas were increased in females of all groups except the low dose of tipranavir. These tumors were also increased in male mice at the high-dose of tipranavir and the tipranavir/ritonavir combination group. Hepatocellular carcinoma incidence was increased in female mice given the high dose of tipranavir and both sexes receiving tipranavir/ritonavir. The combination of tipranavir and ritonavir caused an exposure-related increase in this same tumor type in both sexes. The clinical relevance of the carcinogenic findings in mice is unknown. Systemic exposures in mice (based on AUC or Cmax) at all dose levels tested were below those in humans receiving the recommended dose level. Rats were administered 30, 100 or 300 mg/kg/day tipranavir, 100/26.7 mg/kg/day tipranavir/ritonavir in combination, or 10 mg/kg/day ritonavir. No drug-related findings in male rats were observed. At the highest dose of tipranavir, an increased incidence of benign follicular cell adenomas of the thyroid gland was observed in female rats. Based on AUC measurements, exposure to tipranavir at this dose level in rats is approximately equivalent to exposure in humans at the

recommended therapeutic dose. This finding is probably not relevant to humans, because thyroid follicular cell adenomas are considered a rodentspecific effect secondary to enzyme induction.

Tipranavir showed no evidence of mutagenicity or clastogenicity in a battery of five *in vitro* and *in vivo* tests including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, unscheduled DNA synthesis in rat hepatocytes, induction of gene mutation in Chinese hamster ovary cells, a chromosome aberration assay in human peripheral lymphocytes, and a micronucleus assay in mice.

Tipranavir had no effect on fertility or early embryonic development in rats at dose levels up to 1000 mg/kg/day, equivalent to a Cmax of 258 µM in females. Based on Cmax levels in these rats, as well as an exposure (AUC) of 1670 µM·h in pregnant rats from another study, this exposure was approximately equivalent to the anticipated exposure in humans at the recommended dose level of 500/200 mg APTIVUS/ritonavir BID.

(Last reviewed April 2016)

Zalcitabine (HIVID®, ddC)

(HIVID® no longer manufactured as of 12 December 2006)

Zalcitabine is a synthetic nucleoside analogue of the naturally occurring nucleoside 2'-deoxycytidine in which the 3'-hydroxyl group is replaced by hydrogen. Within cells, zalcitabine is converted to the active metabolite, dideoxycytidine-5'-triphosphate (ddCTP) by cellular enzymes. Dideoxycytidine-5'-triphosphate serves as an alternative substrate to deoxycytidine triphosphate (dCTP) for HIV-reverse transcriptase and inhibits the *in vitro* replication of HIV by competitive inhibition of viral DNA synthesis due to premature chain termination.

Repeated administration of very high doses of zalcitabine (1000 mg/kg/day) for 13 weeks produced an increased incidence of thymic lymphoma in B6C4F1 mice. The development of thymic lymphoma is considered to be unique to the mouse, as no such lymphomas were observed in dogs, rabbits, cynomolgus monkeys and rats treated with HIVID®, and hence not clinically relevant. Lymphoma has been identified as a consequence of HIV infection. This most likely represents a consequence of prolonged immunodeficiency and not antiviral therapy.

Human peripheral blood lymphocytes were exposed to zalcitabine, with and without metabolic activation and at 1.5mcg/mL and higher, dose-related increases in chromosomal aberration were seen. Oral doses of zalcitabine at 2500 and 4500 mg/kg were clastogenic in the mouse micronucleus assay.

Fertility and reproductive performance were assessed in rats at plasma concentrations up to 2142 times those achieved with the maximum recommended human dose (MRHD) based on AUC measurements. No adverse effects on rate of conception or general reproductive performance were observed. The highest dose was associated with embryolethality and evidence of teratogenicity. The next lower dose studied (plasma concentrations equivalent to 485 times the MRHD) was associated with a lower frequency of embryotoxicity but not teratogenicity.

Zalcitabine is assigned FDA Pregnancy Category C status. It has been shown to be teratogenic in mice at calculated exposure levels of 1365 and 2730 times that the MRHD (based on AUC measurements). In rats, zalcitabine was teratogenic at a calculated exposure level of 2142 times the MRHD but not an exposure level of 485 times the MRHD. In a perinatal and postnatal study in the rat, a high incidence of

hydrocephalus was observed in the F1 offspring derived from litters of dams treated with 1071 (but not 485) times the MRHD (based on AUC measurements).

Increased embryolethality was observed in pregnant mice at doses 2730 times the MRHD and in pregnant rats above 485 (but not 98) times the MRHD (based on AUC measurements). Average fetal body weight was significantly decreased in mice at doses of 1365 times the MRHD and in rats at 2142 times the MRHD (based on AUC measurements). In a perinatal and postnatal study, the learning and memory of a significant number of F1 offspring were impaired, and they tended to stay hyperactive for a longer period of time. These effects, observed at a calculated exposure level of 1071 (but not 485) times the MRHD (based on AUC measurements) were considered to result from extensive damage to or gross underdevelopment of the brain of these F1 offspring consistent with the finding of hydrocephalus.

There are no adequate and well-controlled studies of zalcitabine in pregnant women. Zalcitabine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Fertile women should not receive zalcitabine unless they are using effective contraception during therapy.

(References: HIVID Core Data Sheet Version 1.2 Approved April 14, 2003; HIVID USPI Revised: September 2002)

(Last reviewed February 2016)

Zidovudine (RETROVIR®, ZDV)

RETROVIR is the brand name for zidovudine (formerly called azidothymidine [AZT]), a pyrimidine nucleoside analogue active against HIV-1, and is indicated for the prevention of maternal-fetal HIV-1 transmission.

Pregnancy: Zidovudine is assigned FDA Pregnancy Category C status.

In a fertility and reproduction study, male rats were dosed for 85 days prior to mating and females for 26 days prior to mating and throughout gestation and lactation. No fetal malformations or variations occurred in this study, but the mid- and high-doses were both embryotoxic, increasing the number of early resorptions and decreasing litter sizes. No embryotoxic effects occurred in untreated females mated with treated males. No evidence of teratogenicity was found in rats given oral doses of zidovudine of up to 500 mg/kg/day on days 6 through 15 of gestation. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats of 66 to 226 times the peak human plasma concentrations.

In a rat reproductive toxicity study, there was an increase in early resorptions and a decrease in litter size at 150 or 450 mg/kg/day of zidovudine. When treated males were mated to virgin, untreated females, all reproductive parameters were normal in the untreated females, indicating that the embryotoxic effect of the drug was not likely mediated by a genotoxic or other effect in the male.

In one of two studies in pregnant rabbits, the incidence of fetal resorptions was increased in rabbits given 500 mg/kg/day. There was no evidence of a teratogenic effect at any dose level. The doses used in these studies resulted in peak zidovudine plasma concentrations in rabbits of 12 to 87 times mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours).

In another developmental toxicity study, pregnant rats received zidovudine at doses of 3000 mg/kg/day (very near the median lethal dose of 3683 mg/kg/day) which produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily exposure [AUC] in humans given 600 mg/day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations including absent tail, anal atresia, fetal edema, situs inversus, diaphragmatic hernia, bent limb bones, atlas occipital defect and vertebral and/or rib anomalies. There was also a significant increase in the number of litters with bent ribs, reduced ossification of the vertebral arches, and presacral vertebrae. However, there were no signs of teratogenicity at doses up to one fifth the lethal dose (600 mg/kg/day or less).

A separate peri- and post-natal study was conducted in pregnant rats given doses of 0, 50, 150 and 400 mg/kg/day from day 17 of gestation through to day 21 of lactation. There were no adverse effects noted in either generation. The reproductive capacity of those F1 generation pups which were raised to sexual maturity was not affected.

Pharmacokinetics and Transmission: Zidovudine pharmacokinetics have been studied in a Phase I study of 8 women during the last trimester of pregnancy. Zidovudine pharmacokinetics were similar to those of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics.

In humans, treatment with zidovudine during pregnancy reduced the rate of maternal-fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to 7.8% for infants born to mothers treated with zidovudine. A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant women with CD4+ cell counts of 200 to 1818 cells/mm^3 to determine the utility of zidovudine for the prevention of maternal-fetal HIV-transmission (ACTG-076). Oral zidovudine was initiated between 14 and 34 weeks of pregnancy, followed by intravenous administration during labor and delivery. Following birth, 363 neonates received oral zidovudine Syrup for 6 weeks. The study showed a statistically significant difference in the incidence of HIV-1 infection in the neonates (based on viral culture from peripheral blood) between the group receiving zidovudine and the group receiving placebo. Zidovudine was well tolerated by mothers and infants. There was no difference in pregnancy-related adverse events between the treatment groups. Congenital abnormalities occurred with similar frequency between infants born to mothers who received zidovudine and infants born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

Fertility: Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area, had no effect on fertility judged by conception rates.

Carcinogenicity: In standard oral carcinogenicity bioassays evaluating mice and rats (60 females and 60 males in each group), no evidence of carcinogenicity was seen in males of either species. Initial single daily doses were 30, 60 and 120 mg/kg/day in mice and 80, 220 and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30 and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91, and then 300 mg/kg/day on day 279. In female mice, seven late-appearing (after 19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, one squamous cell papilloma and one squamous polyp) occurred in animals given the highest dose (40 mg/kg/day). One late-appearing squamous cell papilloma occurred in the vagina of a middle dose animal (30 mg/kg/day). No vaginal tumors were found in female mice at the lowest dose (20 mg/kg/day). In rats, two late-appearing (after 20 months), non-metastasizing vaginal

squamous cell carcinomas occurred in animals given the highest dose (300 mg/kg/day). No vaginal tumors occurred at the low or middle doses in rats.

To determine if exposure to zidovudine prenatally and continuing for the lifetime of the animals would alter the pattern of carcinogenicity seen in the standard lifetime oral carcinogenicity bioassay in mice, two transplacental carcinogenicity studies were conducted. One study administered zidovudine at doses of 20 mg/kg per day or 40 mg/kg per day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately three times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~ 1000 mg/kg nonpregnant body weight or ~ 450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.
It is not known how predictive the results of rodent carcinogenicity studies may be for humans. At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Mutagenesis: Zidovudine is an antiviral agent, which is a potent inhibitor of the replication of HIV. In nonclinical oral toxicology studies in rats and monkeys, the principal toxicologic finding was reversible macrocytic anemia, which occurred at 150–500 mg/kg/day in rats and 35–300 mg/kg/day in monkeys. Zidovudine was mutagenic in a 5178Y/TK+/- mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes. No effects were seen in a single dose intravenous bone marrow cytogenetic assay in rats. Positive results were noted in micronucleus studies in mice and rats after repeated doses. Patients should be informed that the major toxicities of zidovudine are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection.

In a randomized, double-blind, placebo-controlled trial in HIV-1-infected women and their neonates conducted to determine the utility of zidovudine for the prevention of maternal-fetal HIV-1 transmission, zidovudine Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following birth. The most commonly reported adverse reactions were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1,000 cells/mm3). Anemia occurred in 22% of the neonates who received zidovudine and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving zidovudine compared with neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with zidovudine. Neutropenia in neonates was reported with similar frequency in the group that received zidovudine (21%) and in the group that received placebo (27%). The long-term consequences of in utero and infant exposure to zidovudine are unknown.

(Last reviewed October 2014)

Appendix F: Methods

In an effort to assure that the Registry collects, analyzes, and presents information which is accurate and useful to the health care provider, the Registry continues to review and update its processes and procedures. These methods are presented in detail in the Registry's Monitoring, Analysis, and Termination plan (42) and are summarized here for reference.

The Registry conforms to the FDA Guidance for Industry: Establishing Pregnancy Exposure Registries (31, 32), the Guidelines for Good Pharmacoepidemiology Practices (GPP) (33), and the FDA Guidance on Pharmacovigilance (34).

In order to permit comparisons with population-expected rates, the Registry adopts definitions and best practices from two primary reference Registries, the Metropolitan Atlanta Congenital Defects Registry (MACDP) and the Texas Birth Defects Registry (TBDR) (3,4,5,6,7). Because population representativeness is a concern with any external comparison group, the use of multiple complimentary comparators is advisable. The TBDR covers the state of Texas which has a large population with a demographic distribution similar to that of the US overall. Therefore, the TBDR was added as a second external comparison group in addition to the MACDP.

Institutional Review Board (IRB) Review

The Registry is committed to the highest standards of ethical conduct; assuring patient rights, including protection of patient privacy, is a very high priority for the Registry. For this reason the Registry sought and obtained IRB approval from Western IRB (WIRB®) in March 2000. With the IRB approval of the protocol, the Registry was granted a waiver from having to obtain patient informed consent. The IRB reviews the Registry protocol annually with annual status reports required. Additionally, the Registry reviews data privacy issues on a regular basis.

HIPAA Privacy Rule: Protecting Personal Health Information in Research

The HIPAA Privacy Rule allows covered entities (e.g., health care providers) to disclose protected health information (PHI) without subject authorization if the covered entity obtains documentation that an Institutional Review Board has waived the requirement for authorization (35).

On April 29, 2003, Western Institutional Review Board (WIRB) approved a request for a waiver of authorization for use and disclosure of PHI. WIRB determined that documentation received from this Registry satisfies the three requirements for a waiver of authorization. These requirements are:

1. The use or disclosure of the PHI involves no more than minimal risk to the individuals, based on the following elements:

    a. an adequate plan to protect identifiers from improper use and disclosure;

    b. an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law); and

    c. adequate written assurances that the PHI will not be reused or redisclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use of disclosure of PHI would be permitted by HIPAA.

2. The research could not be practicably conducted without access to and use of the PHI; and

3. The research could not practicably be conducted without the waiver.

The Board determined that a waiver of authorization for use of the following PHI is needed and approved for this research:

> Information about subjects on antiretroviral drugs during pregnancy, including dates of services, estimated date of delivery, date of last menstrual period, dates of exposure to antiretroviral drugs and date of pregnancy outcome.

Registration and Follow-up

The Antiretroviral Pregnancy Registry collects data on use of abacavir, adefovir dipivoxil, amprenavir, atazanavir, darunavir, delavirdine mesylate, didanosine, dolutegravir, efavirenz, elvitegravir/cobicistat, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, stavudine, telbivudine, tenofovir alafenamide, tenofovir disoproxil fumarate, tipranavir, zalcitabine and zidovudine during pregnancy. There are risks associated with any new chemical entity or combination therapy and the historic precedent of less specific antiviral agents causing genetic damage. The Registry requests information on antiretroviral therapy, though there may be other exposures to other drugs, which are not systematically collected. As more data are collected in the Registry, clinicians will be provided with updated information on the use of these drugs during pregnancy.

Registration is voluntary. Health professionals are strongly encouraged to enroll their antiretroviral-exposed pregnant patients into the Registry as early in the pregnancy as possible, preferably before prenatal testing is done to maximize the validity of the data by minimizing the potential biases introduced. Certain minimal information must be provided in order to register or enroll a patient.

Patients are followed through health care providers who provide information on maternal risk factors, pregnancy outcome, and neonatal health. Information is provided on a short registration form, with follow-up obtained at the outcome of the pregnancy. In the month of the expected date of delivery, a short follow-up form is sent to the health care provider with a copy of the original Antiviral Therapy During Pregnancy Form to ascertain the pregnancy outcome and completion of the antiviral therapy information. Additional follow-up is not sought from subsequent health care providers. Information can be provided to the Registry over the phone or by faxing, mailing, or emailing completed forms. Copies of the current forms are included in this report and are also available on the website.

In an attempt to limit the bias in the analysis, the Registry has begun assembling a group of providers who have committed in writing to report to the Registry every prospective antiretroviral therapy exposure during pregnancy that comes to their site. This will allow the Registry to include every report from that site as an evaluable case. As the number of cases from these sites increases, the Registry will be able to analyze these cases separately. Providers are encouraged to participate in this group.

Registration Process

The minimum requirements for an evaluable case are: a prospective report with clear information on the antiretroviral therapy exposure during pregnancy, source of the report, enough information to search for duplicate reporting of a case (e.g., LMP, EDD, maternal age). If follow-up information on the outcome of the pregnancy is unavailable, a case may be considered lost to follow-up. Cases were rendered unevaluable or lost to follow-up if the reporting health care provider could no longer locate the patient to provide pregnancy outcome data, if after numerous attempts, there are no follow-up data forthcoming from the health care provider, or if the birth outcome is missing or indication of a defect is marked as unknown. **Only data from evaluable prospective cases with known outcomes were summarized in this report.**

To preserve the patient's confidentiality, registration is conducted through the health care provider rather than the patient. The Registry *assigns* patient LOG ID numbers rather than using a patient ID chosen by the provider. This is the ID with which the Registry communicates to the site regarding a patient. To obtain a Registry-assigned LOG ID:

- **Notify the Registry:** The health care provider should notify the Registry of the pregnancy exposure by phone, mail, email or fax (as early in pregnancy as possible, preferably before prenatal testing for defects is done). The Registry will assign a sequential number to the provider for that patient. This number is used to identify the patient when communicating with the Registry for follow-up.

  (If necessary, a block of numbers may be obtained by providers who enroll patients into the Registry on a regular basis.)

- **Patient Log:** The Registry provides a patient log sheet as a possible way a provider might cross-reference the identity of the patient at the site to the Registry LOG ID. (This log sheet is for the provider's use only and must be kept in a secure place separate from the patient charts to protect patient confidentiality at the site.)

The Registry prefers and encourages prospective registration, which is defined as registration of a pregnancy prior to knowledge of the pregnancy outcome. The outcome of pregnancy is defined at the time of delivery or fetal loss, or when a defect reported at enrollment is detected on a prenatal test (e.g., structural defect noted on an ultrasound). Retrospective reports (i.e., reports made after the pregnancy outcome is known), are welcomed and carefully reviewed by the Registry. However, retrospective reports may be biased toward more abnormal outcomes and are less likely to be representative of the general population experience. Therefore, the retrospective outcomes are summarized independent of the prospective outcomes. Due to difficulty in obtaining follow-up, retrospective reports with outcomes without defects over two years prior to receipt by the Registry are not included. Retrospective reports of exposed infants with defects can be useful in the identification of patterns of defects suggestive of common etiology.

*The Registry is interested in identifying and receiving written commitment from providers who are willing to report **all** of their site's antiretroviral pregnancy exposures to the Registry. The Registry encourages providers to become part of this special group. Please contact the Registry by mail, email, phone, or fax to receive more information on how to participate. Emails can be sent to SM_APR@INCResearch.com. For US and Canada Call 800-258-4263 or Fax 800-800-1052 (or Fax to 910-256-0637 for International). For UK, Germany, and France call toll free 00800-5913-1359 or Fax 00800-5812-1658. For Brazil Fax 0800-892-1472. For Europe call +32-2-714-5028 or Fax +32-2-714-5024. Complete ascertainment of cases from a site decreases the potential selection bias. As the number of cases from these sites*

becomes larger, the Registry will conduct a sub-set analysis of these data.

A sample copy of the data collection form is included in this report, or may be obtained by contacting the Registry, or printing from the www.APRegistry.com website. Patient registration may be completed by mail, email (SM_APR@INCResearch.com), fax transmission to 800-800-1052 (US, Canada), +1-910-256-0637 (International), or by calling the Registry at 800-258-4263 (US, Canada). For UK, Germany, France toll-free call 00800-5913-1359 or Fax 00800-5812-1658. For Brazil, Fax 0800-892-1472. For Europe call +32-2-714-5028 or Fax +32-2-714-5024. After receipt of the registration information, the Registry will send a follow-up form and a copy of the antiretroviral therapy information reported at registration to ascertain the outcome of the pregnancy and additional therapy information.

Review of Birth Defects Identified

The Advisory Committee reviews all reports of birth defects. Initial review, request for further information (as necessary), and assessment are conducted by a consultant geneticist trained on MACDP classification and the Registry evaluation process by staff at the CDC, Division of Birth Defects and Developmental Disabilities (36). At the semi-annual Steering Committee meeting, the Advisory Committee reviews each of the defect reports with the consultant's evaluations and reaches a consensus on the final assessment.

Classification of Outcomes

The Registry is intended to provide an early signal of teratogenicity associated with prenatal use of antiretroviral therapy for those drugs monitored in the Registry. This is accomplished through monitoring the pregnancy and birth outcomes following pregnancy exposure to an antiretroviral drug. Pregnancy outcomes are mutually exclusive and include spontaneous pregnancy loss, induced abortion, stillbirth, and live birth. Stillbirth refers to fetuses born dead at or after 20 weeks gestation or weighing greater than 500 grams. However, the Registry will accept the health care provider's determination for spontaneous pregnancy loss or stillbirth. From time to time, the Registry receives cases resulting in induced abortion and the reporter is reluctant to code the outcome as such because induced abortions are illegal in the particular country. The Registry is sensitive to such cultural issues. For the purposes of reporting, unspecified abortions are coded as induced when they are received from countries in which induced abortions are illegal.

The Registry defines a birth defect as any major structural or chromosomal defect diagnosed by six years of age, or any cluster of two or more conditional abnormalities. In addition, any structural or chromosomal defect detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, fetus, or deceased infant is evaluated. All birth defects are reviewed and classified by the consultant geneticist using a widely-recognized system for standardized public health surveillance of birth defects (3). The Registry's definition of birth defects is consistent with, but not restricted to this list. Clusters of conditional abnormalities (defects of secondary importance) and data from abortuses of ≥20 weeks, when available, have been included to increase the sensitivity of Registry monitoring. Public health surveillance cases have at least one major defect, regardless of whether conditional defects are also present. The Registry includes these cases, but differs from the public health protocols by additionally considering reports of two (2) or more conditional defects alone as a "defect case", so as to cast as broad a net as possible for outcomes that may be associated with antiretroviral medication use.

The Registry focuses on birth defect data detected and reported during the perinatal period. To protect the privacy of the mother, the Registry limits contact to the health care provider who initiated the report, which is usually the mother's health care provider. Most major structural defects and clusters of conditional abnormalities are readily apparent at birth. However, underascertainment of other birth

defects is possible since follow-up is usually obtained from the mother's health care provider in the immediate postnatal period and not by the infant's pediatrician who is more likely to observe defects not easily detected during the neonatal period (such as some cardiac or intestinal abnormalities). The Registry does update case reports if information is received on any birth defect diagnosed or with signs/symptoms occurring up to six years of age, however, this information is not systematically collected.

Certain conditions, such as hepatomegaly and/or splenomegaly, are considered conditional birth defects if they occur at birth. These conditions can also be acquired after birth. To attempt to avoid misclassifying conditions that are acquired after birth as congenital birth defects, such conditions are not coded as birth defects if they are clearly diagnosed after one week of birth.

The Registry differentiates "conditional" defects, the terminology and classification used by MACDP and TBDR, from "minor" defects, a medical term sometimes applied but which lacks the required specificity for population monitoring. The Registry does not systematically collect, but accepts information on minor abnormalities, as well as transient or infectious conditions or biochemical abnormalities that reporting clinicians deem important. Since these data are not systematically collected, their utility is very limited. It is therefore out of the scope of this Registry to evaluate information on other clinical conditions associated with pregnancy or events at outcome which are not considered defects. These other events are subject to monitoring and evaluation by other sources. Providers are encouraged to report information on events not monitored by the Registry to the manufacturer of the drug and/or the FDA.

Organ System Classification

To facilitate the ability to identify a potential signal, the Registry uses an organ system classification based on the British Pediatric Association (BPA) (37), World Health Organization, and MACDP (3, 4, 5) systems that are in common use in public health birth defect surveillance (11). The classification of similar defects or defects with similar etiology into groups reduces granularity and increases the possibility of identifying a potential signal. Once a potential signal is identified, the individual defect cases can be evaluated.

What follows is the scheme used to place specific defects within an organ system.

The purpose of the list is two-fold. The organ system categories represent groups of defects with presumed common embryologic pathogenesis. Defects are not grouped by genetic or environmental etiology. Syndromes are listed within the organ system categories when all components of the syndrome can be found in that category.

Individual defect terms are the most common in current use. Defects are passively reported using various terminologies, even when the defects themselves are the same. Upon case review, the reported defects are given the standard terminology from the organ system list. This eliminates artifactual variation and facilitates analysis.

The result is a three-level hierarchy of defect classification:

Organ System Classification	***Defect Std Terminology***	***Reported Defect***
Cleft lip and/or palate	Cleft lip of any type without cleft palate	• L cleft lip • Unilateral cleft alveolus • Cleft lip

The value of the system is its ability to decrease granularity to facilitate detection of a potential cluster of events identifying a potential signal. Once the potential signal is identified, reanalysis of the individual

components within the cluster can be conducted to determine whether or not the signal is cause for concern.

Medical terminology and knowledge of embryogenesis does evolve over time. This list will be reviewed intermittently and updated as needed. Also, the standard defect terminology and organ system classifications are relatively general. If a general defect term is used frequently, it will be evaluated to see if more specific terminology is warranted for that defect.

Analysis

An important aspect of the Registry is the Registry Steering Committee comprising the Advisory Committee and Sponsor representatives. The Registry Advisory Committee consists of members from the CDC, FDA, NIH, and private sector. Membership consists of specialists in maternal and fetal medicine, infectious disease, teratology, epidemiology, and biostatistics. The Sponsor Company members are from AbbVie, Alvogen Inc, Amneal Pharmaceuticals LLC, Apotex Inc, Aurobindo Pharma Ltd, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Dr. Reddy's Laboratories (UK) Ltd, F.Hoffmann-La Roche, Gilead Sciences Inc, Hetero Labs Ltd, Lupin Pharmaceuticals, Janssen Scientific Affairs, LLC, Merck & Co. Inc, Mylan Laboratories, Novartis Pharmaceuticals, Prinston, Ranbaxy Inc (a Sun Pharma Company), ScieGen Pharmaceuticals Inc, Sandoz Inc, SigmaPharm Laboratories, Silarx Pharmaceuticals Inc, Strides Shasun Ltd, Sunshine Lake Pharma, Teva Pharmaceuticals, ViiV Healthcare, and West-Ward Pharmaceuticals. This Steering Committee oversees the Registry process and reviews the results from the Registry data. The Antiretroviral Pregnancy Registry Interim Report is prepared semi-annually, summarizing the aggregate data collected by the Registry. Since the report contains historical information as well as new data, each report completely supercedes all previous reports. This report is available to health care providers who treat this specialized population or to any health care provider who requests a report.

Data analysis is conducted on prospective, closed cases for which adequate follow-up exists. In addition, these cases must meet the following minimum criteria for evaluation:

- Documentation that a Registry drug was taken during pregnancy
- Timing of the prenatal exposure to the Registry medication (no broader than which trimester)
- Source of report (patient or health care provider, self-reported or through Sponsor Companies)
- Documentation on whether the patient was enrolled in a study conducted in pregnancy, during the reported pregnancy

As women participating in a clinical study involving use of antiretrovirals in pregnancy must meet certain selection criteria and may be followed more closely than women not participating in such studies, such prospective study cases are analyzed separately from the prospective Registry reports.

The outcome data are presented by the earliest trimester of exposure to an antiretroviral regimen. For this Registry, gestational weeks are calculated beginning from the first day of the last menstrual period. (If the date of the last menstrual period is not available, the estimated date of delivery may be used. If the gestation week is inconsistent with the exposure dates and/or the date of outcome [outside $\pm$ 1 week for the first trimester, outside $\pm$ 2 weeks for the second and third trimesters] and a corrected estimated date of delivery [i.e., generally by ultrasound] is available, the corrected estimated date of delivery is used for gestational week calculations.) The second trimester begins at week 14, and the third trimester begins at week 28.

To ease interpretation of the data and to calculate prevalence of birth defects in live infants among various treatment regimens, the actual treatment regimens received are grouped according to their component drug classifications, i.e., nucleoside analog reverse transcriptase inhibitors (NRTI), nucleotide reverse transcriptase inhibitors (NtRTI), non-nucleoside analog reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), entry inhibitors (EI), and integrase inhibitors (InSTI). Each regimen is then reported as a combination of its corresponding drug classifications. However, if there is more than one drug within the classification, only one occurrence is counted. The calculations of prevalence are patterned after the CDC population-based birth defects surveillance system, which includes all major defects meeting the MACDP case definition for a defect occurring in infants/fetuses of at least 20 weeks gestational age (5). The prevalence of birth defects is calculated by dividing the number of outcomes with reported birth defects by the total number of live births. Spontaneous losses and induced abortions with or without birth defects are excluded from the denominator to be consistent with the calculation used by the MACDP, which is the primary comparator for the Registry. Defects reported in pregnancies terminating before 20 weeks are included in this report (Appendix C) and reviewed with other related defects, but not included in rate calculations. MACDP birth defect rates published in 2007 differ from previously published rates in part due to re-classification of congenital cardiac defects that resulted in improved specificity of cardiac diagnoses and elimination of normal physiologic variants and obligatory shunt lesions (6). Beginning with 2001 data, the TBDR case definition includes all major defects in the calculation of birth defect rates regardless of the gestational age at outcome (7). Prior to then, only pregnancy outcomes occurring at 20 weeks gestation or greater were actively identified. As the behavior of a specific antiretroviral may differ widely from others in its drug classification, it is reasonable to prepare an analysis that would highlight potential increased risk for a given compound. For such an analysis, exposures to a given antiretroviral will be summarized according to the earliest trimester of that exposure.

Studies have shown that risk of spontaneous pregnancy loss in the general population is high early in pregnancy and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 14-22% (38). Although the Steering Committee carefully reviews each pregnancy outcome, calculation of risk of spontaneous pregnancy losses attributable to drug intervention overall is outside the scope of the Registry and should not be attempted because pregnancies in this Registry may be reported at variable and imprecise times during gestation. Further, the reader is reminded of the context in which this Registry is conducted, i.e., generally an HIV-infected population, often with advanced disease, at possibly increased risk of adverse outcomes of pregnancy unrelated to teratology. This Registry is not designed to monitor these unrelated effects.

The Advisory Committee uses the following concepts to review the data: The general population risk of birth defects meeting the CDC criteria is approximately 3% of live births (39, 40). The overall prevalence of birth defects by year (1968-1999 ranges from 2% to 5%). The baseline risk of a specific birth defect may be as low as 1-2 per 1000 live births or less.

Given the inherent difficulties in identifying a comparison group, three different methods are used to review the data for signals of teratogenicity. First, the prevalence of birth defects in the Registry is compared to the prevalence observed in population-based birth defect surveillance systems including the MACDP and TBDR. The MACDP reports a total prevalence of birth defects identified among births from 1968 through 2003 of 2.67%; the prevalence of birth defects identified among births in the years that most closely mirror the years APR has been in operation (1989-2003) was 2.72% (95% CI 2.68, 2.76)[*] (5). The TBDR reports an overall prevalence of birth defects of 4.17% (95% CI 4.15, 4.19) for deliveries during

[*] Because population-based surveillance does not involve sampling, MACDP does not publish confidence intervals (CIs). The CIs reported around MACDP rates in this report were calculated by the Registry.

2000 through 2009 among women who were residents of Texas at the time of delivery (7). The prevalence of “early diagnoses” is important for Registry comparisons since the majority of outcome reports are from obstetricians who may have limited access to diagnoses made after the day of birth. The MACDP, TBDR, and other population-based registries ascertain defect cases by active review of medical records. This Registry’s methods differ by using voluntary registration with active solicitation of outcome data.

As a second method of analysis, an internal comparison is made between the risk of birth defects among women with first trimester exposures to antiretroviral medications and the risk of birth defects among women with second or third trimester exposures to antiretroviral medications. Prevalence ratios and 95% confidence intervals (41) are calculated to assess the presence or absence of any excess risk associated with timing of the exposure. A third is a qualitative analysis of cases for the emergence of any unique defects or patterns of defects.

For all birth defects combined, a cohort of 200 newborns exposed to antiretroviral drugs in the first trimester is sufficient to detect a 2.2 fold increased risk of birth defects compared to a general US population prevalence of 3% (40), with 80% power and a Type I error rate of 5%. Once the Registry experience with an individual drug reaches this threshold of 200 first trimester exposures, the drug specific overall birth defect rate and 95% CI is calculated and reported. A cohort of 1000 is sufficient to detect a 1.5 fold increased risk of birth defects. For specific defects, the power to detect an increased risk varies depending on the frequency of the defect in the population and the evolving size of the exposed group.

Defect Monitoring Plan

The intent of the Registry is to provide useful information to health care providers on the outcomes of pregnancy following prenatal exposure to antiretroviral therapy, including determination if there is a signal that might indicate a potential risk of a major defect in the offspring. Therefore, it is necessary to determine in the evaluation of the cumulative data what the indicators of a signal or pattern are and what course of action will be taken when the signal is noted. The Registry may never have sufficient power to detect a risk for a particular rare outcome to a particular drug. However, the Registry Steering Committee has developed a process for determining what constitutes a signal, how it is reviewed, and what action might be taken should such a signal be seen. For example, the “Rule of Three” convention adopted by the Registry specifies that once 3 similar birth defects have accumulated with any specific exposure or exposure combination, these cases are flagged for immediate review. The monitoring process is detailed in the Birth Defect Monitoring, Analysis, and Registry Termination Plan for the Antiretroviral Pregnancy Registry (42) (monograph available upon request).

Information about the Registry can be found in other Registry publications and presentations (43 - 84).

Appendix G: Data Collection Forms

Registry Enrollment / Patient Enrollment Forms

The case-registration approach for collecting information depends on the continued participation of health care providers who register patients and assist in providing follow-up information postpartum. The assistance of health care providers who have provided information to this Registry is greatly appreciated and the help of others is eagerly sought.

The antiretrovirals being followed in this Registry include: lopinavir+ritonavir (KALETRA®, ALUVIA®, LPV/r) and ritonavir (NORVIR®, RTV) manufactured by **AbbVie**; nevirapine (generic) manufactured by **Alvogen Inc**; entecavir (generic) manufactured by **Amneal Pharmaceuticals LLC**; abacavir (generic), lamivudine (generic), nevirapine (generic), nevirapine ER (generic), tenofovir disoproxil fumarate (generic), and tenofovir disoproxil fumarate+emtricitabine (generic) manufactured by **Apotex Inc**; abacavir (generic), didanosine (generic), entecavir (generic), lamivudine (generic), lamivudine+zidoudine (generic), nevirapine (generic), nevirapine ER (generic), stavudine (generic) and zidovudine (generic) manufactured by **Aurobindo Pharma Ltd**; nevirapine (VIRAMUNE®, VIRAMUNE® XR™, NVP) and tipranavir (APTIVUS®, TPV) manufactured by **Boehringer Ingelheim Pharmaceuticals Inc**; atazanavir (REYATAZ®, ATV), atazanavir+cobicistat (EVOTAZ®, EVO), didanosine (VIDEX®, VIDEX® EC, ddI), efavirenz (SUSTIVA®, STOCRIN®, EFV), entecavir (BARACLUDE®, ETV), and stavudine (ZERIT®, d4T) manufactured by **Bristol-Myers Squibb Company**; lamivudine+tenofovir disoproxil fumarate (generic), nevirapine (generic), stavudine (generic) and zidovudine (generic) manufactured by **Cipla Ltd**; abacavir+lamivudine (generic) manufactured by **Dr. Reddy's Laboratories (UK) Ltd**; enfuvirtide (FUZEON®, T-20), saquinavir (FORTOVASE®, SQV-SGC), saquinavir mesylate (INVIRASE®, SQV-HGC), saquinavir soft gel (Fortovase®, SQV-SGC – no longer manufactured as of 06 July 2006) and zalcitabine (HIVID®, ddC) manufactured by **F.Hoffman-La Roche**; adefovir dipivoxil (HEPSERA®, ADV), cobicistat (TYBOST®, COBI), efavirenz+emtricitabine+tenofovir disoproxil fumarate (ATRIPLA®, ATR), elvitegravir (VITEKTA®, EVG), elvitegravir+cobicistat+emtricitabine+tenofovir alafenamide (GENVOYA®, GEN), elvitegravir+cobicistat+emtricitabine+tenofovir disoproxil fumarate (STRIBILD®, STB), emtricitabine (EMTRIVA®, FTC), emtricitabine+tenofovir alafenamide (DESCOVY®, DVY), rilpivirine+emtricitabine+tenofovir alafenamide (ODEFSEY®, ODE), rilpivirine+emtricitabine+tenofovir disoproxil fumarate (COMPLERA®, CPA; EVIPLERA®, EPA), tenofovir alafenamide (VEMLIDY®, TAF), tenofovir disoproxil fumarate (VIREAD®, TDF) and tenofovir disoproxil fumarate+emtricitabine (TRUVADA®, TVD) manufactured by **Gilead Sciences Inc**; abacavir (generic), efavirenz (generic), lamivudine (generic), lamivudine+tenofovir disoproxil fumarate (generic), nevirapine (generic), stavudine (generic), tenofovir disoproxil fumarate (generic), zidovudine (generic) and zidovudine+lamivudine (generic) manufactured by **Hetero Labs Ltd**; darunavir (PREZISTA®, DRV), darunavir+cobicistat (PREZCOBIX™, PCX), etravirine (INTELENCE®, ETR) and rilpivirine (EDURANT®, RPV) manufactured by **Janssen Scientific Affairs, LLC**; abacavir+lamivudine+Zidovudine (generic), lamivudine (generic) and zidovudine+lamivudine (generic) manufactured by **Lupin Pharmaceuticals, Inc**; efavirenz (STOCRIN®, EFV), indinavir (CRIXIVAN®, IDV), lamivudine+raltegravir (DUTREBIS™, DUT), and raltegravir (ISENTRESS®, RAL) manufactured by **Merck & Co. Inc**; abacavir (generic), didanosine (generic), lamivudine (generic), lamivudine+zidovudine (generic), nevirapine (generic), stavudine (generic) and zidovudine (generic) manufactured by **Mylan Laboratories**; telbivudine (SEBIVO®, TYZEKA®, LdT) manufactured by **Novartis Pharmaceuticals**; nelfinavir (VIRACEPT®, NFV) licensed and manufactured by **Pfizer Inc** and distributed by **ViiV HealthCare**; nevirapine (generic) manufactured by **Prinston**; zidovudine (generic) manufactured by **Ranbaxy Inc (a Sun Pharma Company)**; nevirapine ER (generic) manufactured by **Sandoz Inc**; nevirapine (generic) manufactured by **ScieGen Pharmaceuticals Inc**; adefovir dipivoxil (generic) manufactured by **SigmaPharm Laboratories**; abacavir (generic),

lamivudine+zidovudine (generic) and nevirapine (generic) manufactured by **Strides Shasun Ltd**; zidovudine (generic) manufactured by **Sunshine Lake Pharma**; abacavir+lamivudine (generic), darunavir (generic), didanosine (generic), entecavir (generic), nevirapine (generic), and zidovudine+lamivudine (generic) manufactured by **Teva Pharmaceuticals**; abacavir (ZIAGEN®, ABC), abacavir+dolutegravir+lamivudine (TRIUMEQ®, TRI), abacavir+lamivudine (EPZICOM®, EPZ), abacavir+lamivudine+zidovudine (TRIZIVIR®, TZV), amprenavir (AGENERASE®, APV), delavirdine mesylate (RESCRIPTOR®, DLV), dolutegravir (TIVICAY®, DTG), fosamprenavir calcium (LEXIVA®, FOS), lamivudine (EPIVIR®, 3TC), lamivudine+zidovudine (COMBIVIR®, ZDV+3TC), maraviroc (SELZENTRY®, CELSENTRI®, MVC), zidovudine (RETROVIR®, ZDV) and zidovudine (generic) manufactured by **ViiV HealthCare**; ritonavir (generic), and zidovudine (generic) manufactured by **West Ward Pharmaceuticals;** efavirenz co-marketed by **Bristol-Myers Squibb Company** (SUSTIVA®, EFV) and **Merck & Co. Inc** (STOCRIN®, EFV); efavirenz/emtricitabine/tenofovir disoproxil fumarate combination co-marketed by **Bristol-Myers Squibb Company** and **Gilead Sciences Inc**, (ATRIPLA®, ATR); and lamivudine (generic), lopinavir+ritonavir (generic) manufactured by **Silarx Pharmaceuticals Inc** (marketed by Lannett).

The Registry encourages the reporting of all known pregnancy exposures to a Registry drug, but prospectively reported cases are preferred. Registry enrollment and follow-up forms may be obtained by contacting the Pregnancy Registry or the included data forms may be photocopied. Prospective or retrospective notifications of prenatal exposures to therapies followed by the Registry can be registered by contacting the Registry via mail, email, phone, or fax.

Instructions for Completing Forms

Patient Anonymity and Patient Identifiers

The Registry makes every effort to assure patient confidentiality within the Registry. The Registry does not collect identifying information such as maternal date of birth, initials, or chart number. The patient identifier is a Registry-assigned number provided to the reporter at the time the patient is enrolled (patient LOG ID).

Patient LOG ID numbers can be obtained by calling, emailing, or faxing the Registry Office for a number (or a block of numbers, for providers who register patients on a regular basis). The Registry also provides a Patient Log as a possible way the reporter might cross-reference the patient with the Registry ID number. Whatever method is used, this record must be kept in a secure place separate from patient charts to assist in protecting patient confidentiality at your site.

Prospective Registration

Registration and Therapy Forms (To be completed when notifying Registry of prenatal exposure while patient is still pregnant.)

- Contact the Registry via phone, email or fax to obtain a patient ID number

Mailing Address:	***Telephone:***	***Fax:***
Antiretroviral Pregnancy Registry 1011 Ashes Drive Wilmington, NC 28405	+1-800-258-4263 (toll free US, Canada) +32-2-714-5028 (Europe) (00800) 5913 1359 (toll free UK, Germany, France)	(800) 800-1052 (toll free US, Canada) +1-910-256-0637 (International) +32-2-714-5024 (Europe) (00800) 5812 1658 (toll free UK, Germany, France) 0800-892-1472 (Brazil)

Email: SM_APR@INCResearch.com

***Website*:** www.APRegistry.com (for data forms and information)

  - Track the Registry-assigned patient ID number with your own identification of the patient
  - Secure the tracking log to protect patient confidentiality
- Photocopy the Registration Form pages from the report or print from the APR Website
- Complete as much information as is available at the time of reporting
- Report as early as possible after the pregnancy exposure is known
- Return the Registration Forms to the Registry by mail, email or fax

Follow-up: In the month of the estimated date of delivery, the reporter will be sent a two-page Follow-Up Form with a copy of the originally submitted Antiviral Therapy during Pregnancy Form. Please complete the information on the Follow-up Form and update the Antiviral Therapy during Pregnancy Form with any therapy modifications or additions since registration.

Retrospective Registration

Registration and Follow-Up Forms (To be completed when notifying Registry of prenatal exposure *after* the pregnancy outcome is known.)

- Contact the Registry via phone, email or fax to obtain a patient ID number

Mailing Address:	***Telephone:***	***Fax:***
Antiretroviral Pregnancy Registry 1011 Ashes Drive Wilmington, NC 28405	+1-800-258-4263 (toll free US, Canada) +32-2-714-5028 (Europe) (00800) 5913 1359 (toll free UK, Germany, France)	(800) 800-1052 (toll free US, Canada) +1-910-256-0637 (International) +32-2-714-5024 (Europe) (00800) 5812 1658 (toll free UK, Germany, France) 0800-892-1472 (Brazil)

Email: *SM_APR@INCResearch.com*

***Website*:** www.APRegistry.com (for data forms and information)

  - Track the Registry-assigned patient ID number with your own identification of the patient
  - Secure the tracking log to protect patient confidentiality
- Photocopy both the Registration, Therapy and Follow-Up Forms pages or print from the APR Website
- Complete as much information as is available to you
- Return the Registration, Therapy and Follow-Up Forms to the Registry (by mail, email or fax)

Data Forms included (see next 8 pages)

Keep in a secure place to protect patient confidentiality

HCP #

ANTIRETROVIRAL PREGNANCY REGISTRY
PATIENT LOG

Call the Registry Office for Patient ID Numbers
800-258-4263 or 910-256-0238

In an effort to assure patient confidentiality and anonymity the Registry does not collect identifying information (e.g., initials, chart number, date of birth) on patients enrolled in the Registry. The identifier used to refer to your patient for further follow-up on the outcome of this pregnancy will be a Registry assigned Patient (Log) ID number.

This log is provided for your convenience. You may want to use this to track your Registry patients and to easily cross-reference the APR Registry assigned Patient (Log) ID with your patient.

THIS IS FOR YOUR USE ONLY, DO NOT RETURN THIS TO THE REGISTRY.

Please call the Registry Office at 1-800-258-4263 if you have questions.

Patient **(Log)** ID *Assigned by the Registry*	Suggested information to use to reference this patient when Registry follow-up is necessary			
	Patient Name	Chart number	EDD	Date APR form completed
03000	*Jane Doe*	*123656*	*Jun. 1, 2008*	*Dec. 3, 2007*

Phone: (US, Canada) 800-258-4263 (Toll Free) or 910-256-0238
Phone: (International) 910-256-0238
Phone: (UK, Germany, France) 00800-5913-1359 (Toll Free)
Phone: (Europe): +32-2-714-5028

CONFIDENTIAL

The Antiretroviral Pregnancy Registry

Instructions for Completing the REGISTRATION FORM

General Guideline: Date format should always be entered as *DD/MMM/YYYY*

Patient (Log) ID: The Registry assigned Log ID number.

Date patient first seen during this pregnancy: Provide the date first seen in *DD/MMM/YYYY* format.

1. Maternal Information

1.1 Clinical Study: Indicate if the patient is participating in a clinical study by checking "Yes", "No", or "Unknown".

- If no, move to Subsection1.2
- If yes, provide the study protocol number and indicate whether the study was conducted in pregnant women by checking "Yes" or "No"

1.2 Last Menstrual Period (LMP): Provide the start date for the LMP in *DD/MMM/YYYY* format.

1.3 Corrected Estimated Date of Delivery (CEDD): Provide the CEDD based on the 20 week prenatal test, especially if this is the date being used to calculate gestational age for medication exposures and outcome. If a date is entered here, prenatal test name(s) and date(s) must be entered in Section 2.1.

1.4 Patient Age: Provide age of the pregnant woman at time of conception.

1.5 Race: Check the appropriate box for the pregnant woman's race.

2. Prenatal Tests

2.1 Prenatal Test Done: Indicate if a prenatal test was done by checking "Yes", "No", or "Unknown".

- If no, move to Section 3: Clinical Indicators.
- If yes, provide the date in *DD/MMM/YYYY* format, or the gestational age, the prenatal test was performed and the name of the prenatal test (i.e., Ultrasound, Amniocentesis, MSAFP). If "Other", specify the prenatal test performed.

2.2 Evidence of a Structural Defect: Indicate if a structural defect(s) was identified on a prenatal test by checking "Yes", "No" or "Unknown" by each prenatal test done.

- If no, move to Section 3: Clinical Indicators.
- If yes, specify the structural and/or chromosomal defect(s).

3. Clinical Indicators (at the START of pregnancy)

3.1 Indication for ARV (Check all that apply)

3.2 Earliest CD4 + T-cell Categories (in this pregnancy): Check the appropriate range for the counts as they were as close to the beginning of the pregnancy (not applicable should be marked if the patient is not HIV infected).

3.3 Worst Disease Severity Indicator (by history):

- **HIV:** Check the appropriate category for the worst disease severity experienced by the patient at any time since becoming infected (not applicable should be marked if the patient is not HIV infected). Clinical categories A, B and C are as defined by the CDC www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm
  - **Category A:** Consists of one or more of the CDC defined Category A conditions in a person with documented HIV infection. Conditions in Categories B and C must not have occurred.
  - **Category B:** Consists of symptomatic conditions in an HIV-infected person not included in Category C and meeting at least one of the two Category B conditions. For classification purposes, someone previously treated for a Category B condition but who is now asymptomatic should be classified in Category B.
  - **Category C:** Includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.
  - **Category D:** CD4 <200 cells/µL
- **Hepatitis:** Check the appropriate category for the worst disease severity experienced by the patient at any time since becoming infected (not applicable should be marked if the patient does not have hepatitis).

Phone Contact: US/Canada Phone: 800-258-4263 (Toll Free)
UK, Germany, France Phone: 00800-5913-1359 (Toll Free)
International Phone:+32-2-714-5028 (Europe)
Address: Research Park, 1011 Ashes Drive, Wilmington, NC 28405
Internet: www.APRegistry.com

Revised (February 2016)

The Antiretroviral Pregnancy Registry

Instructions for Completing the Antiviral Therapy During Pregnancy Form

- **Med Code:** Indicate the code number from the list provided. If a drug is not listed, provide the name of the drug.
- **Total Daily Dose:** Provide the total daily dose with units (e.g., 80 mg, 2 tabs, 2 mg/kg/hr, etc.).
- **Route:** Provide the code "1" for oral, "2" for IV, and "3" for subcutaneous (sub-Q).
- **Pt taking Meds at Conception?:** "1" if yes at conception, "2" if during pregnancy, "3" if unknown.
- **Date Treatment Began or Gestational Age Course Began:**
  - Provide start date in *DD/MMM/YYYY* format, ***OR***
  - Provide gestational age course began. If gestational age is known, check the calculation source: LMP or Corrected EDD. If CEDD is checked, prenatal test name(s) and date(s) must be entered on page 1 Section 2.1.
- **Date Treatment Stopped or Ongoing:**
  - Provide date or gestation week treatment stopped in *DD/MMM/YYYY* format, ***OR***
  - Check "Ongoing" if treatment continues following outcome of pregnancy.

Please write "unk" or "N/A" on the forms if any information is unknown or not applicable.

The Registry is not designed to monitor all types of events that might occur during pregnancy, labor and delivery, or other neonatal or post-natal events other than defects. If such events occur the provider is encouraged to contact the manufacturer of the individual drug and/or the FDA. FDA can be reached by faxing the information to 800-FDA-0178 or at http://www.fda.gov/Safety/MedWatch/default.htm

Phone Contact:	US/Canada Phone: 800-258-4263 (Toll Free) UK, Germany, France Phone: 00800-5913-1359 (Toll Free) International Phone:+32-2-714-5028 (Europe)
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Internet:	www.APRegistry.com

Revised (February 2016)

ANTIRETROVIRAL PREGNANCY REGISTRY

REGISTRATION FORM

Fax to: +1-800-800-1052 (US, Canada)
+1-910-256-0637 (International) or +32-2-714-5024 (Europe)
0800-5812-1658 (UK, Germany, France)
0800-892-1472 (Brazil)
Email to: SM_APR@INCResearch.com

FOR OFFICE USE ONLY (1)

Registry Patient ID _____ HCP ID _____

Prospective ☐ Retrospective ☐ 100% Provider ☐

Registry date of notification _____ _____ _____ ☐ Phone
DD MMM YYYY

Patient (Log) ID: _____ *Registry assigned ID number or Sponsor MCN*

Country of report origin_____ **State *(U.S. only)***_____

Date patient first seen during this pregnancy or Sponsor date of notification of pregnancy
Date: _____ _____ _____
DD MMM YYYY

1. MATERNAL INFORMATION

1.1 Is the patient enrolled in a clinical study? *(treatment or observational study)* ☐ Yes ☐ No ☐ Unknown

If yes, provide the protocol number _____

Was the clinical study conducted in pregnant women? ☐ Yes ☐ No ☐ Unknown

1.2 Last Menstrual Period _____ _____ _____
DD MMM YYYY

1.3 Corrected EDD _____ _____ _____ *(e.g., by ultrasound)*
DD MMM YYYY

1.4 Patient Age: _____ *(at conception)*

1.5 Race: ☐ White ☐ Black ☐ Hispanic ☐ Asian ☐ Other (specify) _____

2. PRENATAL TESTS

2.1 Was a prenatal test done?

☐ No *(go to section 3)*

☐ Yes *(complete below and question 2.2)*

Date OR Gestational Age when test(s) done:

(✓) test(s)		2.2 Is there evidence of a structural defect from one or more of these prenatal tests?
☐	Ultrasound _____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	Ultrasound _____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	Amniocentesis _____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	Cystic Fibrosis Mutation Analysis_____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	Fetal Echo _____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	First Trimester Screen _____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	MSAFP/serum markers _____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	Nuchal Translucency _____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	Other (specify):_____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	Unknown *(go to section 3)*	

3. CLINICAL INDICATORS (at the ***START*** of pregnancy)

3.1 Indication for ARV *(√all that apply)*:

☐ HIV Infected
☐ HIV Non-Infected
☐ Post-Exposure Prophylaxis (PEP)
☐ Pre-Exposure Prophylaxis (PrEP)
☐ Hepatitis B
☐ Hepatitis C

For additional descriptions of categories refer to the 1993 CDC revised classification system, December 1992 issue of MMWR

3.2 Earliest CD4+ T-cell Categories *(in this pregnancy)*

☐ ≥ 500 cells/μL
☐ 200-499 cells/μL
☐ <200 cells/μL
☐ Not applicable

3.3 Worst Disease Severity Indicator (by history):

HIV

☐ A. Asymptomatic, acute (primary) HIV or PGL (persistent generalized lymphadenopathy)
☐ B. Symptomatic, not (A) or (C) conditions
☐ C. Other AIDS-indicator conditions
☐ D. CD4 <200 cells/μL
☐ E. Not applicable

Hepatitis

☐ A. Compensated liver disease (Pugh score <7)
☐ B. Decompensated liver disease (Pugh score ≥7)
☐ C. Not applicable

Complete applicable information on: ANTIVIRAL THERAPY DURING PREGNANCY Form

HEALTH CARE PROVIDER INFORMATION

Name _____ Specialty _____

Address _____ Phone _____

_____ Fax _____

Alternate Contact _____ Email _____

Provider's Signature _____ Date _____ _____ _____
DD MMM YYYY

ANTIRETROVIRAL PREGNANCY REGISTRY
ANTIVIRAL THERAPY DURING PREGNANCY
(Initiated at registration and completed at follow-up)

FOR OFFICE USE ONLY (2)
Registry ID_____
HCP ID_____
☐ Update

Complete as much of this page as applicable at Registration. A copy of this form will be sent to you in the expected month of delivery for completion.

Patient (Log) ID: _____*The Registry assigned, non-patient identifying patient ID or Sponsor MCN*

4. ANTIVIRAL THERAPY DURING PREGNANCY

4.1. Use the med. codes below for antiviral medication taken during pregnancy. If not coded, ***Specify Medication****.*

1. Abacavir (ZIAGEN®, ABC) – ViiV/GSK
1.1 Abacavir generic – Hetero
1.2 Abacavir generic – Apotex
1.3 Abacavir generic- Mylan
1.4 Abacavir generic- Strides
1.5 Abacavir generic - Aurobindo
1.99 Abacavir (unknown manufacturer)
2. Didanosine (VIDEX®, VIDEX® EC, ddI) – BMS
2.1 Didanosine generic – Teva
2.2 Didanosine generic – Aurobindo
2.3 Didanosine generic – Mylan
2.99 Didanosine (unknown manufacturer)
3. Efavirenz (SUSTIVA®, EFV) – BMS
3.1 Efavirenz (STOCRIN™, EFV) – Merck
3.2 Efavirenz generic – Hetero
3.99 Efavirenz (unknown manufacturer)
4. Lamivudine (EPIVIR®, 3TC) – ViiV/GSK
4.1 Lamivudine generic – Hetero
4.2 Lamivudine+tenofovir df generic – Hetero
4.3 Lamivudine generic – Apotex
4.4 Lamivudine generic – Aurobindo
4.5 Lamivudine generic – Silarx/Lannett
4.6 Lamivudine generic – Lupin
4.7 Lamivudine generic – Mylan
4.99 Lamivudine (unknown manufacturer)
5. Lamivudine+zidovudine (COMBIVIR®, ZDV+3TC) – ViiV/GSK
5.1 Lamivudine+zidovudine generic – Hetero
5.2 Lamivudine+zidovudine generic – Teva
5.3 Lamivudine+zidovudine generic – Aurobindo
5.4 Lamivudine+zidovudine generic – Lupin
5.5 Lamivudine+zidovudine generic – Strides
5.6 Lamivudine+zidovudine generic- Mylan
5.99 Lamivudine+zidovudine (unknown manufacturer)
6. Nelfinavir (VIRACEPT®, NFV) – ViiV
7. Nevirapine (VIRAMUNE®, VIRAMUNE® XR™, NVP) – BI
7.1 Nevirapine generic – Hetero
7.2 Nevirapine generic – Prinston
7.3 Nevirapine generic – Sciegen
7.4 Nevirapine/nevirapine ER generic – Apotex
7.5 Nevirapine/nevirapine ER generic – Aurobindo
7.6 Nevirapine generic – Strides
7.7 Nevirapine ER generic – Sandoz
7.8 Nevirapine generic – Cipla
7.9 Nevirapine ER generic – Alvogen
7.10 Nevirapine generic-Teva
7.11 Nevirapine/nevirapine ER generic – Mylan
7.99 Nevirapine (unknown manufacturer)
8. Ritonavir (NORVIR®, RTV) – Abbvie
8.1 Ritonavir generic – West-Ward
8.99 Ritonavir (unknown manufacturer)
9. Saquinavir (FORTOVASE®, SQV-SGC) – Roche (*no longer manuf.)*
10. Saquinavir mesylate (INVIRASE®, SQV-HGC) – Roche
11. Stavudine (ZERIT®, d4T) – BMS
11.1 Stavudine generic – Mylan
11.2 Stavudine generic – Aurobindo
11.3 Stavudine generic – Cipla
11.4 Stavudine generic – Hetero
11.99 Stavudine generic (unknown manufacturer)
12. Zalcitabine (HIVID®, ddC) – Roche (*no longer manuf.)*
13. Zidovudine (RETROVIR®, ZDV) – ViiV/GSK
13.1 Zidovudine oral generic – Ranbaxy
13.2 Zidovudine oral generic – ViiV/GSK
13.3 Zidovudine oral generic – West-Ward
13.4 Zidovudine oral generic – Aurobindo
13.5 Zidovudine oral generic – Cipla
13.6 Zidovudine oral generic – Mylan
13.7 Zidovudine oral generic – Hetero
13.99 Zidovudine oral (unknown manufacturer)
14. Amprenavir (AGENERASE®, APV) – ViiV/GSK
15. Indinavir (CRIXIVAN®, IDV) – Merck
16. Delavirdine mesylate (RESCRIPTOR®, DLV) – ViiV/GSK
17. Lopinavir+ritonavir (KALETRA®, ALUVIA®, LPV/r) – Abbvie
17.1 Lopinavir+ritonavir generic – Silarx/Lannett
17.99 Lopinavir+ritonavir (unknown manufacturer)
18. Abacavir+lamivudine+zidovudine (TRIZIVIR®, TZV) – ViiV/GSK
18.1 Abacavir+lamivudine+zidovudine generic – Lupin
18.99 Abacavir+lamivudine+zidovudine (unknown manufacturer)
19. Tenofovir disoproxil fumarate (VIREAD®, TDF) – Gilead
19.1 Tenofovir disoproxil fumarate generic – Hetero
19.2 Tenofovir disoproxil fumarate generic – Apotex
19.99 Tenofovir disoproxil fumarate (unknown manufacturer)
20. Adefovir dipivoxil (HEPSERA®, ADV) – Gilead
20.1 Adefovir dipivoxil generic – SigmaPharm
20.99 Adefovir dipivoxil (unknown manufacturer)
21. Enfuvirtide (FUZEON®, T-20) – Roche
22. Atazanavir (REYATAZ®, ATV) – BMS
23. Emtricitabine (EMTRIVA®, FTC) – Gilead
24. Fosamprenavir calcium (LEXIVA®, FOS) – ViiV/GSK
25. Abacavir+lamivudine (EPZICOM®, KIVEXA®, EPZ) – ViiV/GSK
25.1 Abacavir+lamivudine generic – Teva
25.2 Abavavir+lamivudine generic – Dr. Reddy's/Reddy/betapharm
25.99 Abacavir+lamivudine (unknown manufacturer)
26. Tenofovir disoproxil fumarate+emtricitabine (TRUVADA®, TVD) – Gilead
26.1 Tenofovir disoproxil fumarate+emtricitabine generic – Apotex
26.99 Tenofovir disoproxil fumarate+emtricitabine (unknown manufacturer)
27. Entecavir (BARACLUDE®, ETV) – BMS
27.1 Entecavir generic – Teva
27.2 Entecavir generic – Aurobindo
27.3 Entecavir generic – Amneal
27.99 Entecavir (unknown manufacturer)
28. Tipranavir (APTIVUS®, TPV) – BI
29. Efavirenz+tenofovir disoproxil fumarate+emtricitabine (ATRIPLA®, ATR) – Gilead
30. Telbivudine (TYZEKA®, LdT) – Novartis
30.1 Telbivudine (SEBIVO®, LdT) – Novartis
31. Darunavir (PREZISTA®, DRV) – Janssen
31.1 Darunavir generic – Teva
31.99 Darunavir (unknown manufacturer)
32. Raltegravir (ISENTRESS® RAL) – Merck
33. Maraviroc (SELZENTRY®, CELSENTRI®, MVC) – ViiV/GSK
34. Etravirine (INTELENCE®, ETR) – Janssen
35. Rilpivirine (EDURANT®, RPV) – Janssen
36. Rilpivirine+emtricitabine+tenofovir disoproxil fumarate (COMPLERA®, CPA; EVIPLERA®, EPA) – Gilead
37. Elvitegravir+cobicistat+emtricitabine+tenofovir disoproxil fumarate (STRIBILD®, STB) – Gilead
38. Dolutegravir (TIVICAY®, DTG) – ViiV/GSK
39. Elvitegravir (VITEKTA®, EVG) – Gilead
40. Cobicistat (TYBOST®, COBI) – Gilead
41. Abacavir+dolutegravir+lamivudine (TRIUMEQ®, TRI) – ViiV/GSK
42. Darunavir+cobicistat (PREZCOBIX™, PCX) – Janssen
43. Atazanavir+cobicistat (EVOTAZ™, EVO) – BMS
44. Lamivudine+raltegravir (DUTREBIS™, DUT) – Merck
45. Elvitegravir+cobicistat+emtricitabine+tenofovir alafenamide (GENVOYA®, GEN) – Gilead
46. Rilpivirine+emtricitabine+tenofovir alafenamide (ODEFSEY®, ODE) – Gilead
47. Emtricitabine+tenofovir alafenamide (DESCOVY®, DVY) – Gilead
48. Tenofovir alafenamide (VEMLIDY®, VEM) – Gilead

4.2. In the following table, describe each course or change in route for each applicable therapy.

Course	***Med. Code* (1-48) or if no code indicated, please write medication name and indicate if generic**	***Blinded therapy?***	***Total Daily Dose***	***Unit*** *- mg/day - tab. /cap. - mg/kg/hr - mL*	***Route*** *(enter code)* *1 = oral 2 = IV 3 = sub-Q/IM*	***Pt Taking Med. Prior to Conception?*** *1 = Yes 2 = No 3 = Unknown*	***Date Treatment Course Began (DD/MMM/YYYY) OR Gestational Age Course Began (0 weeks = prior to conception)*** If gestational age, calculation source: ☐ *(LMP)* ☐ *(corrected EDD)*	***Date Treatment Stopped (DD/MMM/YYYY), Gestational Week Course stopped OR Ongoing?*** (Note: Ongoing = ongoing following delivery)
		☐						or ☐ ongoing
		☐						or ☐ ongoing
		☐						or ☐ ongoing

Fax to: +1-800-800-1052 (US, Canada) 00800-5812-1658 (UK, Germany, France)
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0800-892-1472 (Brazil)
Email to: SM_APR@INCResearch.com

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The Antiretroviral Pregnancy Registry

Instructions for completing the FOLLOW-UP FORMS

General Guideline: Date format should always be entered as *DD/MMM/YYYY*

Patient (Log) ID: The Registry assigned Log ID number.

Please indicate **UNK** or **N/A** for any data points where the information is unknown or not applicable.

1. Maternal Information

Clinical Study: Indicate if the patient is participating in a clinical study by checking "Yes", "No", or "Unknown".

- If no, move to Subsection 2 and do not check a response for "Was the clinical study conducted in pregnant women?"
- If yes, provide the study protocol number and check "Yes," "No" or "Unknown" for "Was the clinical study conducted in pregnant women?"

2. Fetal Outcome

If there are multiple outcomes (e.g., twins, triplets) complete a Follow-up Form for each baby.

2. 1 **Birth Defect Noted:** *Was a structural birth defect noted?* Check "Yes", "No", or "Unknown".

- If no, move to section 2.2: Outcome.
- If yes, list each specific defect in Section 3: Birth Defects.
- If unknown, the case will not be included in the Registry analysis.

2.2 **Outcome:** Check the applicable outcome: "Live Infant", "Spontaneous abortion*", "Induced abortion", or "Stillbirth*".

*(A **spontaneous abortion** is defined by the Registry as a fetal loss occurring earlier than 20 weeks. A **stillbirth** is a fetal death occurring greater than or equal to 20 weeks, or if the fetus weighs 500 grams or more.)

- If either Spontaneous or Induced abortion or Stillbirth is checked, list the factors that may have had an impact on the fetal loss in Section 4: Fetal Loss.

2.3 **Date of Outcome:** Provide the outcome date of the live infant or date the fetal loss occurred in *DD/MMM/YYYY* format.

2.4 **Gender:** Check the appropriate gender: "Male" or "Female".

2.5 **Length:** Provide the length of the infant at outcome and the appropriate metric used ("centimeter" or "inch").

2.6 **Gestational Age:** Provide the gestational age at outcome.

2.7 **Birth Weight:** Provide the birth weight of the infant at outcome and the appropriate metric used (grams or pounds/ounces).

2.8 **Head Circumference:** Provide the infant's head circumference at outcome and the appropriate metric used ("centimeter" or "inch").

3. Birth Defects

- List the structural birth defect(s)
- Indicate if the defect(s), was attributed to the antiviral therapy by recording:
  - 1 for Yes
  - 2 for No
  - 3 for Unknown
- Indicate other factors that might have contributed to this outcome by recording:
  - 1 for Maternal Age
  - 2 for Unknown
  - 3 for Other, specify. *If other, please specify the contributing factor.*

4. Fetal Loss (Stillbirth, Spontaneous or Induced Abortion)

Provide factors other than the birth defects that may have had an impact on the fetal loss.

****ANTIVIRAL THERAPY DURING PREGNANCY FORM**

Update the "Antiviral Therapy During Pregnancy" data form provided at Registration once outcome is obtained.

The Registry is not designed to monitor all types of events that might occur during pregnancy, labor and delivery, or other neonatal or post-natal events other than defects. If such events occur the provider is encouraged to contact the manufacturer of the individual drug and/or FDA. FDA can be reached by faxing the information to 800-FDA-0178 or at http://www.fda.gov/medwatch/.

Phone Contact:	US/Canada Phone: 800-258-4263 (Toll Free) UK, Germany, France Phone: 00800-5913-1359 (Toll Free) International Phone: +32-2-714-5028 (Europe)
Address:	Research Park, 1011 Ashes Drive, Wilmington, NC 28405
Internet:	www.APRegistry.com

Revised (February 2016)

ANTIRETROVIRAL PREGNANCY REGISTRY FOLLOW-UP FORM

Fax to: 800-800-1052 (US, Canada)
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0800-892-1472 (Brazil)
Email to: SM_APR@INCResearch.com

FOR OFFICE USE ONLY (3)
Registry Patient ID _____ HCP ID _____
Date Case Closed _____ _____ _____ ☐ Phone
DD MMM YYYY

Patient (Log) ID: _____ ***The Registry assigned, non-patient identifying patient ID number or Sponsor Manufacturer Control Number (MCN)***

1. MATERNAL INFORMATION

1.1 Is the patient enrolled in a clinical study? *(treatment or observational study)* ☐ Yes ☐ No ☐ Unknown

If yes, provide the protocol number _____

Was the clinical study conducted in pregnant women? ☐ Yes ☐ No ☐ Unknown

2. FETAL OUTCOME

2.1 Birth Defect Noted? ☐ Yes *(If yes, list on page 4)* ☐ No ☐ Unknown

2.2 Outcome:
☐ Live Infant
☐ Abortion, Spontaneous
☐ Abortion, Induced
☐ Stillbirth

FOR REGISTRY USE ONLY
Baby ID: _____

If a fetal loss, go to page 4: Birth Defects (section 3) and/or other factors that may have contributed to the fetal loss (section 4)

2.3 Date of Outcome: _____ _____ _____ (DD MMM YYYY)

2.4 Gender: ☐ Male ☐ Female

2.5 Length: _____ ☐ cm. ☐ in.

2.6 Gestational Age: _____ weeks

2.7 Birth Weight: _____ ☐ grams ☐ lbs/oz.

2.8 Head Circumference: _____ ☐ cm. ☐ in.

NOTES:

- **If DEFECT or FETAL LOSS, go to page 4**
- **Please update the ANTIVIRAL THERAPY DURING PREGNANCY FORM when reporting pregnancy outcome. The form includes the initial information provided to the Registry at registration.**

HEALTH CARE PROVIDER INFORMATION

Name _____ Specialty _____
Address _____ Phone _____
_____ Fax _____
_____ Email _____
Alternate Contact _____

Provider's Signature _____ Date _____ _____ _____ (DD MMM YYYY)

ANTIRETROVIRAL PREGNANCY REGISTRY FOLLOW-UP FORM

FOR OFFICE USE ONLY (4)

Registry Patient ID _____

Patient (Log) ID: _____ ***Registry assigned ID number or Sponsor MCN***

Complete this page ONLY if there is a <u>birth defect</u> or information on a <u>fetal loss</u> (stillbirth, spontaneous or induced abortion)

3. BIRTH DEFECTS – *List birth defects below.*

	Birth defect *(list birth defect)*	***Was the defect attributed to antiviral therapy?*** *1 = Yes* *2 = No* *3 = Unknown*	***Other factors that might contribute to this outcome*** *1 = Maternal age* *2 = Unknown* *3 = Other, specify*
1.			
2.			
3.			
4.			
5.			
6.			

4. FETAL LOSS (STILLBIRTH, SPONTANEOUS OR INDUCED ABORTION)
List factors, other than birth defects, that may have had an impact on the fetal loss.

1.	
2.	
3.	
4.	

Please <u>update</u> the ANTIVIRAL THERAPY DURING PREGNANCY FORM when reporting pregnancy outcome. The form includes the initial information provided to the Registry at registration.

Thank you for your participation in the Antiretroviral Pregnancy Registry

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