THE ANTIRETROVIRAL PREGNANCY REGISTRY

Interim Report

1 JANUARY 1989 THROUGH 31 JANUARY 2013

(Issued: June 2013)
(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 The data contained in this report will become out-of-date within 6 months of the report's issue date.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

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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 2013.

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 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.

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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, efavirenz, elvitegravir, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, stavudine, telbivudine, 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:

Mailing Address:	***Telephone:***	***FAX:***
Antiretroviral Pregnancy Registry Research Park 1011 Ashes Drive Wilmington, NC 28405	+1-800-258-4263 (toll free US, Canada) +1-910-256-0238 (International) or +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) or +32-2-714-5024 (Europe) (00800) 5812 1658 (toll free UK, Germany, France) 888-259-5618 (Brazil)

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.

Alvarez-McLeod, Africa P MD, MPH
Arencibia, Damai RN
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Bronaugh, Madeline RN, MSN
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Weis, Nina MD
Wilkes, Helen

Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 – 31 January 2013*

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 155.) 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 enrolls 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.

Data Summary

Primary Registry Analysis (Prospective Reports): In review of the data through 31 January 2013, 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 2.9 (95% confidence interval (CI): 2.5 - 3.4, i.e., 195 outcomes with defects of 6666 live births (Table 7). The prevalence of defects is not significantly different from the prevalence of

*Drugs included: abacavir (ZIAGEN®, ABC), abacavir/lamivudine (EPZICOM®, EPZ), abacavir/lamivudine/zidovudine (TRIZIVIR®, TZV), adefovir dipivoxil (HEPSERA®, ADV), amprenavir (AGENERASE®, APV), atazanavir sulfate (REYATAZ®, ATV), darunavir (PREZISTA®, DRV), delavirdine mesylate (RESCRIPTOR®, DLV), didanosine (VIDEX®, VIDEX® EC, ddI), efavirenz (SUSTIVA®, STOCRIN®, EFV), efavirenz/emtricitabine/ tenofovir DF (ATRIPLA® ATR), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (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/zidovudine (COMBIVIR®, ZDV+3TC), lopinavir/ritonavir (KALETRA®, ALUVIA®, LPV/r), maraviroc (SELZENTRY®, CELSENTRI®, MVC), nelfinavir (VIRACEPT®, NFV), nevirapine (VIRAMUNE®, VIRAMUNE® XR™, NVP), raltegravir (ISENTRESS®, RAL), rilpivirine (EDURANT®, RPV), rilpivirine/emtricibitine/tenofovirDF (COMPLERA®, CPA; EVIPLERA®, EPA), ritonavir (NORVIR®, RTV), saquinavir (FORTOVASE®, SQV-SGC), saquinavir mesylate (INVIRASE®, SQV-HGC), stavudine (ZERIT®, d4T), telbivudine (SEBIVO®, TYZEKA®, LdT), tenofovir DF (VIREAD®, TDF), tenofovir DF/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.

defects among women with an initial exposure during the second and/or third trimester (2.8 per 100 live births) (prevalence ratio: 1.04, 95% CI: 0.86, 1.25).

Measured against 15062 live births with exposure at any time during pregnancy, there were 434 outcomes with birth defects identified, a prevalence of 2.9 birth defects per 100 live births (95% CI: 2.6 - 3.2). This proportion is not significantly different than the CDC's birth defects surveillance system (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% confidence interval: 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 confidence intervals (CIs). The CIs reported around MACDP rates in this report were calculated by the Registry. Additionally, ascertainment from CDC's active surveillance system does not rely on voluntary reports.

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 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 population based Metropolitan Atlanta Congenital Defects Program (MACDP) (lower bound of the confidence interval for didanosine (3.0%) and nelfinavir (2.9%) is slightly above the higher bound (2.76%) for the comparator MACDP rate). 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 abacavir, atazanavir, didanosine, efavirenz, indinavir, 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 emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, tenofovir, 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 18 among the 735

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.

First Trimester Exposure

Regimen	Defects/Live Births	Prevalence (95% Confidence Interval)
Lamivudine	135/4273	3.2% (2.6%, 3.7%)
Zidovudine	128/3932	3.3% (2.7%, 3.9%)
Ritonavir	47/2096	2.2% (1.6%, 3.0%)
Tenofovir	42/1800	2.3% (1.7%, 3.1%)
Emtricitabine	30/1230	2.4% (1.6%, 3.5%)
Nelfinavir	47/1210	3.9% (2.9%, 5.1%)
Lopinavir	24/1049	2.3% (1.5%, 3.4%)
Nevirapine	31/1049	3.0% (2.0%, 4.2%)
Abacavir	27/880	3.1% (2.0%, 4.4%)
Atazanavir sulfate	17/813	2.1% (1.2%, 3.3%)
Stavudine	21/803	2.6% (1.6%, 4.0%)
Efavirenz	18/735	2.4% (1.4%, 3.9%)
Didanosine	20/413	4.8% (3.0%, 7.4%)
Indinavir	7/288	2.4% (1.0%, 5.0%)

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, 13 infants with defects were identified among 279 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 4.7 (95% CI: 2.5 - 7.8) (Table 12). The number of defects identified with an initial exposure in the second or third trimester is 22 among 1405 live births, and the prevalence of birth defects per 100 live births is 1.6 (95% CI: 1.0 - 2.4). 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 primary anomaly accounting for the observed difference from the primary analysis is minor and self-limiting cardiovascular defects detected on echocardiogram. To date, we have received 41 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. The Registry notes modest but statistically significant elevations of overall defect rates with didanosine and nelfinavir compared with its population based comparator, the MACDP. 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. Health care providers are encouraged to report eligible patients to the Registry at 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 this paragraph verbatim. Editors are reminded of this requirement and encouraged to permit the paragraph to be exempted from any word count restrictions.

SUMMARY OF CHANGES: JULY 2012 TO JANUARY 2013

Primary Prospective Analysis	***July 2012***	***January 2013***
Pregnancies Reported	17,523	17,978
Pending	521	406
Lost to follow-up	1604	1695
With follow-up data	15,398	15,877
Earliest Exposure		
1st trimester exposures	7186	7493
2nd trimester	6111	6246
3rd trimester	2099	2136
Unknown (defects only)	2	2
Outcomes	15,672	16,159
Defects/Live births		
1st trimester	190/6388 3.0% (95% CI: 2.6% - 3.4%)	195/6666 2.9% (95% CI: 2.5% - 3.4%)
2nd/3rd trimester	230/8222 2.8% (95% CI: 2.4% - 3.2%)	237/8394 2.8% (95% CI: 2.5% - 3.2%)
Any trimester	422/14,612 2.9 % (95% CI: 2.6% - 3.2%)	434/15,062 2.9 % (95% CI: 2.6% - 3.2%)
1st to 2nd/3rdtrimester prevalence ratio	1.06 (95% CI: 0.88, 1.28)	1.04 (95% CI: 0.86, 1.25)
Lamivudine	133/4185 3.2% (95% CI: 2.7% - 3.8%)	135/4273 3.2% (2.7% - 3.7%)
Zidovudine	127/3864 3.3% (95% CI: 2.7% - 3.9%)	128/3932 3.3% (2.7% - 3.9%)
Ritonavir	45/1923 2.3% (95% CI: 1.7% - 3.1%)	47/2096 2.2% (1.6% - 3.0%)
Tenofovir	39/1612 2.4% (95% CI: 1.7% - 3.3%)	42/1800 2.3% (1.7% - 3.1%)
Emtricitabine	27/1068 2.5% (95% CI: 1.7% - 3.7%)	30/1230 2.4% (1.6% - 3.5%)
Nelfinavir	47/1207 3.9% (95% CI: 2.9% - 5.2%)	47/1210 3.9% (2.9% - 5.1%)
Nevirapine	31/1036 3.0% (95% CI: 2.0% - 4.2%)	31/1049 3.0% (2.0% - 4.2%)
Lopinavir	23/969 2.4% (95% CI: 1.5% - 3.5%)	24/1049 2.3% (1.5% - 3.4%)
Abacavir	26/848 3.1% (95% CI: 2.0% - 4.5%)	27/880 3.1% (2.0% - 4.4%)
Atazanavir	16/746 2.1% (95% CI: 1.2% - 3.5%)	17/813 2.1% (1.2% - 3.3%)
Stavudine	21/802 2.6% (95% CI: 1.6% - 4.0%)	21/803 2.6% (1.6% - 4.0%)
Efavirenz	18/702 2.6% (95% CI: 1.5% - 4.0%)	18/735 2.4% (1.4% - 3.9%)
Didanosine	20/413 4.8% (95% CI: 3.0% - 7.4%)	20/413 4.8% (3.0% - 7.4%)
Indinavir	7/287 2.4% (95% CI: 1.0% - 5.0%)	7/288 2.4% (1.0% - 5.0%)
Clinical Studies in Pregnancy	***July 2012***	***January 2013***
1st trimester	13/277 4.7% (95% CI: 2.5% - 7.9%)	13/279 4.7% (95% CI: 2.5% - 7.8%)
2nd/3rd trimester	22/1355 1.6% (95% CI: 1.0% - 2.4%)	22/1405 1.6% (95% CI: 1.0% - 2.4%)
1st to 2nd/3rdtrimester prevalence ratio	2.89 (95% CI: 1.47, 5.67)	2.98 (95% CI: 1.52, 5.84)

Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 – 31 January 2013

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 (EPZICOM®, EPZ), abacavir/lamivudine/zidovudine combination (TRIZIVIR®, TZV), adefovir dipivoxil (HEPSERA®, ADV)*, amprenavir (AGENERASE®, APV), atazanavir sulfate (REYATAZ®, ATV), darunavir (PREZISTA®, DRV), delavirdine mesylate (RESCRIPTOR®, DLV), didanosine (VIDEX®, VIDEX® EC, ddI), efavirenz (SUSTIVA®, STOCRIN®, EFV), efavirenz/emtricitabine/tenofovir disoproxil fumarate combination (ATRIPLA, ATR®), 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/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), rilipivirine/emtricitabine/tenofovir disproxil 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 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 155). 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 2013.

* 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, Apotex Inc, Aurobindo Pharma Ltd, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Gilead Sciences Inc, HEC Pharm, Hetero Labs ltd, Ipca Laboratories ltd, Janssen R&D Ireland, Merck & Co. Inc, Mylan Laboratories, Novartis Pharmaceuticals, Pfizer Inc, Prinston, Ranbaxy Inc, Roche, Sciegen Pharmaceuticals Inc, Strides Arcolab Ltd, Teva Pharmaceuticals, and ViiV Healthcare (represented by GlaxoSmithKline). 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. Atazanavir, darunavir, didanosine, elvitegravir/cobicistat, emtricitabine, enfuvirtide, etravirine, maraviroc, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, telbivudine, and tenofovir disoproxil fumarate have an assigned FDA Pregnancy Category B (no evidence of risk in humans) status. Abacavir, adefovir dipivoxil, amprenavir, delavirdine mesylate, entecavir, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, raltegravir, stavudine, tipranavir, zalcitabine, and zidovudine have an assigned FDA Pregnancy Category C (risk cannot be ruled out) status. Efavirenz has been assigned FDA Pregnancy Category D (positive evidence of risk). (See glossary for a more complete description of the FDA Pregnancy Categories and 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, darunavir, delavirdine mesylate, didanosine, efavirenz, elvitegravir/cobicistat, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, stavudine, telbivudine, 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 enrolls 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.

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) (7) and, beginning with the July 2010 Interim Report, are data on 995 exposed pregnancies with outcomes from the NISDI Perinatal Study (8). Also included in the primary analysis are 72 cases from a prospective study in Botswana. The rationale for these inclusions are described on pages 26 and 27, respectively.

REGISTRY (PROSPECTIVE) CASES – PRIMARY ANALYSIS

Through 31 January 2013 there were 17978 prospective cases reported to the Registry (Table 1). There were 406 cases pending the outcome of pregnancy and 1695 lost to follow-up. Thus, there were 15877 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 67 countries. Reports are predominantly from the United States and its territories (78.0%). Reports from countries outside the US comprising ≥0.1% of enrollments include: Brazil (4.4%), the United Kingdom (3.7%), Uganda (3.2%), Argentina (2.4%), South Africa (1.5%), France (1.1%), Botswana (0.5%), Germany (0.5%), Kenya (0.5%), China (0.4%), Zimbabwe (0.4%), Canada (0.3%), Australia (0.2%), Belgium (0.2%), Denmark (0.2%), Ivory Coast – West Africa (0.2%), Japan (0.2%), Scotland (0.2%), Spain (0.2%), Sweden (0.2%), Thailand (0.2%), India (0.1%), Ireland (0.1%), Italy (0.1%), Malaysia (0.1%), , Peru (0.1%), Portugal (0.1%), Russia (0.1%), Switzerland (0.1%), and The Netherlands (0.1%). Countries that have contributed <0.1% of enrollments include Austria, Burkina Faso, Cameroon, Chile, Colombia, Costa Rica, Dominican Republic, Ethiopia, Finland, Ghana, Greece, Guatemala, Hong Kong, Hungary, Indonesia, Israel, Korea, Malawi, Mexico, New Zealand, Nigeria, Norway, Panama, Philippines, Poland, Romania, Saudia Arabia, Senegal, Singapore, Taiwan, Tanzania, Turkey, United Arab Emirates, Uruguay, and Zambia.

Antiretroviral Exposure

Of the 15877 evaluable prospective reports, 7493 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 15877 pregnancies reported, there were 16159 outcomes of pregnancy including 278 multiple births: 15062 live births, 444 spontaneous abortions, 203 stillbirths, and 450 induced abortions. Of the 15062 live births, 6666 had a maternal exposure to antiretroviral therapy during the first trimester. It should be noted that there were 1526 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 2013

	Overall
Pregnancies Enrolled	17978
Pending Cases [1]	406 (2.3%)
Cases Lost to Follow-up [2]	1695 (9.4%)
Reports Used in Analysis	15877 (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 2013

	Primary Analysis	Lost to Follow-up
Pregnancies Enrolled	15877	1695
Age (years)		
N	15691	1376
Median (Interquartile Range)	28.0 (9.0)	28.0 (8.0)
Min - Max	13 - 55	15 - 47
Missing	186	319
CD4+ T-cell Categories at Start of Pregnancy		
≥ 500 µL	4573 (28.8%)	302 (17.8%)
200-499 µL	6671 (42.0%)	425 (25.1%)
<200 µL	2418 (15.2%)	148 (8.7%)
Unknown	457 (2.9%)	335 (19.8%)
N/A	297 (1.9%)	133 (7.8%)
Missing	1461 (9.2%)	352 (20.8%)
Clinical Categories at Start of Pregnancy		
HIV Infected [1]		
A. Asymptomatic, acute(primary) HIV or PGL	11346 (71.5%)	682 (40.2%)
B. Symptomatic, not (A) or (C) conditions	1194 (7.5%)	60 (3.5%)
C. AIDS-indicator conditions	2061 (13.0%)	129 (7.6%)
HIV Uninfected [2]		
HIV prophylaxis [3]	187 (1.2%)	80 (4.7%)
Hepatitis B mono-infected	233 (1.5%)	129 (7.6%)
Unknown	383 (2.4%)	282 (16.6%)
Missing	473 (3.0%)	335 (19.8%)

[1] Includes 163 patients co-infected with HIV and Hepatitis B.
[2] Where antiretroviral drugs have been used for therapy.
[3] Includes both pre- and post-exposure prophylaxis.
Note: The Registry started systematically collecting data on Hepatitis B in January 2003.

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 2013

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies in Primary Analysis	7493	6246	2136	15877
PI	98	24	4	127
NRTI	1413	1686	698	3797
nnRTI	46	3	2	51
NtRTI	197	7	29	233
InSTI	3	2	0	5
PI/NRTI	2283	3158	910	6351
PI/nnRTI	17	1	0	18
PI/NtRTI	10	1	0	11
PI/InSTI	10	0	0	10
NRTI/nnRTI	1164	780	314	2259
NRTI/NtRTI	367	33	21	421
NRTI/InSTI	9	5	2	16
PI/NRTI/nnRTI	240	85	34	359
PI/NRTI/NtRTI	1070	364	88	1522
PI/NRTI/EI	6	0	0	6
PI/NRTI/InSTI	14	0	3	17
PI/nnRTI/NtRTI	5	0	0	5
PI/nnRTI/InSTI	7	3	0	10
NRTI/nnRTI/NtRTI	250	45	12	307
NRTI/NtRTI/InSTI	37	17	6	60
PI/NRTI/nnRTI/NtRTI	165	11	7	183
PI/NRTI/NtRTI/EI	10	1	0	11
PI/NRTI/NtRTI/InSTI	32	10	4	46
NRTI/nnRTI/NtRTI/InSTI	6	2	0	8
PI/NRTI/nnRTI/NtRTI/InSTI	5	1	1	7
PI/NRTI/NtRTI/EI/InSTI	5	0	0	5
Other Combination	24	7	1	32

[1] PI=protease inhibitor, which includes amprenavir, atazanavir, cobicistat, 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, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes elvitegravir, and raltegravir.
[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 7628 birth outcomes with a 1st trimester exposure to an antiretroviral drug, there were 195 reports of defects (183 defects in live births, 5 in stillbirths, and 7 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 infants or fetuses of at least 20 weeks gestational age. This definition is consistent with, but not restricted to the CDC population-based surveillance system definition. The CDC system includes conditional defects only in the presence of a major defect. (See *Classification of Outcomes, page 158.*) 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 (8). See Appendix F for further description of the system.

Of the 16159 pregnancy outcomes, 8529 were in the combined second and/or third trimester exposure group, with 237 reported birth defects (Table 4). This includes 2392 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 110 defects of 4070 live births; for the NRTI + NNRTI group, 33 defects of 1090 births; for the PI + NRTI + NNRTI group, 6 defect of births and in the other combination groups of 650 live births there were 61 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 includes two comparisons. First: rates of defects among first trimester exposed pregnancies are compared with rates among pregnancies with the same exposures beginning only in the second or third trimester. Second: rates of defects are compared with rates among two comparator populations, the Metropolitan Atlanta Congenital Defects Program (MACDP) and the State of Texas Birth Defects Registry (Texas BDR). 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 Texas BDR are active population-based surveillance systems. The MACDP covers all births in 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 Texas BDR monitors all births to women who are residents of the state of Texas at the time of delivery including approximately 400,000 live births annually (10). 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 Metropolitan Atlanta Congenital Defects Program (MACDP) (lower bound of the confidence interval for didanosine (3.0%) 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 abacavir, atazanavir, didanosine, efavirenz, indinavir, 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 emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, tenofovir, 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 Texas BDR.

To date two cases of micropenis with relevant first trimester exposure have been reported. The relationship between micropenis and hypospadias is unclear. No additional cases of hypospadias were reported in this period. 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 18/735 2.4% (1.4%, 3.9%) among the 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.

Table 6 lists the frequencies of defects reported by organ system for prospectively reported first trimester antiretroviral exposures in combination or single treatment regimen. As mentioned previously, the organ system classifications have been redefined to better categorize the defects to be consistent with the CDC's MACDP and the Texas BDR classifications and to increase the potential to identify a possible pattern or signal (9). 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 2013

	With Birth Defects[3] : Without Birth Defects[4]				
	Live Births	Spontaneous Losses	Still-births	Induced Abortions	Overall
Number of Outcomes [5]	411 : 14651	0 : 444	12 : 191	11 : 439	16159
Earliest Exposure [6]					
First Trimester	183 : 6483	0 : 417	5 : 101	7 : 432	7628
Second/Third Trimester	226 : 8168	0 : 27	7 : 90	4 : 7	8529
First Trimester					
PI	2 : 83	0 : 6	0 : 0	0 : 8	99
NRTI	39 : 1215	0 : 41	1 : 14	2 : 123	1435
nnRTI	0 : 38	0 : 2	0 : 0	0 : 6	46
NtRTI	2 : 145	0 : 28	0 : 0	0 : 23	198
InSTI	0 : 2	0 : 0	0 : 0	0 : 1	3
PI/NRTI	62 : 2067	0 : 76	4 : 25	1 : 90	2325
PI/nnRTI	0 : 8	0 : 3	0 : 1	0 : 5	17
PI/NtRTI	0 : 8	0 : 0	0 : 2	0 : 1	11
PI/EI	0 : 3	0 : 0	0 : 0	0 : 0	3
PI/InSTI	1 : 7	0 : 1	0 : 0	0 : 1	10
NRTI/nnRTI	29 : 1013	0 : 71	0 : 20	0 : 54	1187
NRTI/NtRTI	8 : 232	0 : 65	0 : 18	0 : 49	372
NRTI/InSTI	1 : 7	0 : 0	0 : 0	0 : 1	9
nnRTI/NtRTI	0 : 1	0 : 0	0 : 1	0 : 0	2
nnRTI/InSTI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/NRTI/nnRTI	10 : 201	0 : 18	0 : 2	1 : 8	240
PI/NRTI/NtRTI	22 : 973	0 : 61	0 : 9	1 : 36	1102
PI/NRTI/EI	0 : 4	0 : 1	0 : 0	0 : 1	6
PI/NRTI/InSTI	0 : 11	0 : 0	0 : 1	0 : 2	14
PI/nnRTI/NtRTI	1 : 2	0 : 0	0 : 1	0 : 1	5
PI/nnRTI/EI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/nnRTI/InSTI	0 : 6	0 : 1	0 : 1	0 : 0	8
PI/NtRTI/EI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/NtRTI/InSTI	0 : 3	0 : 0	0 : 0	0 : 0	3
PI/EI/InSTI	0 : 3	0 : 0	0 : 0	0 : 0	3
NRTI/nnRTI/NtRTI	5 : 212	0 : 22	0 : 5	1 : 9	254
NRTI/NtRTI/EI	0 : 1	0 : 0	0 : 0	0 : 0	1
NRTI/NtRTI/InSTI	1 : 31	0 : 2	0 : 0	0 : 3	37
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 : 148	0 : 13	0 : 1	1 : 4	167
PI/NRTI/nnRTI/InSTI	0 : 2	0 : 0	0 : 0	0 : 0	2
PI/NRTI/NtRTI/EI	0 : 9	0 : 0	0 : 0	0 : 1	10
PI/NRTI/NtRTI/InSTI	0 : 24	0 : 4	0 : 0	0 : 4	32
PI/NRTI/EI/InSTI	0 : 0	0 : 0	0 : 0	0 : 1	1
PI/nnRTI/NtRTI/EI	0 : 1	0 : 1	0 : 0	0 : 0	2
NRTI/nnRTI/NtRTI/EI	0 : 1	0 : 0	0 : 0	0 : 0	1
NRTI/nnRTI/NtRTI/InSTI	0 : 6	0 : 1	0 : 0	0 : 0	7
NRTI/NtRTI/EI/InSTI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/NRTI/nnRTI/NtRTI/InSTI	0 : 5	0 : 0	0 : 0	0 : 0	5
PI/NRTI/NtRTI/EI/InSTI	0 : 5	0 : 0	0 : 0	0 : 0	5

[1] PI=protease inhibitor, which includes amprenavir, atazanavir, cobicistat, 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, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes elvitegravir, and raltegravir.
[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 278 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 2013
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)
Proportion of defects reported with an exposure to any ART [3]	195/6666		237/8394	
Proportion of defects reported with an exposure to: [3,4]				
Any PI containing regimen	106/3673		156/5332	
Any Amprenavir regimen	1/28		0/12	
Any Atazanavir sulfate regimen	17/813	2.1% (1.2%, 3.3%)	11/416	2.6% (1.3%, 4.7%)
Any Darunavir regimen	4/182		1/130	
Any Fosamprenavir calcium regimen	2/97		2/35	
Any Indinavir regimen	7/288	2.4% (1.0%, 5.0%)	3/163	1.8% (0.4%, 5.3%)
Any Lopinavir regimen	24/1049	2.3% (1.5%, 3.4%)	67/2286	2.9% (2.3%, 3.7%)
Any Nelfinavir regimen	47/1210	3.9% (2.9%, 5.1%)	86/2723	3.2% (2.5%, 3.9%)
Any Ritonavir regimen	47/2096	2.2% (1.6%, 3.0%)	81/2813	2.9% (2.3%, 3.6%)
Any Saquinavir regimen	7/181		9/221	
Any Tipranavir regimen	0/4		0/1	
Any NRTI containing regimen	189/6346		240/8435	
Any Abacavir regimen	27/880	3.1% (2.0%, 4.4%)	32/1168	2.7% (1.9%, 3.9%)
Any Didanosine regimen	20/413	4.8% (3.0%, 7.4%)	20/460	4.3% (2.7%, 6.6%)
Any Emtricitabine regimen	30/1230	2.4% (1.6%, 3.5%)	14/607	2.3% (1.3%, 3.8%)
Any Entecavir regimen	1/50		0/2	
Any Lamivudine regimen	135/4273	3.2% (2.6%, 3.7%)	198/6989	2.8% (2.4%, 3.2%)
Any Stavudine regimen	21/803	2.6% (1.6%, 4.0%)	6/194	3.1% (1.1%, 6.6%)
Any Telbivudine regimen [5]	0/10		0/14	
Any Zalcitabine regimen	2/40		0/12	
Any Zidovudine regimen	128/3932	3.3% (2.7%, 3.9%)	250/8919	2.8% (2.5%, 3.2%)
Any nnRTI containing regimen	48/1692		51/1626	
Any Delavirdine regimen	0/11		0/3	
Any Efavirenz regimen [6]	18/735	2.4% (1.4%, 3.9%)	3/149	2.0% (0.4%, 5.8%)
Any Etravirine regimen	0/38		0/32	
Any Nevirapine regimen	31/1049	3.0% (2.0%, 4.2%)	49/1499	3.3% (2.4%, 4.3%)
Any Rilpivirine regimen	0/6		0/7	
Any NtRTI containing regimen	42/1848		20/891	
Any Adefovir dipivoxil regimen [5]	0/48		0/0	
Any Tenofovir regimen	42/1800	2.3% (1.7%, 3.1%)	20/894	2.2% (1.4%, 3.4%)
Any EI containing regimen	0/32		0/20	
Any Enfuvirtide regimen	0/20		0/16	
Any Maraviroc regimen	0/13		0/4	
Any InSTI containing regimen	3/119		6/109	
Any Raltegravir regimen	3/119		6/109	

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[2] Prevalence and 95% confidence intervals are reported for first trimester exposures to drugs that have a denominator of 200 or greater.
[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 75 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 eighteen 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 and 17) congenital hydronephrosis and variations of vesicoureteral reflux and 18) 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 2013

	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]	Overall First Tri-mester Exposure	Earliest ART Exposure in Second and/or Third Trimester
Pregnancies Identified	3993	7083	1915	2170	37	141	7493	8382
Number of Pregnancies with Multiple Gestations	79	130	30	46	0	2	134	144
Number of Outcomes [2]	4072	7214	1946	2216	37	143	7628	8529
Number of Live Births	3673	6346	1692	1848	32	119	6666	8394
Number of Outcomes with Defects [1,2]	106	189	48	42	0	3	195	237
CNS	8	13	3	3	0	0	13	22
Eye, ear, face and neck	11	21	4	4	0	2	23	31
Cleft lip and/or palate	5	9	1	3	0	1	9	15
Conotruncal heart defects	5	6	0	2	0	0	6	8
Obstructive heart defects - right sided	4	6	4	1	0	0	7	13
Obstructive heart defects - left sided	2	3	1	0	0	0	3	5
Heart - other defects	17	29	9	1	0	0	29	57
Other circulatory system	7	13	4	4	0	0	13	13
Respiratory system	0	1	0	0	0	0	1	1
Upper gastrointestinal system	1	3	0	0	0	0	3	2
Lower gastrointestinal system	6	6	0	0	0	1	8	6
Female genitalia	1	3	0	1	0	0	3	1
Male genitalia	13	22	1	2	0	0	24	11
Renal and urinary system	14	23	6	8	0	0	23	19
Limb reduction/addition defects	16	25	5	11	0	0	26	39
Other musculoskeletal defects	16	44	15	8	0	1	45	57
Skin and skin derivatives	4	6	3	1	0	0	6	10
Chromosome anomaly	11	14	4	4	0	1	16	22
Other organs and organ systems	8	10	3	2	0	1	11	8
Specified syndromes/sequences/associations	10	16	2	5	0	1	16	9

[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, cobicistat, 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, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes raltegravir.
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 195 outcomes with defects among 6666 live births or 2.9% (95% CI: 2.5 - 3.4). Measured against 15062 live births with exposure at any time during pregnancy, there were 434 outcomes with birth defects, a prevalence of 2.9 birth defects per 100 live births (95% CI: 2.6 - 3.2). This proportion is not substantially different than the CDC's population-based birth defects surveillance system (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 confidence intervals (CIs). The CIs reported around MACDP rates in this report were calculated by the Registry. A second population comparator, the Texas Birth Defects Registry, reports an overall prevalence of birth defects of 4.17% (95% CI 4.15, 4.19) for deliveries during 2000 through 2009 among Texas residents (10). 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(2.9 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: 1.04, 95% CI: 0.86, 1.25).

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 2013

	Overall
Number of Live Births	15062
Number of Outcomes with at Least One Defect [1, 2]	434 (2.9%)
95% Confidence Intervals for Prevalence of Birth Defects for Exposures in:	
First Trimester	195/6666 (2.9%) 2.5% - 3.4%
Second/Third Trimester	237/8394 (2.8%) 2.5% - 3.2%
Any Trimester	434/15062 (2.9%) 2.6% - 3.2%
Risk of Defects for First Trimester Exposures Relative to Second/Third Trimester Exposures	1.04 (0.86, 1.25)

[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.

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 Cogenital 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 (7). 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 20). 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 antiretrovlral 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 (8). Birth defects were categorized according to the MACDP coding with the presence of one major defect or two or more conditional defects considered as a case, consistent with APR policy. 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 (11) 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 six 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 (12). 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 2013

	Clinical Studies in Pregnancy
Pregnancies Reported	1673
Age (years)	
N	1667
Median (Interquartile Range)	27.0 (8.0)
Min - Max	13 - 44
Missing	6
CD4+ T-cell Categories at Start of Pregnancy	
≥ 500 µL	284 (17.0%)
200-499 µL	785 (46.9%)
<200 µL	222 (13.3%)
Unknown	6 (0.4%)
N/A	219 (13.1%)
Missing	157 (9.4%)
Clinical Categories at Start of Pregnancy [1]	
HIV Infected [1]	
A. Asymptomatic, acute(primary) HIV or PGL	456 (27.3%)
B. Symptomatic, not (A) or (C) conditions	42 (2.5%)
C. AIDS-indicator conditions	44 (2.6%)
HIV Uninfected [2]	
HIV prophylaxis [3]	0
Hepatitis B mono-infected	365 (21.8%)
Unknown	343 (20.5%)
Missing	423 (25.3%)

[1] Includes 1 patient co-infected with HIV and Hepatitis B
[2] Where antiretroviral drugs have been used for therapy.
[3] Includes both pre- and post-exposure prophylaxis.
Note: The Registry started systematically collecting data on Hepatitis B in January 2003.

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 2013

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Reported	272	764	637	1673
NRTI	152	529	591	1272
PI/NRTI	47	138	12	197
PI/nnRTI	0	7	1	8
NRTI/nnRTI	34	83	25	142
PI/NRTI/nnRTI	7	1	1	9
PI/NRTI/NtRTI	24	5	2	31
Other Combination	8	1	5	14

[1] PI=protease inhibitor, which includes amprenavir, atazanavir, cobicistat, 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, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes raltegravir.
[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 1696 (Table 10) prospectively reported outcomes in this group, there were 279 live births with a first trimester exposure, with 13 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 4.7 (95% CI: 2.5 - 7.8) (Table 12). The number of defects identified with an initial exposure in the second or third trimester was 22. The prevalence of birth defects per 100 live births among women in this group was 1.6 (95% CI: 1.0 - 2.4). The prevalence of defects among offspring of women with first trimester exposure to antiretroviral medications (4.7 per 100 live births) is 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: 2.98, 95% CI: 1.52, 5.84). 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 41 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 2013

	With Birth Defects[3] : Without Birth Defects[4] Live Births	Spontaneous Losses	Still-births	Induced Abortions	Overall
Number of Outcomes [5]	35 : 1649	0 : 1	0 : 11	0 : 0	1696
Earliest Exposure [6]					
First Trimester	13 : 266	0 : 1	0 : 0	0 : 0	280
Second/Third Trimester	22 : 1383	0 : 0	0 : 11	0 : 0	1416
First Trimester					
PI	0 : 3	0 : 0	0 : 0	0 : 0	3
NRTI	7 : 149	0 : 0	0 : 0	0 : 0	156
PI/NRTI	3 : 44	0 : 0	0 : 0	0 : 0	47
NRTI/nnRTI	2 : 35	0 : 1	0 : 0	0 : 0	38
PI/NRTI/nnRTI	1 : 6	0 : 0	0 : 0	0 : 0	7
PI/NRTI/NtRTI	0 : 24	0 : 0	0 : 0	0 : 0	24
NRTI/nnRTI/NtRTI	0 : 3	0 : 0	0 : 0	0 : 0	3
NRTI/NtRTI/InSTI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/NRTI/nnRTI/NtRTI	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, cobicistat, 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, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes raltegravir.
[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 23 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 2013

	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]	Overall First Tri-mester Exposure	Earliest ART Exposure in Second and/or Third Trimester
Pregnancies Enrolled	82	269	45	29	0	1	272	1401
Number of Pregnancies with Multiple Gestations	0	8	4	0	0	0	8	15
Number of Outcomes [2]	82	277	49	29	0	1	280	1416
Number of Live Births	82	276	48	29	0	1	279	1405
Number of Outcomes with Defects [1,2]	4	13	3	0	0	0	13	22
Eye, ear, face and neck	0	0	0	0	0	0	0	1
Cleft lip and/or palate	0	0	0	0	0	0	0	1
Obstructive heart defects - right sided	0	0	0	0	0	0	0	1
Heart - other defects	2	10	2	0	0	0	10	6
Other circulatory system	1	2	1	0	0	0	2	1
Respiratory system	0	0	0	0	0	0	0	1
Female genitalia	0	0	0	0	0	0	0	1
Male genitalia	2	2	1	0	0	0	2	1
Limb reduction/addition defects	0	0	0	0	0	0	0	7
Other musculoskeletal defects	0	3	0	0	0	0	3	8
Skin and skin derivatives	0	2	0	0	0	0	2	0
Chromosome anomaly	0	0	0	0	0	0	0	1
Other organs and organ systems	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, cobicistat, 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, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes raltegravir.
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 2013

	Overall
Number of Live Births	1684
Number of Outcomes with at Least One Defect [1, 2]	35 (2.1%)
95% Confidence Intervals for Prevalence of Birth Defects for Exposures in:	
First Trimester	13/279 (4.7%) 2.5% - 7.8%
Second/Third Trimester	22/1405 (1.6%) 1.0% - 2.4%
Any Trimester	35/1684 (2.1%) 1.4% - 2.9%
Risk of Defects for First Trimester Exposures Relative to Second/Third Trimester Exposures	2.98 (1.52, 5.84)

[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 (13). 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 Texas BDR.

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: 05/13/97 to 06/19/2000]

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: 05/13/97 to 06/19/2000]

	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

Roche will be working with existing HIV and pregnancy registries in Europe and other countries to assess the possible consequences of potential exposure to a manufacturing impurity, ethyl methane sulfonate (EMS), a byproduct of the nelfinavir manufacturing process. Elevated levels of 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. The level at which EMS may be harmful to humans is unknown. The maximum potential exposure to EMS in patients on nelfinavir is considerably lower than doses that induced genotoxic effects in animals.

Roche will continue to work with the APR to keep the Registry updated on findings relevant to nelfinavir. Data regarding pregnancy outcomes will be shared with the APR for inclusion in the Clinical Studies or other sections of the APR reports as appropriate.

More details on EMS in nelfinavir and Roche's response can be found at http://www.roche-hiv.com/portal/eipf/pb/hiv/Roche-HIV.

Pfizer manufactures and markets nelfinavir for the United States, Canada, Puerto Rico, and Japan; there was no recall in these markets.

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 ethyl methanesulfonate (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.pfizerpro.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 (14, 15, 16). Infants are followed for at least 18 months. In a 2005 publication (2005) (16), 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 (16). 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) (17).

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 (18, 19). In their most recent publication (19), 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

* 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.

were no significant differences in infants exposed in the first trimester to efavirenz (5/205, 2.4%) or to didnosine (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 musculosketal, heart and circulatory, and urinary and digestive systems.

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 1990-2012, Reported by the the End of December 2012

	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	4408	1687	2295	2151	17	26	4464	8410
Number of Pregnancies with Multiple Gestations	106	47	45	68	0	0	110	137
Number of Outcomes	4515	1734	2340	2220	17	26	4575	8548
Number of Live Births	4399	1698	2277	2165	11	26	4455	8441
Number of Outcomes with Defects [1,2]	141	58	70	71	0	3	144	240
CNS	13	7	7	6	0	0	13	19
Eye, ear, face and neck	3	1	1	1	0	0	3	11
Cleft lip and/or palate	2	1	1	1	0	0	2	10
Conotruncal heart defects	2	0	2	0	0	0	2	2
Obstructive heart defects, right-sided	4	0	3	1	0	0	4	4
Obstructive heart defects, left-sided	0	0	0	0	0	0	0	3
Heart - other defects	19	7	5	11	0	1	19	22
Other circulatory system	6	2	4	3	0	1	6	4
Respiratory system	2	1	2	1	0	0	2	6
Upper gastrointestinal system	1	0	1	0	0	0	1	1
Lower gastrointestinal system	9	2	5	3	0	1	11	11
Female genitalia	1	0	0	1	0	0	1	0
Male genitalia	8	3	6	5	0	0	8	18
Renal and urinary system	11	3	6	6	0	0	12	20
Limb reduction/addition	19	9	13	6	0	0	19	46
Other musculoskeletal defects	21	8	12	6	0	0	21	41
Skin and skin derivatives	6	3	2	4	0	0	6	14
Chromosome anomaly	16	10	2	13	0	0	16	24
Other organ systems - specified	2	0	1	1	0	0	2	3
Specified syndromes	2	0	0	2	0	0	2	2
Unspecified abnormality	6	6	3	4	0	0	6	7

[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 weeks gestation
[3] Ten cases had first trimester exposure to unspecified antiretroviral drugs, one with an abnormality reported (lower gastrointestinal system).
NB: Pregnancies/outcomes with missing information on exposure to ART or defects are excluded.
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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 1990-2012, Reported by the End of December 2012

Number of live births	12896
Number of outcomes with at least one defect *	384 (3.0%)
95% confidence intervals for % birth defects for exposures in:	
First Trimester	144/4455 (3.2%) 2.7, 3.8
Second/Third Trimester	240/8441 (2.8%) 2.5, 3.2
Any Trimester	384/12896 (3.0%) 2.7, 3.3
Risk of defects for first trimester exposures relative to second/third trimester exposures	1.1 (0.9, 1.4)

Newschaffer and colleagues (20) 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 (21).

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) (22). 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 (23). 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 is 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 (24).

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 (25). 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 (26).

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. (27)

Lorenzi P, Spicher VM, Laubereau B, et al. Antiretroviral therapies in pregnancy: Maternal, fetal and neonatal effects. AIDS 1998;12(18):241. (28)

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. (29)

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 155.) 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 enrolls 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.

Data Summary

Primary Registry Analysis (Prospective Reports): In review of the data through 31 January 2013, 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 2.9 (95% confidence interval (CI): 2.5 - 3.4, i.e., 195 outcomes with defects of 6666 live births (Table 7). The prevalence of defects is not significantly different from the prevalence of

* Drugs included: abacavir (ZIAGEN®, ABC), abacavir/lamivudine (EPZICOM®, EPZ), abacavir/lamivudine/zidovudine (TRIZIVIR®, TZV), adefovir dipivoxil (HEPSERA®, ADV), amprenavir (AGENERASE®, APV), atazanavir sulfate (REYATAZ®, ATV), darunavir (PREZISTA®, DRV), delavirdine mesylate (RESCRIPTOR®, DLV), didanosine (VIDEX®, VIDEX® EC, ddI), efavirenz (SUSTIVA®, STOCRIN®, EFV), efavirenz/emtricitabine/ tenofovir DF (ATRIPLA® ATR), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (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/zidovudine (COMBIVIR®, ZDV+3TC), lopinavir/ritonavir (KALETRA®, ALUVIA®, LPV/r), maraviroc (SELZENTRY®, CELSENTRI®, MVC), nelfinavir (VIRACEPT®, NFV), nevirapine (VIRAMUNE®, VIRAMUNE® XR™, NVP), raltegravir (ISENTRESS®, RAL) ritonavir (NORVIR®, RTV), rilpivirine (EDURANT®, RPV), rilpivirine/emtricibitine/tenofovirDF (COMPLERA®, CPA; EVIPLERA®, EPA), saquinavir (FORTOVASE®, SQV-SGC), saquinavir mesylate (INVIRASE®, SQV-HGC), stavudine (ZERIT®, d4T), telbivudine (SEBIVO®, TYZEKA®, LdT), tenofovir DF (VIREAD®, TDF), tenofovir DF/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.

defects among women with an initial exposure during the second and/or third trimester (2.8 per 100 live births) (prevalence ratio: 1.04, 95% CI: 0.86, 1.25).

Measured against 15062 live births with exposure at any time during pregnancy, there were 434 outcomes with birth defects identified, a prevalence of 2.9 birth defects per 100 live births (95% CI: 2.6 - 3.2). This proportion is not substantially different than the CDC's birth defects surveillance system (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% confidence interval: 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 confidence intervals (CIs). The CIs reported around MACDP rates in this report were calculated by the Registry. Additionally, ascertainment from CDC's active surveillance system does not rely on voluntary reports.

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 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 population based Metropolitan Atlanta Congenital Defects Program (MACDP) (lower bound of the confidence interval for didanosine (3.0%) and nelfinavir (2.9%) is slightly above the higher bound (2.76%) for the comparator MACDP rate). 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 abacavir, atazanavir, didanosine, efavirenz, indinavir, nevirapine, 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 emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, tenofovir 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 18 among the 735

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.

First Trimester Exposure

Regimen	Defects/Live Births	Prevalence (95% Confidence Interval)
Lamivudine	135/4273	3.2% (2.6%, 3.7%)
Zidovudine	128/3932	3.3% (2.7%, 3.9%)
Ritonavir	47/2096	2.2% (1.6%, 3.0%)
Tenofovir	42/1800	2.3% (1.7%, 3.1%)
Emtricitabine	30/1230	2.4% (1.6%, 3.5%)
Nelfinavir	47/1210	3.9% (2.9%, 5.1%)
Lopinavir	24/1049	2.3% (1.5%, 3.4%)
Nevirapine	31/1049	3.0% (2.0%, 4.2%)
Abacavir	27/880	3.1% (2.0%, 4.4%)
Atazanavir sulfate	17/813	2.1% (1.2%, 3.3%)
Stavudine	21/803	2.6% (1.6%, 4.0%)
Efavirenz	18/735	2.4% (1.4%, 3.9%)
Didanosine	20/413	4.8% (3.0%, 7.4%)
Indinavir	7/288	2.4% (1.0%, 5.0%)

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, 13 infants with defects were identified among 279 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 4.7 (95% CI: 2.5 - 7.8) (Table 12). The number of defects identified with an initial exposure in the second or third trimester is 22 among 1405 live births, and the prevalence of birth defects per 100 live births is 1.6 (95% CI: 1.0 - 2.4). 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 primary anomaly accounting for the observed difference from the primary analysis is minor and self-limiting cardiovascular defects detected on echocardiogram. To date we have received 41 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. The Registry notes modest but statistically significant elevations of overall defect rates with didanosine and nelfinavir compared with its population based comparator, the MACDP. 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. Health care providers are encouraged to report eligible patients to the Registry at 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 this paragraph verbatim. Editors are reminded of this requirement and encouraged to permit the paragraph to be exempted from any word count restrictions.

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GLOSSARY AND ABBREVIATIONS

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.

Entry Inhibitor – Compound 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 enfurvitide.)

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.

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.

Integrase Strand Transfer Inhibitor – Integrase strand transfer inhibitors 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. MK-0518 blocks the viral DNA integration, hence its classification as an integrase inhibitor. (Represented in this Registry by 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 (The 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.

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 and tenofovir disoproxil fumarate.)

PHI – protected health information

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

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.

Premature Birth – An infant at outcome <37 weeks gestational age or if gestational age not available, weighing <2500 gms 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.

Texas BDR (Texas Birth Defects Regsitry) – 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	Indinavir	Emtricitabine	Atazanavir
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										
July 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									
July 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								
July 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						
July 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

Report Date	Lamivudine	Zidovudine	Nelfinavir	Stavudine	Nevirapine	Abacavir	Efavirenz	Didanosine	Ritonavir	Lopinavir	Tenofovir	Indinavir	Emtricitabine	Atazanavir
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
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

* 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Enrolled	7493	6246	2136	15877
3TC	4699	5268	1722	11730
ABC	959	830	323	2122
ADV	66	0	0	66
APV	31	5	8	45
ATV	879	320	96	1296
d4T	903	110	87	1110
ddC	61	8	5	75
ddI	471	296	167	944
DLV	13	1	2	16
DRV	199	90	39	330
EFV	865	94	49	1016
ETR	44	24	7	76
ETV	67	2	0	69
FOS	110	23	12	146
FTC	1384	430	178	1994
IDV	334	116	47	504
LdT	18	8	6	32
LPV	1160	1673	612	3450
MVC	13	4	0	17
NFV	1263	1983	730	3988
NVP	1156	961	550	2681
RAL	141	60	50	251
RPV	3	2	0	5
RTV	2283	2067	751	5109
SQV	202	137	86	426
T20	25	6	9	40
TDF	2104	574	319	3001
TMC278	6	4	1	11
TPV	4	0	1	5
ZDV	4311	6060	2836	13236

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, and ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.

Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Enrolled	7493	6246	2136	15877
3TC & NFV & ZDV	694	1527	463	2684
3TC & LPV & RTV & ZDV	421	1136	320	1877
ZDV	540	653	396	1589
3TC & NVP & ZDV	507	647	244	1399
ABC & 3TC & ZDV	249	542	164	955
3TC & ZDV	304	387	108	799
ATV & FTC & RTV & TDF	405	134	13	552
FTC & LPV & RTV & TDF	165	85	21	271
IDV & 3TC & ZDV	139	57	17	213
3TC & TDF & ZDV	195	10	6	211
TDF	141	7	29	177
EFV & 3TC & ZDV	93	56	11	160
EFV & FTC & TDF	105	21	2	128
FTC & TDF	101	7	13	121
3TC & NVP & d4T	101	11	3	115
EFV & 3TC & d4T	109	0	0	109
3TC & NFV & d4T	94	8	0	102
ABC & 3TC & LPV & RTV & ZDV	43	46	10	99
DRV & FTC & RTV & TDF	73	18	0	91
ddI	22	58	11	91
ABC & ATV & 3TC & RTV	74	14	0	88
ATV & 3TC & RTV & ZDV	40	39	7	86
3TC & NFV & NVP & ZDV	27	40	16	83
3TC & RTV & SQV & ZDV	18	42	12	72
3TC	52	10	9	71
ETV	59	1	0	60
ADV	56	0	0	56
ABC & 3TC & NVP & ZDV	24	16	12	52
FTC & RAL & TDF	30	16	4	50
ABC & 3TC & NVP	45	4	0	49
EFV & 3TC & NVP & ZDV	49	0	0	49
FTC & NVP & TDF	45	3	1	49
3TC & SQV & ZDV	31	11	5	47
ABC & 3TC & LPV & RTV	34	10	2	46
3TC & LPV & RTV & TDF & ZDV	22	17	6	45
ABC & 3TC & NFV & ZDV	18	22	5	45
3TC & LPV & NFV & RTV & ZDV	12	23	8	43
EFV & FTC & 3TC & LPV & RTV & TDF & ZDV	40	2	1	43
ATV & 3TC & ZDV	32	8	2	42
DRV & 3TC & RTV & ZDV	11	29	1	41
EFV & 3TC & NFV & ZDV	41	0	0	41
3TC & d4T	36	4	0	40
EFV & 3TC & NVP & d4T	38	0	0	38
ddI & NFV & ZDV	18	15	5	38
ddI & NFV & d4T	32	4	1	37
ABC & ATV & 3TC	30	5	1	36
NFV	27	7	0	34
IDV & 3TC & d4T	31	1	0	32
FTC & FOS & RTV & TDF	25	4	2	31
LdT	17	8	6	31

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
ddI & 3TC & NFV & ZDV	5	16	10	31
ABC & 3TC & TDF & ZDV	20	8	2	30
ATV & 3TC & LPV & RTV & ZDV	12	17	1	30
EFV & FTC & LPV & RTV & TDF	28	1	0	29
FTC & 3TC & LPV & RTV & TDF & ZDV	15	11	2	28
IDV	25	3	0	28
ddI & ZDV	17	9	2	28
EFV	27	0	0	27
ddI & 3TC & NVP & ZDV	0	9	18	27
LPV & RTV	17	7	2	26
ATV & FTC & 3TC & LPV & RTV & TDF & ZDV	17	6	2	25
3TC & LPV & RTV & TDF	20	4	0	24
NVP	17	3	2	22
ddC & ZDV	20	2	0	22
3TC & NVP & TDF	19	2	0	21
3TC & d4T & TDF	21	0	0	21
FTC & NFV & TDF	17	4	0	21
NVP & ZDV	2	0	19	21
ddI & NFV	4	10	7	21
ABC & EFV & 3TC	20	0	0	20
ATV & FTC & RTV & TDF & ZDV	5	2	13	20
ddI & NVP & d4T	14	6	0	20
3TC & LPV & RTV & d4T	15	1	3	19
3TC & NFV & d4T & ZDV	13	4	2	19
3TC & RTV & ZDV	13	5	1	19
FTC & LPV & RTV & TDF & ZDV	10	0	9	19
3TC & LPV & NVP & RTV & ZDV	2	10	6	18
DRV & FTC & RAL & RTV & TDF	13	5	0	18
ABC & FOS & 3TC & RTV	16	1	0	17
ATV & FTC & TDF	11	5	1	17
ddI & 3TC & ZDV	6	9	2	17
3TC & NFV & TDF & ZDV	6	8	2	16
ATV & EFV & FTC & RTV & TDF	14	2	0	16
FTC & LPV & RTV & ZDV	1	10	5	16
ddI & NFV & NVP	3	8	5	16
3TC & NVP & d4T & ZDV	5	7	3	15
FOS & 3TC & RTV & ZDV	10	4	1	15
ddI & NVP & ZDV	12	2	1	15
ABC & ATV & 3TC & RTV & ZDV	9	3	2	14
ATV & 3TC & RTV & TDF	14	0	0	14
ATV & RTV	8	4	2	14
EFV & 3TC & TDF	14	0	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
ATV & FTC & LPV & RTV & TDF	11	2	0	13
EFV & 3TC & LPV & RTV & ZDV	12	1	0	13
IDV & 3TC & NFV & ZDV	9	3	1	13
ABC & ATV & 3TC & RTV & TDF	11	1	0	12

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
ABC & ATV & 3TC & ZDV	8	3	1	12
FTC & RTV & TDF	11	1	0	12
ATV & FTC & 3TC & RTV & TDF & ZDV	10	1	0	11
3TC & NFV	7	2	1	10
3TC & RAL & ZDV	4	4	2	10
ABC & 3TC & LPV & RTV & TDF	7	3	0	10
ABC & 3TC & NFV	8	2	0	10
ETR & 3TC & ZDV	5	5	0	10
FTC & RTV & SQV & TDF	6	4	0	10
IDV & 3TC & RTV & d4T	10	0	0	10
LPV & RTV & ZDV	4	3	3	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
ABC & EFV & d4T	9	0	0	9
ABC & LPV & RTV & TDF	8	1	0	9
ATV & RTV & TDF & ZDV	6	2	1	9
ATV & ddI & RTV & TDF	9	0	0	9
EFV & 3TC & NFV & d4T	9	0	0	9
SQV & ddC & ZDV	9	0	0	9
ddI & 3TC & LPV & RTV & ZDV	6	3	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
ATV & 3TC & RTV & TDF & ZDV	6	2	0	8
ATV & FTC & 3TC & NFV & RTV & TDF & ZDV	8	0	0	8
ATV & FTC & RAL & RTV & TDF	7	1	0	8
DRV & ETR & RAL & RTV	6	2	0	8
ddC	8	0	0	8
ddI & 3TC & LPV & RTV	5	3	0	8
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
ADV & 3TC	7	0	0	7
DRV & FTC & TDF	6	1	0	7
EFV & 3TC & NVP & d4T & ZDV	7	0	0	7
FOS & 3TC & ZDV	5	2	0	7
FTC & TMC278 & TDF	5	2	0	7
IDV & 3TC & d4T & ZDV	7	0	0	7
ddI & 3TC & NFV & d4T & ZDV	7	0	0	7
ddI & IDV & d4T	7	0	0	7
3TC & LPV & RAL & RTV & ZDV	3	0	3	6
3TC & RAL & TDF	6	0	0	6
3TC & SQV & d4T	6	0	0	6
3TC & TDF	6	0	0	6
ABC & EFV & 3TC & NVP	6	0	0	6

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
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 & RAL & RTV	2	0	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 & TDF	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 & TDF	2	0	0	2
ddI & FTC & LPV & RTV & TDF	2	0	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 & RTV & SQV & TDF	2	0	0	2
3TC & LPV & NFV & RTV & SQV & ZDV	0	0	1	1
3TC & LPV & NVP & RTV & TDF	1	0	0	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 & 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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
3TC & NVP & d4T & TDF	1	0	0	1
3TC & RAL	1	0	0	1
3TC & RPV & TDF	1	0	0	1
3TC & RTV	1	0	0	1
3TC & RTV & SQV & TDF	1	0	0	1
3TC & RTV & 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 & 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 & d4T	1	0	0	1
ABC & 3TC & NFV & d4T & TDF	1	0	0	1
ABC & 3TC & NFV & d4T & ZDV	1	0	0	1
ABC & 3TC & NVP & RTV & SQV	1	0	0	1
ABC & 3TC & NVP & d4T & TDF & ZDV	0	1	0	1
ABC & 3TC & RAL & ZDV	0	1	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 & NVP & RTV	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	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
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	1	0	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 & 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 & ZDV	1	0	0	1
ABC & DRV & 3TC & ZDV	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 & RAL & RTV & TDF & ZDV	0	0	1	1
ABC & DRV & FTC & 3TC & TDF	1	0	0	1
ABC & DRV & FTC & LPV & RTV & TDF	1	0	0	1
ABC & DRV & FTC & RTV & TDF	1	0	0	1
ABC & DRV & RTV & TDF	1	0	0	1
ABC & DRV & T20 & 3TC & RTV & TDF & ZDV	1	0	0	1
ABC & EFV	1	0	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 & 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 & ETR & 3TC	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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
ABC & FOS & RTV & TDF	1	0	0	1
ABC & FTC & 3TC & LPV & RTV & TDF & ZDV	1	0	0	1
ABC & FTC & FOS & 3TC & RTV & TDF & ZDV	0	0	1	1
ABC & FTC & NVP & TDF	1	0	0	1
ABC & FTC & TMC278 & TDF	0	1	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
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	1	0	0	1
ABC & ddI & 3TC	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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
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 & RTV & TDF & ZDV	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 & SQV	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 & LdT	1	0	0	1
APV & 3TC & LPV & RTV & TDF	0	1	0	1
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 & 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 & 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 & RTV & d4T	1	0	0	1
ATV & 3TC & RTV & d4T & ZDV	0	0	1	1
ATV & 3TC & TDF	1	0	0	1
ATV & DRV & RTV & TDF & ZDV	1	0	0	1
ATV & DRV & T20 & 3TC & RTV & ZDV	1	0	0	1
ATV & EFV & 3TC & RTV & TDF & ZDV	1	0	0	1
ATV & EFV & 3TC & 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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
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
ATV & FTC & 3TC & LPV & RTV & TDF	1	0	0	1
ATV & FTC & 3TC & NFV & TDF & ZDV	1	0	0	1
ATV & FTC & 3TC & NVP & RTV & 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 & ETR & RTV & TDF	1	0	0	1
ATV & FTC & FOS & 3TC & RTV & TDF & ZDV	1	0	0	1
ATV & FTC & FOS & RTV & TDF	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 & 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 & 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 & 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
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
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	0	0	0	1
DRV & 3TC & LPV & RAL & RTV & ZDV	1	0	0	1
DRV & 3TC & NVP & RTV & ZDV	1	0	0	1

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
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 & RTV & TDF & ZDV	1	0	0	1
ETR & 3TC & LPV & RTV & ZDV	0	1	0	1
ETR & 3TC & RAL & ZDV	0	1	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 & RTV	1	0	0	1
FTC & 3TC & LPV & NFV & RTV & d4T & ZDV	1	0	0	1
FTC & 3TC & LPV & RTV & 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 & LPV & TMC278 & RTV & TDF & ZDV	1	0	0	1
FTC & 3TC & NFV & ZDV	0	1	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
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 & 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 & TDF	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 & RPV & TDF & ZDV	0	1	0	1
FTC & T20 & LPV & RTV & TDF	1	0	0	1
FTC & T20 & RTV & TDF & TPV	1	0	0	1
FTC & TMC278 & TDF & ZDV	0	0	1	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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
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
NFV & NVP	1	0	0	1
NFV & NVP & SQV	1	0	0	1
NFV & NVP & SQV & ddC & ZDV	0	1	0	1
NFV & SQV	1	0	0	1
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 & d4T & TDF & ZDV	0	1	0	1
NVP & ddC & ZDV	1	0	0	1
RAL & TDF & ZDV	1	0	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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

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

Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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 31Jan2013

	First Trimester	Second Trimester	Third Trimester	Overall
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 sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, DRV=darunavir, EFV=efavirenz, ETR=etravirine, ETV=entecavir, 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, 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.	Hemangioma (2"x1"x1") on upper right arm	Temporality: Cannot rule out a possible association[1]
	6.	Trisomy 21	Temporality: Cannot rule out a possible association[1]
	7.	Bilateral skin tags - ears. Preauricular sinus - left ear	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.	Hypospadius, 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]

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.

* 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

	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.	Hydrocele, inguinal hernia	Temporality: Cannot rule out a possible association[1]
	29.	Other and unspecified cranio-synostosis	Temporality: Cannot rule out a possible association[1]
	30.	Ventricular Septal Defect (VSD), Fetal alcohol syndrome	Temporality: Cannot rule out a possible association[1]
		Pyloric stenosis	Temporality: Unable to assess [2]
	31.	Pyloric stenosis, hydrocephaly, hepatomegaly, hydrocele	Temporality: Unable to assess [2]
	32.	Club Foot	Temporality: Unable to assess[2]
	33.	Club Foot	Temporality: Unable to assess[2]
‡	34.	Club Foot	Temporality: Unable to assess[2]
	35.	Club Foot	Temporality: Unable to assess[2]
	36.	Hydrocele, stenosis/obstruction of lacrimal duct	Temporality: Unable to assess[2]
	37.	Congenital adrenal hyperplasia	Temporality: No temporal association [3]
	38.	Truncus arteriosis	Temporality: No temporal association [3]
	39.	Hypoplastic left ventricle	Temporality: No temporal association [3]
	40.	Polydactyly	Temporality: No temporal association [3]
	41.	Balanced AV Septal Defect	Temporality: Cannot rule out a possible association[1]
		Trisomy 21	Temporality: No temporal association [3]
	42.	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 NtRTII(s) Only Regimen:

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

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.

* 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

	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]
	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]

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[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

¥	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, Secundum Atrial Septal Defect	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.	Polydactyly NOS – hand	
¥	55.	Primary hypospadias	Temporality: Cannot rule out a possible association[1]
	56.	Primary hypospadias with chordee	Temporality: Cannot rule out a possible association[1]
	57.	Inguinal hernia	Temporality: Cannot rule out a possible association[1]
	58.	Atrial Septal Defect	Temporality: Cannot rule out a possible association[1]
	59.	Long thin toes	Temporality: Cannot rule out a possible association[1]
		Benign external hydrocephalus, frontal bossing	Temporality: Unable to assess[2]
	60.	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]

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

	61.	Patent Ductus Arteriosus (PDA), suspect Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
		Low-set/widespread thumb, hypoplastic left leg	Temporality: No temporal association [3]
		Left club foot, spine curvature	Temporality: Unable to assess[2]
	62.	Chromosomic aberration, no karyotype done (induced abortion <20 weeks gestation)	Temporality: Unable to assess[2]
	63.	Developmental hip dysplasia	Temporality: Unable to assess[2]
	64.	Muscular Ventricular Septal Defect (VSD)	Temporality: Unable to assess[2]
	65.	Congenital myotonic dystrophy, Hip dysplasia/dislocation	Temporality: Unable to assess[2]
	66.	Club foot	Temporality: Unable to assess[2]
	67.	Microcephaly	Temporality: Unable to assess[2]
	68.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
		AV Canal	Temporality: No temporal association [3]
	69.	Epispadias	Temporality: No temporal association [3]
	70.	Digeorge Syndrome	Temporality: No temporal association [3]
	71.	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]
	1.	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]
	2.	Mild hydronephrosis	Temporality: Cannot rule out a possible association[1]
	3.	Talipes (positional, both feet)	Temporality: Cannot rule out a possible association[1]
	4.	Hypoplastic right ventricle, Pulmonary atresia	Temporality: Cannot rule out a possible association[1]
	5.	Urinary obstruction, duplicated right collecting system with obstructed upper pole moiety (possibly with associated vesicoureteral reflux)	Temporality: Cannot rule out a possible association[1]
	6.	Small muscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
¥	7.	Long bones malformation	Temporality: Cannot rule out a possible association[1]
	8.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association[1]
	9.	Hearing loss, congenital CMV	Temporality: Cannot rule out a possible association[1]
	10.	AV canal	Temporality: Cannot rule out a possible association[1]
	11.	Postaxial polydactyly – both hands	Temporality: Cannot rule out a possible association[1]
	12.	Polydactyly	Temporality: Cannot rule out a possible association[1]
¥	13.	Shortening of right leg	Temporality: Cannot rule out a possible association[1]
	14.	AVSD, Trisomy 21, Distal phalax left thumb does not flex	Temporality: Cannot rule out a possible association[1]
	15.	Micropenis	Temporality: Cannot rule out a possible association[1]
	16.	Intraventricular communication	Temporality: Cannot rule out a possible association[1]

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	17.	Right multicystic kidney	Temporality: Cannot rule out a possible association[1]
	18.	ASD, VSD	Temporality: Cannot rule out a possible association[1]
	19.	Congenital hydronephrosis, vesicoureteral reflux	Temporality: Cannot rule out a possible association[1]
	20.	Umbilical hernia with a small granuloma	Temporality: Cannot rule out a possible association[1]
		Bilateral hip dislocation	Temporality: Unable to assess[2]
¥	21.	Hip dysplasia/dislocation	Temporality: Unable to assess[2]
	22.	Bilateral congenital dislocation of hips	Temporality: Unable to assess[2]
	23.	Hemangioma on nostril	Temporality: Unable to assess [2]
	24.	Congenital talipies	Temporality: Unable to assess [2]
	25.	Left club foot	Temporality: Unable to assess [2]
	26.	Talipes equinovarus	Temporality: Unable to assess [2]
	27.	Failed hearing test, Trisomy 21	Temporality: Cannot rule out a possible association[1]
	28.	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 club foot	Temporality: Unable to assess [2]
	5.	Club foot	Temporality: Unable to assess [2]
	6.	Small ears, small eyes	Temporality: Cannot rule out a possible association[1]
		Syndactyly digits of both hands	Temporality: No temporal association [3]
*	7.	Hemangioma	Temporality: Unable to assess [2]
		Umbilical hernia	Temporality: No temporal association [3]
	8.	Omphalocele	Temporality: No temporal association [3]

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

	1.	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]

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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) + 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, 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]
	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]

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	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.	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]
	22.	Polydactyly	Temporality: No temporal association [3]
	23.	Polydactyly	Temporality: No temporal association [3]
	24.	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]

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]

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.	Pulmonary stenosis	Temporality: Cannot rule out a possible association[1]
		Immature hips (hip dysplasia)	Temporality: Unable to assess [2]
	6.	Postaxial Polydactyly (both hands)	Temporality: No temporal association [3]

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

	1.	Pectus excavatum	Temporality: Cannot rule out a possible association[1]
	2.	Fetal Alcohol Syndrome	Temporality: Cannot rule out a possible association[1]
	3.	Down syndrome with facies, low-set ears, simian crease, trisomy 21	Temporality: Cannot rule out a possible association[1]
	4.	Bilateral polydactyly and feet anomalies, bilateral talipes equinovarus (TEV) positive	Temporality: Cannot rule out a possible association[1]

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	5.	Patent ductus arteriosus (PDA), Patent Foramen Ovale (PFO), cardiomyopathy	Temporality: Cannot rule out a possible association[1]
	6.	Muscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
	7.	Gastroschisis	Temporality: Cannot rule out a possible association[1]
	8.	Dacryocystocele	Temporality: Cannot rule out a possible association[1]
	9.	Trisomy 21	Temporality: Cannot rule out a possible association[1]
	10.	Bilateral polydactyly	Temporality: Cannot rule out a possible association[1]
‡	11.	Premature synostosis of metopic suture	Temporality: Cannot rule out a possible association[1]
	12.	Down syndrome	Temporality: Cannot rule out a possible association [1]
	13.	Micrognathia	Temporality: Cannot rule out a possible association [1]
	14.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	15.	Congenital hydrocephalus	Temporality: Cannot rule out a possible association [1]
	16.	Multicystic left kidney	Temporality: Cannot rule out a possible association [1]
	17.	Enlarged, echogenic left kidney	Temporality: Cannot rule out a possible association [1]
	18.	Micrognathia	Temporality: Cannot rule out a possible association [1]
	19.	Atrial Fenestrations	Temporality: Cannot rule out a possible association [1]
‡	20.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association [1]
	21.	Plagiocephaly	Temporality: Cannot rule out a possible association [1]
‡	22.	Hydroureter	Temporality: Cannot rule out a possible association [1]
	23.	Inguinal hernia	Temporality: Cannot rule out a possible association [1]
‡	24.	Atrial septal defect	Temporality: Cannot rule out a possible association [1]
	25.	Hydrocephalus of anterior lateral ventricle	Temporality: Unable to assess[2]
	26.	Right hip dislocation	Temporality: Unable to assess[2]
	27.	Subglottic stenosis	Temporality: Unable to assess[2]
‡	28.	Talipes calcaneovarus	Temporality: Unable to assess[2]
	29.	Hip dysplasia	Temporality: Unable to assess[2]
	30.	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]
	31.	Syndactyly fingers and toes	Temporality: Cannot rule out a possible association[1]
		Club feet, severe arthrogryposis	Temporality: Unable to assess[2]
	32.	Bilateral hydronephrosis	Temporality: Cannot rule out a possible association[1]

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		Hypoplastic pubic bone, 2 vessel umbilical cord	Temporality: No temporal association [3]
	33.	Trisomy 13	Temporality: Cannot rule out a possible association[1]
		Dysmorphic eyes, patent ductus arteriosus, Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), duodenal atresia, rocker-bottom feet	Temporality: No temporal association [3]
‡	34.	Patent ductus arteriosus	Temporality: Cannot rule out a possible association [1]
		Umbilical hernia	Temporality: No temporal association [3]
	35.	Cardiac axis abnormality	Temporality: Unable to assess[2]
		Dandy Walker Malformation, ventriculomegaly	Temporality: No temporal association [3]
	36.	Atrial Septal Defect (ASD)	Temporality: No temporal association [3]
	37.	Micrognathia, left ear low-set pinna microtia, right ear malformation, small muscular Ventricular Septal Defect (VSD)	Temporality: No temporal association [3]
	38.	Microphthalmos of right eye with a possible coexistent cataract	Temporality: No temporal association [3]
	39.	Small cleft in front gum – very benign	Temporality: No temporal association [3]
	40.	Hand defect (missing digits)	Temporality: No temporal association [3]
	41.	Bicuspid aortic valve, abnormal pulmonic valve and possibly abnormal aorta but no gross aortic coarctation	Temporality: No temporal association [3]
	42.	Polydactyly	Temporality: No temporal association [3]
	43.	Syndactyly, right hand	Temporality: No temporal association [3]
	44.	Hypospadias, mild	Temporality: No temporal association [3]
	45.	Ventricular Septal Defect (VSD) - membranous; diagnosed at 2 months of age	Temporality: No temporal association [3]
	46.	Polydactyly (bilateral hands and feet, postaxial)	Temporality: No temporal association [3]
	47.	Absence of mouth and esophagus, transversed organs	Temporality: No temporal association [3]
	48.	Cleft palate and lip	Temporality: No temporal association [3]
	49.	Hypospadias	Temporality: No temporal association [3]
	50.	Alobar holoprosencephaly (stillbirth), hypotelorism, proboscis	Temporality: No temporal association [3]
	51.	Polydactyly (bilateral)	Temporality: No temporal association [3]
	52.	Hypospadias	Temporality: No temporal association [3]
	53.	Cleft lip & palate	Temporality: No temporal association [3]
	54.	Sacrococcygeal teratoma	Temporality: No temporal association [3]
	55.	Cleft lip and palate	Temporality: No temporal association [3]
	56.	Choanal atresia	Temporality: No temporal association [3]
	57.	Cleft lip	Temporality: No temporal association [3]
	58.	Sacral tissue mass, tethered spinal cord	Temporality: No temporal association [3]
	59.	Cardiomegaly, Ebstein anomaly/dysplastic tricuspid valve, pulmonary atresia	Temporality: No temporal association [3]
	60.	Urethral stricture	Temporality: No temporal association [3]
	61.	Polydactyly	Temporality: No temporal association [3]
	62.	Bilateral cleft lip	Temporality: No temporal association [3]
	63.	Ectopic left kidney	Temporality: No temporal association [3]
	64.	Choanal atresia	Temporality: No temporal association [3]
	65.	Polydactyly left hand – postaxial	Temporality: No temporal association [3]
	66.	Polydactyly left hand – postaxial	Temporality: No temporal association [3]
	67.	Toes not well formed on both feet	Temporality: No temporal association [3]

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	68.	Atrial septal defect, 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.	Anomaly of Myocardium	Temporality: Cannot rule out a possible association[1]
	11.	Trisomy 18, Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
‡	12.	Mild bilateral renal pelviectasis	Temporality: Cannot rule out a possible association[1]
	13.	Cataracts, umbilical hernia	Temporality: Cannot rule out a possible association[1]
	14.	Trisomy 17	Temporality: Cannot rule out a possible association[1]
	15.	Arrhythmia	Temporality: Cannot rule out a possible association[1]
	16.	Congenital icthyosis	Temporality: Cannot rule out a possible association[1]
	17.	Bilateral hydronephrosis, Bilateral cystic kidneys, Grade 4 VUR on right	Temporality: Cannot rule out a possible association[1]
	18.	Pigmentary mosaicism	Temporality: Cannot rule out a possible association[1]
	19.	Abnormal face, low set ears, narrow eyes	Temporality: Cannot rule out a possible association[1]
	20.	Small ventricular defect	Temporality: Cannot rule out a possible association[1]
	21.	Congenital CMV, microcephaly	Temporality: Cannot rule out a possible association[1]
	22.	L renal cyst	Temporality: Cannot rule out a possible association[1]
	23.	Vesicoureter junction obstruction, ASD, mild left pulmonary artery stenosis	Temporality: Cannot rule out a possible association[1]
‡	24.	Ventricular septal defect	Temporality: Cannot rule out a possible association[1]
	25.	Ventricular septal defect	Temporality: Cannot rule out a possible association[1]
	26.	Hydroureter	Temporality: Cannot rule out a possible association[1]
	27.	Atrial septal defect	Temporality: Cannot rule out a possible association[1]
‡	28.	Atrial septal defect, ventricular septal defect	Temporality: Cannot rule out a possible association[1]

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	29.	Venticular septal defect	Temporality: Cannot rule out a possible association[1]
	30.	Dysmorphic features	Temporality: Cannot rule out a possible association[1]
		Club foot	Temporality: Unable to assess [2]
	31.	Trisomy 21, PDA	Temporality: Cannot rule out a possible association[1]
		AV Canal	Temporality: No temporal association [3]
	32.	Ventricular septal defect	Temporality: Cannot rule out a possible association[1]
		Bilateral cleft lip and palate, aortic stenosis, small aortic arch, persistent left SVC, translocation of chromosomes 21 and 22	Temporality: No temporal association [3]
	33.	Hypospadias	Temporality: No temporal association [3]
	34.	Right Cryptorchism	Temporality: Cannot rule out a possible association[1]
		Hypospadias	Temporality: No temporal association [3]
	35.	Atrial septal defect	Temporality: Cannot rule out a possible association[1]
		Tricuspid stenosis	Temporality: No temporal association [3]
	36.	Ears mildly low-set (spontaneous abortion <20 weeks gestation)	Temporality: No temporal association [3]
		Ambiguous genitalia	Temporality: Unable to assess[2]
	37.	Polydactyly	Temporality: No temporal association [3]
	38.	Tethered cord, lipomeningocele, right kidney duplicated collecting system	Temporality: No temporal association [3]
	39.	Cleft palate, micrognathia	Temporality: No temporal association [3]
‡	40.	Other and unspecified polydactyly	Temporality: No temporal association [3]
	41.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
	42.	Congenital toxoplasmosis	Temporality: No temporal association [3]
	43.	Hydronephrosis of the left kidney with mild pelviectasis of the right collecting system	Temporality: No temporal association [3]
	44.	Gastroschisis	Temporality: No temporal association [3]
	45.	Omphalocele	Temporality: No temporal association [3]
	46.	Polydactyly (foot), long fingers, short ears with folded helices, low hairline front and posterior	Temporality: No temporal association [3]
	47.	Polydactyly (Extra digit left hand)	Temporality: No temporal association [3]
	48.	Polydactyly	Temporality: No temporal association [3]
	49.	Mild hypospadius	Temporality: No temporal association [3]
	50.	Diaphragmatic hernia	Temporality: No temporal association [3]
	51.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
	52.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
	53.	Cleft lip and palate	Temporality: No temporal association [3]
	54.	Cleft lip on the left	Temporality: No temporal association [3]
	55.	Missing artery in heart	Temporality: No temporal association [3]
	56.	Branchial cleft cyst	Temporality: No temporal association [3]
	57.	Polydactyly	Temporality: No temporal association [3]
	58.	S1-2 hemivertebra	Temporality: No temporal association [3]
	59.	Small perimembranous Ventricular Septal Defect (VSD), mild tricuspid regurgitation	Temporality: No temporal association [3]
	60.	Midmuscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
	61.	Frontal Ventricular Septal Defect (VSD), hearing loss	Temporality: Cannot rule out a possible association[1]

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62.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
63.	Secundum Atrial Septal Defect (ASD)/Stretched Patent Foramen Ovale (PFO)	Temporality: Cannot rule out a possible association[1]
64.	Undescended testes	Temporality Cannot rule out a possible association[1]
	Polydactyly (hand), Tetrology of Fallot	Temporality: No temporal association [3]
65.	Cleft palate	Temporality: No temporal association [3]
66.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
	Double outlet right ventricle	Temporality: No temporal association [3]
67.	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]
68.	Hydrocephalus NOS	Temporality: Cannot rule out a possible association[1]
	Dandy Walker	Temporality: No temporal association [3]
69.	Down Syndrome, Facial features of Down Syndrome	Temporality: Cannot rule out a possible association[1]
	Cardiac abnormalities	Temporality: No temporal association [3]
70.	Bilateral club feet	Temporality: Unable to assess[2]
71.	Right club foot	Temporality: Unable to assess[2]
72.	Umbilical cord anomaly	Temporality: Unable to assess[2]
73.	Failed right ear hearing test	Temporality: Unable to assess[2]
74.	Left club foot	Temporality: Unable to assess [2]
75.	Congenital dislocated hips	Temporality: Unable to assess [2]
76.	Hypoplastic kidneys	Temporality: Unable to assess [2]
77.	Trisomy NOS	Temporality: Cannot rule out a possible association [1]
78.	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]
79.	Trisomy 18, Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association [1]
	Overriding aorta	Temporality: No temporal association [3]
80.	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]
81.	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]
82.	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]
83.	Transposition of major vessels	Temporality: No temporal association [3]
	Atrial septal defect	Temporality: Cannot rule out a possible association [1]
84.	P,[;ja;pce;e. Sacra; Agemesos. Fised ;pwer extre,otoes	Temporality: No temporal association [3]
	Dysmorphic featires. Low set ears	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

*	85.	Dysgenesis of the Corpus Callosum	Temporality: Unable to assess [2]
		Neural tube defect, Chiari II malformation	Temporality: No temporal association [3]
*	86.	Trisomy 18	Temporality: Unable to assess [2]
		Unspecified heart anomaly	Temporality: No temporal association [3]
	87.	Hirschprung's disease	Temporality: No temporal association [3]
	88.	Bilateral polydactyly – postaxial	Temporality: No temporal association [3]
	89.	Absence of hand/fingers	Temporality: No temporal association [3]
	90.	Dandy Walker Malformation	Temporality: No temporal association [3]
	91.	Trisomy 21	Temporality: No temporal association [3]
	92.	Pulmonary valve atresia/stenosis/hypoplasia with IVS	Temporality: No temporal association [3]
	93.	Syndacytly toes, 2nd thumb on right hand	Temporality: No temporal association [3]
	94.	Renal agenesis – left	Temporality: No temporal association [3]
	95.	Gastroschisis	Temporality: No temporal association [3]
	96.	Polydactyly (extra partial 5th finger on right)	Temporality: No temporal association [3]
	97.	Polydactyly	Temporality: No temporal association [3]
	98.	Polydactyly – preaxial	Temporality: No temporal association [3]
	99.	Vascular ring around trachea	Temporality: No temporal association [3]
	100.	Gastroschisis	Temporality: No temporal association [3]
	101.	Duplicated right renal collecting system	Temporality: No temporal association [3]
*	102.	Other specified anomaly of nose	Temporality: No temporal association [3]
*	103.	Polydactyly – postaxial Hand	Temporality: No temporal association [3]
*	104.	Gastroschisis	Temporality: No temporal association [3]
	105.	Ectopic kidney, Hirshsprung disease	Temporality: No temporal association [3]
‡	106.	Anencephaly	Temporality: No temporal association [3]
	107.	Myelomemingocele without hydrocephalus	Temporality: No temporal association [3]
	108.	Polydactyly – postaxial hand	Temporality: No temporal association [3]
	109.	Truncus arteriosus	Temporality: No temporal association [3]
	110.	Menkes syndrome	Temporality: No temporal association [3]
‡	111.	Polydactyly – postaxial hand	Temporality: No temporal association [3]
‡	112.	Umbilical hernia	Temporality: No temporal association [3]
		Fusion of vulva	Temporality: Unable to assess [2]

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

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]

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[3] No temporal association

	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	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	Temporality: Cannot rule out a possible association[1]
‡	15.	Ventricular septal defect	Temporality: Cannot rule out a possible association[1]
	16.	Ventricular septal defect	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) + 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]

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[3] No temporal association

‡	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]
‡	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:

	2.	Patent Foramen Ovale (PFO), trivial tricuspid regurgitation, mild mitral regurgitation, Wolff-Parkinson-White	Temporality: Cannot rule out a possible association[1]
	3.	Muscular Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
	4.	Ventricular Septal Defect (VSD), Trisomy 21	Temporality: Cannot rule out a possible association[1]
	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]

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) + InSTI(s) Regimen:

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

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

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

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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[3] No temporal association

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	No temporal association [3]

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.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
	Cardiac murmur- Gr II-III/ VI	Temporality: No temporal association [3]
11.	Panhypopituitarism, congenital anomalies of brain, musculoskeletal system, larynx, trachea & bronchus (cerebral dysgenesis, cartilaginous dysplasia)	Temporality: Cannot rule out a possible association[1]
12.	Polydactyly (bilateral hands).	Temporality: Cannot rule out a possible association[1]
13.	Polydactyly	Temporality: Cannot rule out a possible association[1]
14.	Malformation of external genitalia	Temporality: Cannot rule out a possible association[1]
15.	Bilateral club feet (equinovarus)	Temporality: Cannot rule out a possible association[1]
16.	Multiple rhabdomyomas in left ventrical and atrium, tuberosis sclerosis	Temporality: Cannot rule out a possible association[1]
17.	Congenital spine malformation	Temporality: Cannot rule out a possible association[1]
18.	Livedo reticularis, splenomegaly	Temporality: Cannot rule out a possible association[1]

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Retrospective Reports (continued)

19.	Holoprosencephaly, facial anomaly	Temporality: Cannot rule out a possible association[1]
20.	Pulmonary valve atresia/stenosis/hypoplasia	Temporality: Cannot rule out a possible association[1]
21.	Macula Abnormal	Temporality: Cannot rule out a possible association[1]
22.	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]
23.	Ventricular Septal Defect (VSD), hepatosplenomegaly	Temporality: Cannot rule out a possible association[1]
24.	Inguinal hernia (resolved spontaneously at two months)	Temporality: Cannot rule out a possible association[1]
25.	Holoprosencephaly, cleft lip and palate, chromosome 18p deletion, cryptorchidism	Temporality: Cannot rule out a possible association[1]
26.	Strabismus, dysmorphic features of face and skull, atrophy of maculae and pigmental retinitis, cerebral atrophy	Temporality: Cannot rule out a possible association[1]
27.	Facial dysmorphism	Temporality: Cannot rule out a possible association[1]
28.	Trisomy 21	Temporality: Cannot rule out a possible association[1]
29.	Alopecia, cavum septum pellucidum	Temporality: Cannot rule out a possible association[1]
30.	Hypospadias	Temporality: Cannot rule out a possible association[1]
31.	Polycystic kidney	Temporality: Cannot rule out a possible association[1]
	Connective tissue disorder, arthropathy	Temporality: Unable to assess[2]
32.	Hydrocephalus	Temporality: Cannot rule out a possible association[1]
33.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
34.	Congenital Ventricular Defect	Temporality: Cannot rule out a possible association[1]
35.	Right Ventricular Hypertrophy	Temporality: Cannot rule out a possible association[1]
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.	Cardiac malformation	Temporality: Unable to assess[2]
43.	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]
44.	Albinism	Temporality: No temporal association [3]
45.	Hepatosplenomegaly, enlarged tongue, mongoloid appearance. Chromosomal evaluation showed no abnormalities	Temporality: No temporal association [3]
46.	Cleft lip and palate	Temporality: No temporal association [3]
47.	Large omphalocele including liver, spleen, and intestine (induced abortion <20 weeks gestation)	Temporality: No temporal association [3]

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48.	Congenital exomphalos	Temporality: No temporal association [3]
49.	Dysmorphogenesis, bilateral deformity of feet, left hip dislocation, vertical talus of left foot	Temporality: No temporal association [3]
50.	Transposition of great vessels	Temporality: No temporal association [3]
51.	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:

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 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]
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]

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	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: apical muscular	Temporality: Cannot rule out a possible association[1]
	46.	Congenital heart malformation	Temporality: Cannot rule out a possible association[1]
		Suspected Trisomy 18	Temporality: Unable to assess[2]

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[3] No temporal association

Retrospective Reports (continued)

	47.	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]
	48.	Aorta hypoplasia	Temporality: Cannot rule out a possible association[1]
		Congenital malformation of fetus	Temporality: Unable to assess[2]
	49.	Craniostenosis	Temporality: Cannot rule out a possible association[1]
		Abdominal hernia, congenital anomaly	Temporality: Unable to assess[2]
	50.	Abdominal hernia, cryptorchism Murmur	Temporality: Cannot rule out a possible association[1]
		Congenital talipes (talus valgus)	Temporality: Unable to assess [2]
*	51.	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]
	52.	Talus Valgus, craniostenosis	Temporality: Unable to assess[2]
	53.	Trisomy 18	Temporality: Unable to assess[2]
	54.	Hypochromic Skin Around Right Eye and Mouth/Hanartomatous	Temporality: Unable to assess[2]
	55.	Bilateral club feet	Temporality: Unable to assess[2]
	56.	Unspecified heart anomaly	Temporality: Unable to assess[2]
	57.	Congenital anomaly, abdominal hernia	Temporality: Unable to assess[2]
		Cryptorchism	Temporality: Cannot rule out a possible association[1]
	58.	Triploidy	Temporality: Cannot rule out a possible association[1]
	59.	Cardiomyopathy Neonatal	Temporality: Cannot rule out a possible association[1]
		Aortic Stenosis	Temporality: No temporal association [3]
	60.	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]
	61.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association[1]
		Down syndrome	Temporality: No temporal association [3]
	62.	Hypospadias	Temporality: No temporal association [3]
	63.	Congenital toxoplasmosis (spontaneous abortion ≥ 20 weeks gestation)	Temporality: No temporal association [3]

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

1.	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]
2.	Retrognathia	Temporality: Cannot rule out a possible association[1]
3.	Polycystic right kidney	Temporality: Cannot rule out a possible association[1]
4.	Pulmonary abnormalities, bone abnormalities (induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association[1]
5.	Left kidney oligohydramnios (severe), abnormally enlarged with pyelectasis	Temporality: Cannot rule out a possible association[1]
6.	Single ventricle, pulmonary atresia, discontinuous pulmonary arteries, dextrocardia, asplenia, situs inversus, heterotaxia syndrome	Temporality: Cannot rule out a possible association[1]
7.	Extended lumbosacral meningomyelocele	Temporality: Cannot rule out a possible association[1]

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Retrospective Reports (continued)

	8.	Hydrocephalic, patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association[1]
	9.	Congenital torticollis	Temporality: Cannot rule out a possible association[1]
	10.	Trisomy 21 (questionable, induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association[1]
	11.	Frontal osteoma, deviated right 3-4 fingers, asymmetric feet	Temporality: Cannot rule out a possible association[1]
	12.	Bilateral absent kidney, dysplastic kidney	Temporality: Cannot rule out a possible association[1]
	13.	Ependymal cyst	Temporality: Cannot rule out a possible association[1]
	14.	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]
	15.	Defective hearing in one ear	Temporality: Cannot rule out a possible association[1]
	16.	Dandy Walker malformation, cystic hygroma/ nuchal edema (spontaneous abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association[1]
	17.	Cleft palate	Temporality: Cannot rule out a possible association[1]
	18.	Bilateral clubfeet, hydrocephalus, lumbosacral meningomyelocele with Arnold-Chiari malformation (induced abortion ≥ 20 weeks gestation)	Temporality: Cannot rule out a possible association[1]
	19.	Abnormal right auditory evoked potentials were evidenced at 22 months	Temporality: Cannot rule out a possible association[1]
	20.	Central cleft palate	Temporality: Cannot rule out a possible association[1]
	21.	Congenital hernia, Ventricular Septal Defect (VSD), labial fissure	Temporality: Cannot rule out a possible association[1]
	22.	Interventricular Septal Defect (VSD), persistent ductus botalli	Temporality: Cannot rule out a possible association[1]
	23.	Agenesis of the corpus callosum	Temporality: Cannot rule out a possible association[1]
	24.	Septo-optic dysplasia, hypoplasia of cerebellum	Temporality: Cannot rule out a possible association[1]
	25.	Possible spinal defect	Temporality: Cannot rule out a possible association[1]
	26.	Omphalocele	Temporality: Cannot rule out a possible association[1]
	27.	Left eye ptosis, left hydrocele	Temporality: Cannot rule out a possible association[1]
	28.	Abnormal urethral meatus	Temporality: Cannot rule out a possible association[1]
	29.	Agenesis of left hand below wrist	Temporality: Cannot rule out a possible association[1]
ф	30.	Dandy Walker variant, mild ventriculomegaly	Temporality: Cannot rule out a possible association[1]
¥	31.	Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association[1]
	32.	Umbilical hernia, hypopigmentation	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]

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[3] No temporal association

Retrospective Reports (continued)

	35.	Spina Bifida/Chiari	Temporality: Cannot rule out a possible association[1]
	36.	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]
	37.	Posterior cervical hygroma, hydrops (induced abortion <20 weeks gestation), bilateral club feet	Temporality: Unable to assess[2]
	38.	Omphalocele	Temporality: Unable to assess[2]
	39.	No brain stem (spontaneous abortion <20 weeks gestation)	Temporality: Unable to assess[2]
ф	40.	Patent Foramen Ovale	Temporality: Unable to assess[2]
	41.	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]
	42.	Mitral valve stenosis, Pulmonary valve stenosis	Temporality: No temporal association [3]

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.	Myelomeingocele with hydrocephalus/Arnold-Chiari malformation	Temporality: Cannot rule out a possible association[1]
	8.	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]
	9.	Anomaly in cardiac rhythm	Temporality: Cannot rule out a possible association[1]
	10.	Anomaly of cardiac rhythm, anomaly of myocardium	Temporality: Cannot rule out a possible association[1]
	11.	Angioma	Temporality: Unable to assess[2]
ф	12.	Talipes Equinovarus	Temporality: Unable to assess[2]
ф	13.	Plydactyly – postaxial hand	Temporality: Unable to assess[2]

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.	Pulmonary atresia with intact ventricular septum	Temporality: Unable to assess[2]
	3.	Hypospadias – angled penis	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]

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Retrospective Reports (continued)

	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.	VSD	Temporality: Cannot rule out a possible association [1]
	12.	Erb Palsy	Temporality: Cannot rule out a possible association [1]
	13.	Unspecified heart anomaly	Temporality: Unable to assess[2]
	14.	Left superior vena cava	Temporality: Unable to assess[2]
	15.	Esophageal Atresia/tracheoesophageal fistula, vertebral malformation	Temporality: Unable to assess[2]
	16.	Left club foot	Temporality: Unable to assess[2]
	17.	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.	Bilateral pyelocaliceal dilation	Temporality: Cannot rule out a possible association[1]
	6.	Cleft palate	Temporality: Cannot rule out a possible association[1]
	7.	Hypoplastic Right Ventricle, Tricuspid Atresia	Temporality: Cannot rule out a possible association[1]
	8.	Varus (inward) anomaly of foot	Temporality: Unable to assess[2]
ф	9.	Gastroschisis	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]

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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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]
ф¥	6.	Plagiocephaly	Temporality: Unable to assess[2]
	7.	Right ventricle hypoplasia, pulmonary valve atresia, quazi-atresia of tricuspid valve, cardiomegaly left ventricle	Temporality: Unable to assess[2]
	8.	Wolf-Hirschhorn phenotype	Temporality: No temporal association [3]

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.	Functional, undiagnosed cardiac murmurs (I, II/VI SEM)	Temporality: Cannot rule out a possible association[1]
	13.	Small Atrial Septal Defect (ASD)	Temporality: Cannot rule out a possible association[1]
	14.	Ventricular Septal Defect (VSD)	Temporality: Cannot rule out a possible association[1]
	15.	Fetal arrhythmia	Temporality: Cannot rule out a possible association[1]
	16.	Congenital anomalies of heart (hypertrophic cardiomyopathy)	Temporality: Cannot rule out a possible association[1]
	17.	Abnormal fetal heart rate/rhythm	Temporality: Cannot rule out a possible association[1]

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Retrospective Reports (continued)

18.	Congenital obstructive defects of renal pelvis and ureter, cardiac murmur	Temporality Cannot rule out a possible association[1]
19.	Right ureteral pelvic junction obstruction	Temporality: Cannot rule out a possible association[1]
20.	Microcephalus	Temporality: Cannot rule out a possible association[1]
21.	Polydactyly	Temporality: Cannot rule out a possible association[1]
22.	Congenital talipes equinovarus	Temporality: Cannot rule out a possible association[1]
23.	Trisomy 21	Temporality: Cannot rule out a possible association[1]
24.	Macroglossia, oblique palpebral fissures	Temporality: Cannot rule out a possible association[1]
25.	Hypertrophic cardiomyopathy	Temporality: Cannot rule out a possible association[1]
26.	Hepatosplenomegaly	Temporality: Cannot rule out a possible association[1]
27.	Hernia (left ovary)	Temporality: Cannot rule out a possible association[1]
28.	Macrocephaly	Temporality: Cannot rule out a possible association[1]
29.	Cardiac arrhythmia	Temporality: Cannot rule out a possible association[1]
30.	Hepatomegaly, cardiac rhythm disorder	Temporality: Cannot rule out a possible association[1]
31.	Convergent strabismus, torticollis, pedipes valgus	Temporality: Cannot rule out a possible association[1]
32.	Hollow feet, twisted right foot	Temporality: Cannot rule out a possible association[1]
33.	Albinism, nystagmus	Temporality: Cannot rule out a possible association[1]
34.	Multiple exostosis	Temporality: Cannot rule out a possible association[1]
35.	Inguinal hernia, hydrocele, strabismus	Temporality: Cannot rule out a possible association[1]
36.	Renal dilatation (left)	Temporality: Cannot rule out a possible association[1]
37.	Skeletal dysplasia (with bowed femurs)	Temporality: Cannot rule out a possible association[1]
38.	Patent Foramen Ovale (PFO)	Temporality: Cannot rule out a possible association[1]
39.	Hypertrophic cardiomyopathy	Temporality: Unable to assess[2]
40.	Genu valgum	Temporality: Unable to assess[2]
41.	Ventricular Septal Defect (VSD)	Temporality: Unable to assess[2]
42.	Right club foot	Temporality: Unable to assess[2]
43.	Left ventricular hypertrophy	Temporality: Unable to assess[2]
	Scaphocephaly	Temporality: No temporal association [3]
44.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
45.	Asymptomatic Ventricular Septal Defect (VSD)	Temporality: No temporal association [3]
46.	Diaphragmatic hernia	Temporality: No temporal association [3]
47.	Two-vessel cord, hypoplastic left heart and mitral atresia	Temporality: No temporal association [3]
48.	Mitral valve atresia	Temporality: No temporal association [3]

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49.	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]
50.	Ventricular Septal Defect (VSD), diaphragmatic hernia	Temporality: No temporal association [3]
51.	Polydactyly (left hand)	Temporality: No temporal association [3]
52.	Enlarged penis (>97 percentile)	Temporality: No temporal association [3]
53.	Double-outlet right ventricle and Ventricular Septal Defect (VSD)	Temporality: No temporal association [3]
54.	Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD)	Temporality: No temporal association [3]
55.	Cleft palate	Temporality: No temporal association [3]
56.	Acrania, sacral neural tube defect, bilateral cleft upper palate, contracted lower limbs	Temporality: No temporal association [3]
57.	Atrial septal defect (ASD)	Temporality: No temporal association [3]
58.	Hypospadias	Temporality: No temporal association [3]
59.	Missing/depressed right angularis muscle and absent orbicularis muscle, small patent ductus arteriosus (PDA)	Temporality: No temporal association [3]
60.	Congenital obstructive defect of renal pelvis and ureter	Temporality: No temporal association [3]
61.	Congenital subluxation of hip (unilateral)	Temporality: No temporal association [3]
62.	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]
63.	Congenital anomalies of larynx, trachea, and bronchus (congenital anterior subglottis web)	Temporality: No temporal association [3]
64.	Cardiac murmurs, congenital anomalies of brain (right choroid plexus cyst)	Temporality: No temporal association [3]
65.	Congenital musculoskeletal deformities of skull, face and jaw. Microcephalus seizures	Temporality: No temporal association [3]
66.	Polydactyly (left foot)	Temporality: No temporal association [3]
67.	Polydactyly (left hand)	Temporality: No temporal association [3]
68.	Nonspecific abnormality of skull/head, questionable click of left hip	Temporality: No temporal association [3]
69.	Congenital heart disease (biventricular hypertrophy), cardiomegaly	Temporality: No temporal association [3]
70.	Cardiac murmurs	Temporality: No temporal association [3]
71.	Cardiac murmur	Temporality: No temporal association [3]
72.	Cardiac murmur	Temporality: No temporal association [3]
73.	Potter's syndrome	Temporality: No temporal association [3]
74.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
75.	Congenital anomaly of genital organs (ambiguous genitalia)	Temporality: No temporal association [3]
76.	Atrial septal defect (ASD)	Temporality: No temporal association [3]
77.	Polydactyly (hand)	Temporality: No temporal association [3]
78.	Congenital subluxation of hip (unilateral), toxic erythema	Temporality: No temporal association [3]
79.	Polydactyly (hand)	Temporality: No temporal association [3]
80.	Hypospadias, epispadias	Temporality: No temporal association [3]
81.	Abnormal left ventricle	Temporality: No temporal association [3]
82.	Atrial septal defect (ASD)	Temporality: No temporal association [3]
83.	Hypospadias, microphallus	Temporality: No temporal association [3]
84.	Microcephalus	Temporality: No temporal association [3]
85.	Congenital stenosis of pulmonary valve, congenital anomaly of biliary tract	Temporality: No temporal association [3]
86.	Amniotic band syndrome right ankle	Temporality: No temporal association [3]
87.	Polydactyly (left hand)	Temporality: No temporal association [3]
88.	Hypoplastic left ventricle/atresic aortic arch	Temporality: No temporal association [3]

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[3] No temporal association

89.	Finger tag, heart murmur	Temporality: No temporal association [3]
90.	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]
91.	Talipes varus	Temporality: No temporal association [3]
92.	Fetal hydronephrosis	Temporality: No temporal association [3]
93.	Hypospadias	Temporality: No temporal association [3]
94.	Congenital megacolon	Temporality: No temporal association [3]
95.	Congenital megacolon	Temporality: No temporal association [3]
96.	Complex heart disease, aortic outflow obstruction	Temporality: No temporal association [3]
97.	Syndactyly of right 3-4 fingers, syndactyly of left 3-4 toes, left cleft lip	Temporality: No temporal association [3]
98.	Left chonal atresia, possible flattened facies, possible positional plagiocephaly	Temporality: No temporal association [3]
99.	Congenital dislocated hip (left)	Temporality: No temporal association [3]
100.	Duodenal atresia, cardiac malformation	Temporality: No temporal association [3]
101.	Mild strabismus, abnormal left ear	Temporality: No temporal association [3]
102.	Pulmonary atresia	Temporality: No temporal association [3]
103.	Microcephaly, dilated left cerebral ventricle	Temporality: No temporal association [3]
104.	Malrotation of small intestine	Temporality: No temporal association [3]
105.	Cleft lip and palate	Temporality: No temporal association [3]
106.	Right Ventricular Hypoplasia	Temporality: No temporal association [3]
107.	Polydactyly NOS - Hand	Temporality: No temporal association [3]
108.	Cleft lip	Temporality: No temporal association [3]
109.	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]
110.	Congenital anomaly NOS	Temporality: Unable to assess[2]
	Single umbilical artery	Temporality: No temporal association [3]
111.	Pulmonary stenosis, umbilical hernia, brown nevus	Temporality: Cannot rule out a possible association [1]
	Supernumerary nipple	Temporality: No temporal association [3]
112.	Angioma (nape of neck)	Temporality: Cannot rule out a possible association[1]
	Umbilical hernia	Temporality: No temporal association [3]
113.	Ptosis, strabismus, nystagmus	Temporality: Cannot rule out a possible association[1]
	Epicanthal folds	Temporality: No temporal association [3]
114.	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 NRTI(s) Only Regimen:

ф	1.	Mitochondriopathy	Temporality: Cannot rule out[1]
		White matter degeneration	Temporality: Unable to assess[2]

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	Corpus callosum hypoplasia	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 PI(s) only Regimen:

1.	Anomaly in cardiac rhytym, anomaly of myocardium	Temporality: Cannot rule out a possible association [1]

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	Temporality: Cannot rule out a possible association[1]
15.	Left hydronephrosis	Temporality: Cannot rule out a possible association [1]
16.	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]
17.	Trisomy 18, Ventricular septal defect	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]
18.	Craniosynostosis	Temporality: Unable to assess[2]

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[3] No temporal association

Retrospective Reports (continued)

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

	3.	Microcephaly	Temporality Cannot rule out a possible association[1]
	4.	Occipital plagiocephaly	Temporality: Unable to assess[2]
	5.	Undescended testicles	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.	Acrania with exencephaly (induced abortion >20 weeks gestation)	Temporality Cannot rule out a possible association[1]
*	4.	Renal agenesis, imperforate anus, anomaly of intestinal rotation, prunebelly syndrome, mega bladder	Temporality Cannot rule out a possible association[1]
	5.	Bilateral Extranumerary Digits – Postaxial Hand	Temporality: Unable to assess[2]
	6.	Ventricular Septal Defect (VSD)	Temporality: Unable to assess[2]
	7.	Pyelectasis, Down syndrome	Temporality: Cannot rule out a possible association[1]
		Tetralogy of Fallot	Temporality: No temporal association [3]
	8.	Hypospadias	Temporality: No temporal association [3]

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.	Fetal Alcohol Syndrome	Temporality Cannot rule out a possible association[1]
		Microcephaly, posterior segment anomaly, dysmorphic facies, other specified anomaly of the eye	Temporality: Unable to assess[2]
	3.	Umbilical hernia, strabismus	Temporality: Unable to assess[2]
	4.	Dysmelia of right hand	Temporality: Unable to assess[2]

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5.	Hypospadias (presumed male)	Temporality: Unable to assess[2]
6.	Short segment Hirschsprung's Disease, bilateral supernumary nipples	Temporality: Unable to assess[2]
7.	Microcephaly	Temporality: Unable to assess[2]
8.	Intestinal atresia	Temporality: Unable to assess[2]
9.	Biventricular hypertrophy, tricuspid regurgitation, Patent Foramen Ovale (PFO), patent ductus arteriousus (PDA)	Temporality: Unable to assess[2]
10.	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]
11.	Polydactyly (bilateral hands, left foot)	Temporality: Unable to assess[2]
12.	Communicating hydrocephalus, Ex vacuo ventriculomegaly	Temporality: Unable to assess[2]
13.	Talipes valgus	Temporality: Unable to assess[2]
14.	Potter's sequence	Temporality: Unable to assess[2]

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

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

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

1.	Gastrointestinal malformation, Tetralogy of Fallot	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]
2.	Clinodactyly, short fingers	Temporality: Unable to assess[2]

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

1.	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.	Right-sided aortic arch/double aortic arch/vascular ring, anomaly of trachea	Temporality: Unable to assess[2]
12.	Coarctation of aorta	Temporality: Unable to assess[2]
13.	Club foot	Temporality: Unable to assess[2]

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

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[3] No temporal association

	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.	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]

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]
	3.	Syndactyly, congenital jaw malformation, congenital club foot, cleft lip and palate	Temporality: Unable to assess[2]
	4.	Pulmonary stenosis	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:

	1.	Plagiocephaly	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]

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[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)	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 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	No temporal association [3]
4.	Clitoromegaly with hyperkalemia	Temporality: Cannot rule out a possible association[1]
	Polydactyly, syndactyly (both big toes)	No temporal association [3]

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[3] No temporal association

5.	Pectus excavatum	Temporality: Cannot rule out a possible association[1]
6.	Down Syndrome	Temporality: Cannot rule out a possible association[1]
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.	Syndactyly (fingers without fusion of bone)	Temporality: No temporal association [3]
11.	Hemivertibra (S2-S3)	Temporality: No temporal association [3]
12.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
13.	Venticular Septal Defect (VSD)	Temporality: No temporal association [3]
14.	Hypospadias	Temporality: No temporal association [3]
15.	Polydactyly	Temporality: No temporal association [3]
16.	Polydactyly (bilateral)	Temporality: No temporal association [3]
17.	Polydactyly (bilateral)	Temporality: No temporal association [3]
18.	Polydactyly (bilateral)	Temporality: No temporal association [3]
19.	Thyroglossal cysts	Temporality: No temporal association [3]
20.	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)	Temporality: Cannot rule out a possible association[1]
	Ventricular Septal Defect (VSD), Perimembranous	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:

3.	Ventricular Septal Defect (VSD), Patent Foramen Ovale (PFO)	Temporality: Cannot rule out a possible association[1]
4.	Inguinal herniation (right)	Temporality: Cannot rule out a possible association[1]
	Herniation of umbilicus	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.

* 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

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 peri-partum 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 2010)

Adefovir dipivoxil (HEPSERA®, ADV)

HEPSERA® is the trade name for Adefovir dipivoxil 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. Hepsera is not recommended for use in children below 12 years of age.

HEPSERA® is assigned FDA Pregnancy Category C status. There are no adequate data on the use of HEPSERA® in pregnant women.

Studies in animals administered adefovir intravenously have shown reproductive toxicity. Studies of HEPSERA® in orally dosed animals do not indicate teratogenic or fetotoxic effects.

HEPSERA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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. Mothers should be instructed not to breast-feed if they are taking HEPSERA® tablets.

Adefovir dipivoxil was mutagenic in the in vitro mouse lymphoma cell assay (with or without metabolic activation), but was not clastogenic in the in vivo mouse micronucleus assay.

Adefovir was not mutagenic in microbial mutagenicity assays involving *Salmonella typhimurium* (Ames) and *Escherichia coli* in the presence and absence of metabolic activation. Adefovir-induced chromosomal aberrations in the in vitro human peripheral blood lymphocyte assay without metabolic activation.

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).

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 sulfate (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.

Risk Summary
Atazanavir has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate. However, because the studies in humans cannot rule out the possibility of harm, REYATAZ should be used during pregnancy only if clearly needed.

Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have occurred in pregnant women using REYATAZ in combination with nucleoside analogues. Nucleoside analogues are associated with an increased risk of lactic acidosis syndrome. Hyperbilirubinemia occurs frequently in patients who take REYATAZ, including pregnant women. 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.

Clinical Considerations
Dosing During Pregnancy and the Postpartum Period:
REYATAZ should not be administered without ritonavir.
REYATAZ should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
For pregnant patients, no dose 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 H_2-receptor antagonist **or** tenofovir, 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 H_2-receptor antagonist *and* tenofovir in treatment-experienced pregnant women.

No dose 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.

Human Data
Clinical Trials: 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 <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 the upper limit of normal). There were no cases of lactic acidosis observed in clinical trial AI424-182. Atazanavir drug concentrations in fetal umbilical cord blood were approximately 12–19% 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 <40 mg/dL that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis.

Antiretroviral Pregnancy Registry Data: As of January 2010, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 635 exposures to atazanavir-containing regimens (425 exposed in the first trimester and 160 and 50 exposed in second and third trimester, respectively). Birth defects occurred in 9 of 393 (2.3%) live births (first trimester exposure) and 5 of 212 (2.4%) 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 atazanavir and overall birth defects observed in the APR.

Animal Data: In animal reproduction studies, there was no evidence of 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 post-natal development studies in the rat, atazanavir caused body weight loss or weight gain suppression in the animal offspring with maternal drug exposure (AUC) 1.3 times the human exposure at this clinical dose. However, maternal toxicity also occurred at this exposure level. (Last reviewed September 2011)

Cobicistat , (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. COBI has no antiretroviral activity against HIV-1, HBV or HCV. Cobicistat is one of the components of the single tablet regimen, Stribild™, which contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate and is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve. Please refer to the local prescribing information for Stribild™.

Stribild™ is assigned Pregnancy Category B status. Studies of cobicistat in animals have shown no evidence of teratogenicity or an effect on reproductive function. 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 1.8 and 4.3 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. Stribild™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

Cobicistat is not genotoxic and did not affect fertility in male or female rats at daily exposures (AUC) approximately 4-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 1.2-fold higher than human exposures at the recommended 150 mg daily dose.

(Last reviewed August 2012)

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 [*see Warnings and Precautions (5.11), Use in Specific Populations (8.1), Clinical Pharmacology (12.3) and Nonclinical Toxicology (13.2)*]. 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 6 to < 18 years of age and weighing at least 44 lbs (20 kg) [*see Adverse Reactions (6.6)*, *Clinical Pharmacology (12.3) and Clinical Studies (14.4)*]. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults [*see Adverse Reactions (6.6)*]. Please see *Dosage and Administration (2.2)* for dosing recommendations for pediatric subjects 6 to < 18 years of age and weighing at least 44 lbs (20 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 2012).

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 April 2011)

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 April 2010)

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.

Reproductive Risk Potential: Pregnancy Category D. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving SUSTIVA®. Barrier contraception must always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of SUSTIVA is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of SUSTIVA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

There are no adequate and well-controlled studies in pregnant women. SUSTIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options. As of July 2009, the Antiretroviral Pregnancy Registry has received prospective reports of 661 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (606 pregnancies). Birth defects occurred in 14 of 501 live births (first-trimester exposure) and 2 of 55 live births (second/third-trimester exposure). One of these prospectively reported defects was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported: however, this case included severe oblique facial clefts and amniotic banding, a known associate with anophalmia. There have been four retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of SUSTIVA® has not been established, similar defects have been observed in preclinical studies of efavirenz.

Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital days 20-150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day of SUSTIVA. Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of SUSTIVA. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans given 600 mg once daily of SUSTIVA.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to SUSTIVA®, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800 258-4263.

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats. Because of the potential for HIV transmission and the potential for serious adverse effects in nursing infants, mothers should be instructed not to breast-feed if they are receiving SUSTIVA.

Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. In studies in which rats were administered efavirenz at doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above background were observed. The systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans receiving the 600-mg/day dose. The exposure in rats was lower than that in humans. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, efavirenz showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an *in vivo* mouse bone marrow micronucleus assay. Given the lack of genotoxic activity of efavirenz, the relevance to humans of neoplasms in efavirenz-treated mice is not known.

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

Women receiving SUSTIVA should be instructed to avoid pregnancy. A reliable form of barrier contraception must always be used in combination with other methods of contraception, including oral or other hormonal contraception. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of SUSTIVA is recommended. Women should be advised to notify their physician if they become pregnant, or plan to become pregnant, while taking SUSTIVA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential harm to the fetus. (Last reviewed April 2010)

Elvitegravir (ELVITEGRAVIR™, EVG)

Elvitegravir is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor, and is one of the components of the single tablet regimen, Stribild™, which contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate and is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve. Please refer to the local prescribing information for Stribild™.

Stribild™ is assigned Pregnancy Category B status. 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. Stribild™ 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 Stribild™ do not breast-feed their infants.

Safety and effectiveness of EVG 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 August 2012)

Emtricitabine (EMTRIVA®, FTC)

EMTRIVA® is the brand name of emtricitabine, Emtricitabine is a nucleoside analogue of cytidine with activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus (HBV). Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate, which competitively inhibits 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 in patients four months of age and older.

EMTRIVA® is assigned Pregnancy Category B status. Reproductive studies were conducted in rats, mice, and rabbits. Animal studies (performed at 60 to120-fold human exposure) did not indicate harmful effects of emtricitabine with respect to fertility, pregnancy, fetal development, parturition or postnatal development.

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

It is not known whether emtricitabine is secreted into human milk. Therefore, it is recommended that mothers being treated with EMTRIVA® do not breast-feed their infants.
Mutagenesis: Emtricitabine was not mutagenic or clastogenic in conventional genotoxicity assays.

Carcinogenicity: Long-term carcinogenicity studies of emtricitabine in rats and mice did not show any carcinogenicity potential. (Last reviewed September 2011)

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 m^2 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 m^2 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)

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 with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

This indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment- naïve and lamivudine resistant adult 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 subects with HIV/HBV co-infection who have received prior lamivudine therapy.

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 (hemangiomas of ovaries and uterus and hemangiosarcomas of spleen) were increased at exposures 24 times those in humans; combined adenomas and carcinomas were also 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 April 2010)

Etravirine (INTELENCE®, ETR)

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

In patients who have experience virologic failure on an NNRTI-containg regimen, do not use INTELENCE® in combination with only N[t]RTIs.

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. Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of foetal harm. INTELENCE® 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. 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: The safety and efficacy of INTELENCE have not been established in pediatric patients less than 6 years of age or in treatment-naïve paediatric

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. [*See Nonclinical Toxicology (13.2)*.]

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 2012).

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 2010)

Indinavir (CRIXIVAN®, IDV)

Please refer to the package circular for full product information. Indinavir sulfate (CRIXIVAN®) is a potent and selective inhibitor of human immunodeficiency virus (HIV) protease. Indinavir in combination with antiretroviral agents is indicated for the treatment of HIV infection. In vitro studies indicate that cytochrome P-450 3A4 (CYP3A4) is the major enzyme responsible for formation of the six oxidative metabolites of indinavir. Indinavir is eliminated rapidly from the body, with a half-life of approximately 1.8 hours following a single dose. Multiple dosing at 800 mg every 8 hours did not result in significant accumulation of indinavir in the body.

Indinavir is assigned FDA Pregnancy Category C status. 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 levels 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 indinavir. It is unknown whether indinavir administered to the mother in the perinatal period will exacerbate physiologic hyperbilirubinemia in neonates. 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.

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

The optimal dosing regimen for use of indinavir in pregnant patients has not been established. 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). The mean indinavir plasma AUC0-8hr at weeks 30-32 of gestation (n=11) was 9231 nM●hr, which is 74% (95% CI: 50%, 86%) lower than that observed 6 weeks postpartum. Six of these 11 (55%) patients had mean indinavir plasma concentrations 8 hours post-dose (Cmin) below assay threshold of reliable quantification. The pharmacokinetics of indinavir in these 11 patients at 6 weeks postpartum were generally similar to those observed in non-pregnant patients in another study. 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.

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 2010)

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 (>6 months of age) populations.
Long-term carcinogenicity studies utilizing a 2:1 combination of lopinavir/ritonavir in rats and mice have been completed. There were no carcinogenic effects in rats dosed at levels of 10/5, 20/10 or 50/25 mg/kg/day of lopinavir/ritonavir. In this study, the mean drug exposures at the high dosages (50/25 mg/kg/day) were approximately 0.5-times (lopinavir) and 0.8 times (ritonavir) the exposures in humans with the recommended therapeutic dose of 400/100 mg BID. In mice dosed at levels of 20/10, 60/30 and 120/60 mg/kg/day of lopinavir/ritonavir, the incidences of benign hepatocellular adenomas, and combined incidences of hepatocellular adenomas and carcinomas in both male and female mice receiving the high dosage (120/60 mg/kg/day) were higher than the controls. Based on AUC measurements, the drug exposure at the high dose was approximately 2-fold (lopinavir) to 5-fold (ritonavir) higher than the exposures in humans with the recommended therapeutic dose. The increase tumor incidence was considered to have resulted from drug-related mitogenic stimuli and not genotoxicity. Such a tumor response in the murine liver is generally considered not to have a human correlate at anticipated clinical exposures, and therefore, the increases in the liver tumors in the mouse study were considered to have little human clinical relevance. However, 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/ritonavir is labeled FDA Pregnancy Category C.

***Antiretroviral Pregnancy Registry*:** As of January 2011, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 2458 exposures to lopinavir containing regimens (738 exposed in the first trimester and 1720 exposed in the second and third trimester). Birth defects occurred in 16 of the 738 (2.2%) live births (first trimester exposure) and 41 of the 1720 (2.4%) 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 lopinavir and overall birth defects observed in the APR. To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

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

Animal Data: No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. 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 2012)

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-foetal 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 foetal 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 foetuses. In an oral embryo-foetal 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 tumour, 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 April 2011)

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. (Last reviewed April 2010)

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

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.

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 >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.

Raltegravir (ISENTRESS®, RAL)

Raltegravir (ISENTRESS®, RAL) is a human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI).
Indications and usage: In combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. The safety and efficacy of ISENTRESS® have not been established in treatment-naïve adult patients or pediatric patients.

Pregnancy: ISENTRESS® is assigned FDA Pregnancy Category C status. 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: Breast-feeding is not recommended while taking ISENTRESS®. In addition, it is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. 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: Safety and effectiveness of ISENTRESS® in pediatric patients less than 16 years of age have not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term (2-year) carcinogenicity studies of raltegravir in rodents are ongoing. 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.

RILPIVIRINE (EDURANT® RPV)

EDURANT®, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients.

This indication is based on Week 48 safety and efficacy analyses from 2 randomized, double-blinded, active-controlled, Phase 3 trials in treatment-naïve subjects and Week 96 safety and efficacy analyses from a Phase 2b trial in treatment-naïve subjects.

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 compared to patients with HIV-1 RNA less than 100,000 copies/mL at the start of therapy
• 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 lamivudine/emtricitabine associated resistance 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. 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: Safety and effectiveness in pediatric patients 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.

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.

Ritonavir has a broad spectrum of activity against HIV types 1 and 2, including zidovudine-resistant HIV in a variety of transformed and primary human cell lines. Clinical trials with ritonavir at a dose of 600 mg twice daily, alone or in combination with nucleoside analogues, demonstrated profound reductions in viral RNA levels and substantial increases in CD4 cell counts among patients across a wide spectrum of HIV disease. In a Phase III trial ritonavir treatment compared with placebo led to decreases of approximately 50% in mortality and disease progression in patients with advanced disease who continued to receive various nucleoside analogue regimens. Ritonavir is labeled for use in combination with other antiretroviral agents or as monotherapy for the treatment of HIV-infection.

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 is labeled Pregnancy Category B. 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. 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.

There is minimal information on ritonavir use in pregnant women from clinical trials and postmarketing surveillance. However, the use of ritonavir with lamivudine and zidovudine in HIV infected pregnant women is currently being evaluated in ACTG Study 354. In addition, a multicenter trial to study ritonavir use for the

prevention of vertical transmission of HIV infection in treatment naïve pregnant women is being conducted in Thailand. Because animal studies are not always predictive of human response, ritonavir should be used during pregnancy only if clearly needed.

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 infectious HIV. 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 virus 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. (Last reviewed April 2010)

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

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 April 2010)

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.

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 (RT) 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.

VIREAD® is indicated for the treatment of chronic hepatitis B in adults.

VIREAD® is assigned FDA Pregnancy Category B status. Reproductive studies were conducted in rats and rabbits. 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.

VIREAD® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies it has been shown that tenofovir is excreted into milk. It is not known whether tenofovir is excreted in human milk. Therefore, it is recommended that mothers being treated with VIREAD® do not breast-feed their infants.

Tenofovir disoproxil fumarate did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumors, considered likely related to high local concentrations in the gastrointestinal tract at the high dose of 600 mg/kg/day. The mechanism of tumor formation in mice and potential relevance for humans is uncertain.

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 September 2011)

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 2010)

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. (Last reviewed April 2010).

(References: HIVID Core Data Sheet Version 1.2 Approved April 14, 2003; HIVID USPI Revised: September 2002)

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 tumours 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 tumours 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 tumours was noted with no increase in tumours 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 tumours 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 tumours 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 2010).

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. The Registry conforms to the FDA Guidance for Industry: Establishing Pregnancy Exposure Registries (30, 31), the Guidelines for Good Pharmacoepidemiology Practices (GPP) (32), and the FDA Guidance on Pharmacovigilance (33).

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 (34).

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.

The Registration and Follow-up

The Antiretroviral Pregnancy Registry collects data on use of abacavir, adefovir dipivoxil, amprenavir, atazanavir, darunavir, delavirdine mesylate, didanosine, efavirenz, elvitegravir/cobicistat, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, stavudine, telbivudine, 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 or mailing completed forms. Copies of the current forms are included in this report.

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 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. Retrospective reports, i.e., reports after the outcome of the pregnancy 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 to receive more information on how to participate. (Call 800-258-4263 or 910-256-0238 or Fax 800-800-1052 or 910-256-0637.) For UK, Germany, France toll free call 00800-5913-1359 or Fax 00800-5812-1658.* For Brazil Fax 888-259-5618. *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, FAX transmission to 800-800-1052 (US, Canada), +1-910-256-0637 (International), or by calling the Registry at 800-258-4263 (US, Canada) or +1-910-256-0238 (International). For UK, Germany, France toll free call 00800-5913-1359 or Fax 00800-5812-1658. For Brazil, Fax 888-259-5618. 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 is 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 (35). 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 abortion and the reporter is reluctant to code the type of abortion 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 the CDC MACDP system (3). The Registry's definition of birth defects is consistent with, but not restricted to the CDC list. Clusters of conditional abnormalities (as defined by CDC MACDP) and data from abortuses of ≥20 weeks, when available, have been included to increase the sensitivity of Registry monitoring. All MACDP cases have at least one major defect, regardless of whether conditional defects are also present. The Registry includes these cases, but differs from the MACDP protocol 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 does not systematically collect, but accepts information on minor abnormalities, 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 has developed an organ system classification based on the CDC MACDP terminology (9). 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.

The organ classification system is based on the British Pediatric Association (BPA) (36) and the MACDP (3, 4, 5). 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 comprised of 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, Apotex Inc, Aurobindo Pharma Ltd, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Gilead Sciences Inc, HEC Pharm, Hetero Labs Ltd, Ipca Laboratories Ltd, Janssen R&D Ireland, Merck & Co. Inc, Mylan Laboratories, Novartis Pharmaceuticals, Pfizer Inc, Prinston, Ranbaxy Inc, Roche, Sciegen Pharmaceuticals Inc, Strides Arcolab Ltd, Teva Pharmaceuticals, and ViiV Healthcare (represented by GlaxoSmithKline). 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-classifiaction 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 Texas BDR case definition includes all major defects in the calculation of birth defect rates regardless of the gestational age at outcome (10). Prior to then, only pregnancy outcomes occurring at 20 weeks gestation or greater were activily 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% (37). 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 (38, 39). 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 any 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, administered by the CDC, and the Texas Birth Defects Registry. 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 Texas Birth Defects Registry reports an overall prevalence of birth defects of 4.17% (95% CI 4.15, 4.19) for deliveries during 2000 through 2009 among women who were residents of Texas at the time of delivery (10). The prevalence of “early diagnoses” is important for Registry

[*] 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.

comparisons since the majority of outcome reports are from obstetricians who may have limited access to diagnoses made after the day of birth. 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 (40) 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. The MACDP, Texas BDR, 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.

For all birth defects combined, a cohort of 200 newborns exposed to antiretroviral drugs in the first trimester is sufficientto detect a 2.2 fold increased risk of birth defects compared to a general US population prevalence of 3% (39), with 80% power and a Type I error rate of 5%. 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 (41) (monograph available upon request).

Information about the Registry can be found in other Registry publications and presentations (42 - 74).

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**; abacavir (generic), lamivudine (generic), nevirapine (generic) manufactured by **Apotex Inc**; didanosine (generic), lamivudine (generic), nevirapine (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), didanosine (VIDEX®, VIDEX® EC, ddI), efavirenz (SUSTIVA®, STOCRIN®, EFV), entecavir (BARACLUDE®, ETV), and stavudine (ZERIT®, d4T) manufactured by **Bristol-Myers Squibb Company**; lamivudine (generic), stavudine (generic) and zidovudine (generic) manufactured by **Cipla Ltd**; adefovir dipivoxil (HEPSERA®, ADV), efavirenz+emtricitabine+tenofovir disoproxil fumarate (ATRIPLA®, ATR), elvitegravir+cobicistat+emtricitabine+tenofovir disoproxil fumarate (STRIBILD™, STB), emtricitabine (EMTRIVA®, FTC), rilipivirine+emtricitabine+tenofovir disproxil fumarate (COMPLERA®, CPA; EVIPLERA®, EPA), tenofovir disoproxil fumarate (VIREAD®, TDF) and tenofovir disoproxil fumarate+emtricitabine (TRUVADA®, TVD) manufactured by **Gilead Sciences Inc**; zidovudine (generic) manufactured by **HEC Pharma**; efavirenz (generic), lamivudine (generic), lamivudine+tenofovir dispoproxil fumarate (generic), nevirapine (generic), stavudine (generic), tenofovir disoproxil fumarate (generic), zidovudine (generic) and zidovudine+lamivudine (generic) manufactured by **Hetero Labs Ltd**; darunavir (PREZISTA®, DRV), etravirine (INTELENCE®, ETR) and rilpivirine (EDURANT®, RPV) manufactured by **Janssen R&D Ireland**; indinavir (CRIXIVAN®, IDV) and raltegravir (ISENTRESS®, RAL) manufactured by **Merck & Co. Inc**; didanosine (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**; nevirapine (generic) manufactured by **Prinston**; zidovudine (generic) manufactured by **Ranbaxy**; 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 **Roche**; nevirapine (generic) manufactured by **Sciegen Pharmaceuticals Inc**; nevirapine (generic) manufactured by **Strides Arcolab Ltd**; didanosine (generic) and zidovudine+lamivudine (generic) manufactured by **Teva Pharmaceuticals**; abacavir (ZIAGEN®, ABC), abacavir+lamivudine (EPZICOM®, EPZ), abacavir+ lamivudine+ zidovudine (TRIZIVIR®, TZV), amprenavir (AGENERASE®, APV), delavirdine mesylate (RESCRIPTOR®, DLV), fosamprenavir calcium (LEXIVA®, FOS), lamivudine (EPIVIR®, 3TC), lamivudine+zidovudine (COMBIVIR®, ZDV+3TC), maraviroc (SELZENTRY®, CELSENTRI®, MVC) and zidovudine (RETROVIR®, ZDV) manufactured by **ViiV HealthCare (represented by GlaxoSmithKline)**; 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 zidovudine (generic) manufactured by, **GlaxoSmithKline** (distributed by TEVA Pharmaceuticals Industries Ltd) and **Roxane** (distributed by Boehringer Ingelheim).

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 mail, phone, or fax to the Registry.

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 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 Form - (To be completed when notifying Registry of prenatal exposure while patient is still pregnant.)

REGISTER VIA PHONE OR FAX: contact the Registry Office for patient ID number
US, CANADA (toll-free): 800-258-4263 (Telephone), or (local) 910-256-0238
800-800-1052 (Fax)
INTERNATIONAL: +1-910-256-0238 (Telephone)
+1-910-256-0637 (Fax)
UK, GERMANY, FRANCE (toll-free): 00800-5913-1359 (Telephone)
00800-5812-1658 (Fax)
EUROPE: +32-2-714-5028 (Telephone)
+32-2-714-5024 (Fax)
Brazil: 888-259-5618 (Fax)

- 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
- 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 Form to the Registry (by mail 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 Office for a patient ID #at:
  US, CANADA (toll-free): 800-258-4263 (Telephone) or (local) 910-256-0238
  800-800-1052 (Fax)
  INTERNATIONAL: +1-910-256-0238 (Telephone)
  +1-910-256-0637 (Fax)
  UK, GERMANY, FRANCE (toll-free): 00800-5913-1359 (Telephone)
  00800-5812-1658 (Fax)
  EUROPE: +32-2-714-5028 (Telephone)
  +32-2-714-5024 (Fax)
  Brazil: 888-259-5618 (Fax)
  - 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 and Follow-Up Forms pages
- Complete as much information as is available to you.

Mail the completed form(s) to:

Antiretroviral Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405

Register via FAX:

(800) 800-1052 (toll free US, Canada)
+1-910-256-0637 (International) or
+32-2-714-5024 (Europe)
(00800) 5812 1658 (toll free UK, Germany, France)
888-259-5618 (Brazil)

Data Forms included (see next 7 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 form 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
10111	*Jane Doe*	*123656*	*01 Jan 2009*	*03 Jun 2008*

The Antiretroviral Pregnancy Registry
Instructions for Completing the REGISTRATION FORMS

General Guideline: Date format should always be entered as *DD/MMM/YYYY*

Patient (Log) ID: The Registry assigned Log ID number.

Date first seen during this pregnancy: Provide the date first seen in *DD/MMM/YYYY* format.

Maternal Information

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 check "Yes" or "No" if conducted in pregnant women

Last Menstrual Period (LMP): Provide the LMP date in *DD/MMM/YYYY* format.

Corrected Estimated Date of Delivery (EDD): Provide the EDD based on the 20 week prenatal test, especially if this is the date being used to calculate gestational age for medication exposures and outcome.

Patient Age: Provide age of the pregnant woman at time of conception.

Race: Check the appropriate box for the pregnant woman's race.

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, of when the prenatal test was performed and what prenatal test was conducted (ie., 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, provide the structural and/or chromosomal defect(s).

Clinical Indicators (at the START of pregnancy)

3.1 **Clinical Categories as Defined by the CDC:** www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm

Check ***all*** appropriate categories as they apply as close to the beginning of the pregnancy as possible.

- **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.

3.2 **CD4 + T-cell Categories:** 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 positive).

3.3 **Hepatitis Severity Indicator:** Check the appropriate indication for severity of the hepatitis at a time as close to the beginning of the pregnancy as possible (not applicable should be marked if the patient does not have hepatitis or if Pugh score is not yet known).

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., stavudine 80 mg, ZDV (IV) 650 mg).
- **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.
- **Gestation Week Course Began:** Indicate the gestation week (if unknown and a date the therapy began is available, that is sufficient) when treatment began.
- **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. This will help to ensure the Registry is calculating from the same date.
- **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

ANTIRETROVIRAL PREGNANCY REGISTRY
REGISTRATION FORM

Fax to: +1-800-800-1052 (US, Canada)
+1-910-256-0637 (International) or +32-2-714-5024 (Europe)
00800-5812-1658 (UK, Germany, France)
+1-888-259-5618 (Brazil)

FOR OFFICE USE ONLY (1)
Registry Patient ID _____ HCP ID _____
Prospective ☐ Retrospective ☐ 100% provider ☐
Country _____ State _____
Report type Original U/L ☐ MP ☐ Current U/L ☐ MP ☐
Registry date of notification _____ _____ _____ ☐ Phone

Patient (Log) ID: _____ ***Registry assigned ID number or Sponsor MCN***

Note: To help assure patient anonymity the Registry uses a Registry assigned patient ID to refer to your patient to obtain follow-up and outcome information.

Date patient first seen during this pregnancy
Date: _____ _____ _____ (M D Y)

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 trial 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 when test(s) done:

2.2 Is there evidence of a structural defect from one or more of these prenatal tests?

(✓) test(s)		2.2
☐	Ultrasound _____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	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 _____
☐	MSAFP/serum markers _____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____
☐	Other: _____ date	☐Yes ☐No ☐Unknown. If yes, Specify defect _____

☐ Unknown *(go to section 3)*

3. CLINICAL INDICATORS (at the ***START*** of pregnancy)

3.1 Clinical Categories *(√all that apply at the **start** of pregnancy)*:
☐ A. Asymptomatic, acute (primary) HIV or PGL*
☐ B. Symptomatic, not (A) or (C) conditions
☐ C. Other AIDS-indicator conditions and/or CD4<200
☐ D. HIV prophylaxis
☐ E. Hepatitis B (HBV)
☐ F. Hepatitis C (HCV)

*PGL-persistent generalized lymphadenopathy

For additional descriptions of categories refer to the 1993 CDC revised classification system, December 1992 issue of MMWR

3.2 CD4+ T-cell Categories *(at **start** of pregnancy)*
☐ ≥ 500 μL
☐ 200-499 μL
☐ <200 μL
☐ Not applicable

3.3 Hepatitis Severity Indicator *(at **start** of pregnancy):*
☐ 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 _____ _____ _____ (M D Y)

ANTIRETROVIRAL PREGNANCY REGISTRY
ANTIVIRAL THERAPY DURING PREGNANCY
(Initiated at registration and completed at follow-up)

FOR OFFICE USE ONLY: (2)
Registry ID_____
☐ Update

Patient (Log) ID: _____ ***The Registry assigned, non-patient identifying patient ID number or Sponsor MCN***

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.

4. ANTIVIRAL THERAPY DURING PREGNANCY

1. Use the med. codes below for antiviral medication taken during pregnancy. If not coded, ***Specify Medication****.*

1.	**Abacavir (ZIAGEN®, ABC)**
1.1	**Abacavir generic – Hetero**
1.2	**Abacavir generic – Apotex**
1.99	**Abacavir (unknown manufacturer)**
2.	**Didanosine (VIDEX®, VIDEX® EC, ddI)**
2.1	**Didanosine generic – Teva Pharmaceuticals**
2.2	**Didanosine generic – Aurobindo**
2.3	**Didanosine generic – Mylan**
2.99	**Didanosine (unknown manufacturer)**
3.	**Efavirenz (SUSTIVA®, EFV)**
3.1	**Efavirenz (STOCRIN®, EFV)**
3.2	**Efavirenz generic – Hetero**
3.99	**Efavirenz (unknown manufacturer)**
4.	**Lamivudine (EPIVIR®, 3TC)**
4.1	**Lamivudine generic – Hetero**
4.2	**Lamivudine+tenofovir df generic – Hetero**
4.3	**Lamivudine generic – Apotex**
4.4	**Lamivudine generic – Aurobindo**
4.99	**Lamivudine (unknown manufacturer)**
5.	**Lamivudine+zidovudine (COMBIVIR®, ZDV+3TC)**
5.1	**Lamivudine+zidovudine generic – Hetero**
5.2	**Lamivudine+zidovudine generic – Teva Pharmaceuticals**
5.3	**Lamivudine+zidovudine generic - Aurobindo**
5.99	**Lamivudine+zidovudine (unknown manufacturer)**
6.	**Nelfinavir (VIRACEPT®, NFV)**
7.	**Nevirapine (VIRAMUNE®, VIRAMUNE® XR™, NVP)**
7.1	**Nevirapine generic – Hetero**
7.2	**Nevirapine generic - Prinston**
7.3	**Nevirapine generic - Sciegen**
7.4	**Nevirapine generic – Apotex**
7.5	**Nevirapine generic – Aurobindo**
7.6	**Nevirapine generic – Strides**
7.99	**Nevirapine (unknown manufacturer)**
8.	**Ritonavir (NORVIR®, RTV)**
9.	**Saquinavir (FORTOVASE®, SQV-SGC)**
10.	**Saquinavir mesylate (INVIRASE®, SQV-HGC)**
11.	**Stavudine (ZERIT®, d4T)**
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)**
13.	**Zidovudine (RETROVIR®, ZDV)**
13.1	**Zidovudine oral generic – Ranbaxy**
13.2	**Zidovudine oral generic – Teva/GSK**
13.3	**Zidovudine oral generic – Roxane/BI**
13.4	**Zidovudine oral generic – Aurobindo**
13.5	**Zidovudine oral generic – Cipla**
13.6	**Zidovudine oral generic – Mylan**
13.7	**Zidovudine oral generic – Hetero**
13.8	**Zidovudine oral generic – HEC Pharm**
13.99	**Zidovudine oral (unknown manufacturer)**
14.	**Amprenavir (AGENERASE®, APV)**
15.	**Indinavir (CRIXIVAN®, IDV)**
16.	**Delavirdine mesylate (RESCRIPTOR®, DLV)**
17.	**Lopinavir+ritonavir (KALETRA®, ALUVIA®, LPV/r)**
18.	**Abacavir+lamivudine+zidovudine (TRIZIVIR®, TZV)**
19.	**Tenofovir disoproxil fumarate (VIREAD®, TDF)**
19.1	**Tenofovir disoproxil fumarate generic - Hetero**
19.99	**Tenofovir disoproxil fumarate (unknown manufacturer)**
20.	**Adefovir dipivoxil (HEPSERA®, ADV)**
21.	**Enfuvirtide (FUZEON®, T-20)**
22.	**Atazanavir sulfate (REYATAZ®, ATV)**
23.	**Emtricitabine (EMTRIVA®, FTC)**
24.	**Fosamprenavir calcium (LEXIVA®, FOS)**
25.	**Abacavir+lamivudine (EPZICOM®, EPZ)**
26.	**Tenofovir disoproxil fumarate+emtricitabine (TRUVADA®, TVD)**
27.	**Entecavir (BARACLUDE®, ETV)**
28.	**Tipranavir (APTIVUS®, TPV)**
29.	**Efavirenz+tenofovir disoproxil fumarate+emtricitabine (ATRIPLA™, ATR)**
30.	**Telbivudine (TYZEKA®, SEBIVO®, LdT)**
31.	**Darunavir (PREZISTA®, DRV)**
32.	**Raltegravir (ISENTRESS® RAL)**
33.	**Maraviroc (SELZENTRY®, CELSENTRI®, MVC)**
34.	**Etravirine (INTELENCE®, ETR)**
35.	**Rilpivirine (EDURANT®, RPV)**
36.	**Rilpivirine+Emtricitabine+Tenovfovir Disoproxil Fumarate (COMPLERA®, CPA; EVIPLERA®, EPA)**
37.	**Elvitegravir+Cobicistat+Emtricitabine+Tenofovir Disoproxil Fumarate (STRIBILD™, STB)**

2. In the following table, describe each course or change in route for each applicable therapy.

***Med. Code* (1-34) or if no code indicated, please write medication name and indicate if generic**		***Total Daily Dose (mg/day or mg/kg/hr)***	***Route (enter code) 1 = oral 2 = IV 3 = sub-Q***	***Pt Taking Med. at Conception? 1 = Yes 2 = No 3 = Unknown***	***Date Treatment Course Began (M/D/Y) OR Gestational Age Course Began (0 weeks = prior to conception)*** If gestational age, calculation source: ☐ *(LMP)* ☐ *(corrected EDD)*	***Date Treatment Stopped (M/D/Y) OR Ongoing?*** (Note: Ongoing = ongoing Following delivery)
Course						
						or ☐ ongoing
						or ☐ ongoing
						or ☐ ongoing
						or ☐ ongoing

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
- If yes, provide the study protocol number and check "Yes" or "No" if conducted in pregnant woman

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 or Induced abortion, or Stillbirth).

- 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 the 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".

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.*

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/.

ANTIRETROVIRAL PREGNANCY REGISTRY
FOLLOW-UP FORM

Fax to: **+1-800-800-1052 (US, Canada)**
+1-910-2560637 (International) or +32-2-714-5024 (Europe)
0800-5812-1658 (UK, Germany, France)
1-888-259-5618 (Brazil)

FOR OFFICE USE ONLY (3)
Registry Patient ID _____ HCP ID _____
Date Case Closed _____ _____ _____ ☐ Phone
☐ Normal Outcome Verified

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 trial 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: Defects (section 3) and/or other factors that may have contributed to the fetal loss (section 4)

2.3 Date of Outcome: _____ _____ _____ (M D Y)

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**
- **Complete the enclosed ANTIVIRAL THERAPY DURING PREGNANCY form. 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 _____ _____ _____ (M D Y)

Antiretroviral Pregnancy Registry Follow–up Form

FOR OFFICE USE ONLY (4)
Registry Patient ID _____

Patient (Log) ID: _____ ***The Registry assigned, non-patient identifying patient ID number or Sponsor Manufacturer Control Number (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.	

<u>Complete</u> the enclosed ANTIVIRAL THERAPY DURING PREGNANCY Form. The form includes the initial information provided to the Registry at registration.

Thank you for your participation in the Antiretroviral Pregnancy Registry.