THE ANTIRETROVIRAL PREGNANCY REGISTRY

Interim Report
For

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 DISOPROXIL FUMARATE (ATRIPLA™, ATR)
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®, NVP)
RALTEGRAVIR (ISENTRESS™, RAL)
RITONAVIR (NORVIR®, RTV)
SAQUINAVIR (FORTOVASE®, SQV-SGC) (FORTOVASE NO LONGER MANUFACTURED AS OF 6 JULY 06)
SAQUINAVIR MESYLATE (INVIRASE®, SQV-HGC)
STAVUDINE (ZERIT®, d4T)
TELBIVUDINE (SEBIVO®, TYZEKA®, LdT)
TENOFOVIR DISOPROXIL FUMARATE (VIREAD®, TDF)
TENOFOVIR DISOPROXIL FUMARATE+EMTRICITABINE (TRUVADA®, TVD)
TIPRANAVIR (APTIVUS®, TPV)
ZALCITABINE (HIVID®, ddC) (HIVID NO LONGER MANUFACTURED AS OF 12 DEC 06)
ZIDOVUDINE (RETROVIR®, ZDV)

1 JANUARY 1989 THROUGH 31 JANUARY 2008

(Issued: June 2008)

A Collaborative Project Managed by Kendle International Inc for:

Abbott Laboratories, Agouron Pharmaceuticals/Pfizer Inc, Aurobindo Pharma Ltd, Barr Laboratories Inc, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Gilead Sciences Inc, GlaxoSmithKline, Hetero USA, Merck & Company Inc, Mylan Laboratories, Novartis Pharmaceuticals, Ranbaxy Inc, Roche, Tibotec BVBA

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 The data contained in this report will become out-of-date within 6 months of the report's issue date.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 (800-258-4263) to ensure you have obtained the most recently published report.
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 5) must be included with any presentation of these data, including emphasis on the limitations of voluntary prenatal drug exposure registries such as this one.
4. When presenting data from the Registry please present Registry contact information and remind the audience that success of the Registry depends on reporting of exposures by health care professionals.
5. Please contact the Antiretroviral Pregnancy Registry staff if you have any questions, see contact information below.

Suggested Citation

Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2008. Wilmington, NC: Registry Coordinating Center; 2008. Available from URL: www.APRegistry.com.

REGISTRY COORDINATING CENTER

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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 2008.

Abacavir, adefovir dipivoxil, amprenavir, atazanavir, darunavir, delavirdine mesylate, didanosine, efavirenz, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, 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 along with representatives from the Sponsor companies constitutes the Registry Steering Committee. The Steering Committee meets to discuss issues, review data, update the report, and discuss the general conduct of the Registry. Members of the Advisory Committee and Sponsor representatives to the Steering Committee are listed below. Committee members are listed alphabetically within their respective group.

Antiretroviral Pregnancy Registry Advisory Committee

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UNC School of Public Health

The Antiretroviral Pregnancy Registry encourages reporting of all prenatal exposures to the therapies followed in the Registry (abacavir, adefovir dipivoxil, amprenavir, atazanavir, darunavir, delavirdine mesylate, didanosine, efavirenz, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, ritonavir, saquinavir, stavudine, telbivudine, tenofovir disoproxil fumarate, tipranavir, zalcitabine, and zidovudine). Patient enrollment forms and instructions begin on page 115. Please direct all enrollments and inquiries to the Antiretroviral Pregnancy Registry Coordinating Center at the following:

Website:	www.APRegistry.com for data forms and information
Mailing Address:	The Antiretroviral Pregnancy Registry Research Park 1011 Ashes Drive Wilmington, NC 28405
Telephone:	800-258-4263 US, Canada (toll-free) +1-910-256-0238 International or +32-2-714-5028 Europe 00800-5913 1359 UK, Germany, France (toll-free)
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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
Andrews, Mary Margaret MD
Arencibia, Damai RN
Bender, Peggy FNP
Boone, Jacqueline RN
Boudreaux, Netta RN
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Cejtin, Helen MD
Clutterbuck, Dan MD
Cormier, Sharon RN
Cubbedge, Laura LPN
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Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 – 31 January 2008*

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 Methods, Appendix E beginning on page 106.) 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.

Given the increasing number of medications and more aggressive approach to therapy, more HIV-infected women may be treated during pregnancy or become pregnant while under treatment. The paucity of prospective data on use and infant outcomes of antiretroviral therapies during pregnancy makes this Registry an essential component of the ongoing program of epidemiologic studies of the safety of these therapies.

Each year the Registry enrolls approximately 900 pregnant women in the US exposed to antiretroviral drugs. This number represents approximately 14% of the 6000-7000 HIV positive women who give birth to live infants annually in the US (2).

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). Also included in the primary analysis are 72 cases from a prospective study in Botswana. The rationale for these inclusions is described on pages 20 and 29 respectively.

*Drugs included: 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 DF (ATRIPLA™ ATR), 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®, NVP), raltegravir (ISENTRESS™, RAL) 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).

Data Summary

Primary Registry Analysis (Prospective Reports): In review of the data through 31 January 2008, 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 3.0 (95% confidence interval (CI): 2.5 - 3.5, i.e., 117 outcomes with defects of 3951 live births (Table 7). The prevalence of defects is not significantly different from the prevalence of defects among women with the first exposure during the second and/or third trimester (2.6 per 100 live births) (prevalence ratio: 1.13, 95% CI: 0.89, 1.43).

Measured against 9400 live births with exposure at any time during pregnancy, there were 261 outcomes with birth defects identified, a prevalence of 2.8 birth defects per 100 live births (95% CI: 2.5 - 3.1). This proportion is not substantially higher than the CDC's birth defects surveillance system (MACDP)[†] (5, 6, 7, 8) 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, an increased frequency for birth defects has been detected for didanosine only. Although no pattern of birth defects has been detected with didanosine, the Committee continues to monitor this increase.

For abacavir, efavirenz, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, and tenofovir, 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 lamivudine 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. (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. In reviewing all reported defects from the prospective Registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the defects reported show no pattern to suggest a common cause.

[†]MACDP, the Metropolitan Atlanta Congenital Defects Program actively searches for birth defects amonth all births in five counties of the metropolitan Atlanta area with approximately 50,000 annual births in a population of about 2.9 million. For more information, see references 5, 6, and 7. 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 (8).

Regimen	First Trimester Exposure Defects/Live Births	Prevalence (95% confidence interval)
Zidovudine	87/2808	3.1% (2.5%, 3.8%)
Lamivudine	85/2784	3.1% (2.4%, 3.8%)
Nelfinavir	33/972	3.4% (2.3%, 4.7%)
Nevirapine	18/737	2.4% (1.5%, 3.8%)
Stavudine	19/651	2.9% (1.8%, 4.5%)
Ritonavir	16/628	2.5% (1.5%, 4.1%)
Abacavir	17/512	3.3% (1.9%, 5.3%)
Tenofovir	11/491	2.2% (1.1%, 4.0%)
Efavirenz	10/364	2.7% (1.3%, 5.0%)
Didanosine	16/353	4.5% (2.6%, 7.3%)
Lopinavir	6/328	1.8% (0.7%, 3.9%)
Indinavir	6/272	2.2% (0.8%, 4.7%)

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, 17 infants with defects were identified among 269 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 6.3 (95% CI: 3.7 - 9.9) (Table 12). The number of defects identified with a first exposure in the second or third trimester is 24/971, and the prevalence of birth defects per 100 live births is 2.5 (95% CI: 1.6 - 3.7). 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. A published analysis from the Women and Infants Transmission Study (WITS) detected a statistically significant elevated rate of hypospadias after first trimester exposure to zidovudine. These data have been incorporated into the primary analysis beginning with the January 2008 Interim Report. The signal has not appeared elsewhere in the primary analysis of the Registry. The Registry will continue to monitor this closely.

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

Primary Registry Analysis (Prospective Reports)

The Registry's analytic approach is to evaluate drugs in all specific classes of antiretroviral therapies. The following specific drugs have large enough groups of exposed women to warrant a separate analysis: abacavir, didanosine, efavirenz, indinavir, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, tenofovir, and zidovudine.

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, an increased frequency for birth defects has been detected for didanosine only. Although no pattern of birth defects has been detected with didanosine, the Committee continues to monitor this increase.

For abacavir, efavirenz, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, and tenofovir, 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 lamivudine 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.

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.

Supplemental Analyses

Retrospective Reports: Retrospective reports are those reported to the Registry after the outcome or perceived outcome of pregnancy is known. 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.

Reports from Clinical Studies in Pregnancy: 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. The Registry will continue to examine data as available from further studies. A published analysis from the Women and Infants Transmission Study (WITS) detected a statistically significant elevated rate of hypospadias after first trimester exposure to zidovudine. The signal has not appeared in the primary analysis of the Registry. The WITS data have been incorporated into the primary analysis beginning with the January 2008 Interim Report. The Registry will continue to monitor hypospadias closely.

Reports from the Published Literature: The registry has not identified a signal in any of the published studies reviewed to date.

Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 – 31 January 2008

INTRODUCTION

The purpose of the Antiretroviral Pregnancy Registry (Registry) is to detect any major teratogenic effects of the following drugs when administered to pregnant women (1): abacavir (ZIAGEN®, ABC), abacavir/lamivudine (EPZICOM®), 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™), 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®, NVP), raltegravir (ISENTRESS™, RAL), 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.

Given the increasing number of medications and more aggressive approach to therapy, more HIV-infected women may be treated during pregnancy or become pregnant while under treatment. The lack of data on use and outcomes of antiretroviral therapies during pregnancy makes such a Registry an essential component of the ongoing program of epidemiologic studies on the safety of these medications. 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 106). 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 2008.

The Antiretroviral Pregnancy Registry is managed by Kendle International Inc., under the sponsorship of Abbott Laboratories, Agouron Pharmaceuticals/Pfizer Inc, Aurobindo Pharma Ltd, Barr Laboratories Inc, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company,

* 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.

Cipla Ltd, Gilead Sciences Inc, GlaxoSmithKline, Hetero USA, Merck & Co. Inc, Mylan Laboratories, Novartis Pharmaceuticals, Ranbaxy Inc, Roche, and Tibotec BVBA. 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, emtricitabine, enfuvirtide, etravirine, maraviroc, nelfinavir, nevirapine, 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, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, 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 900 pregnant women in the US exposed to antiretroviral drugs. This number represents approximately 14% of the 6000-7000 HIV positive women who give birth to live infants annually in the US (2).

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). Also included in the primary analysis are 72 cases from a prospective study in Botswana. The rationale for these inclusions is described on pages pages 20 and 29 respectively.

REGISTRY (PROSPECTIVE) CASES – PRIMARY ANALYSIS

Through 31 January 2008 there were 11209 prospective cases reported to the Registry (Table 1). There were 431 cases pending the outcome of pregnancy and 889 lost to follow-up. Thus, there were 9889 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 52 countries. Reports are predominantly from the United States and its territories (US) (88.8%). Non-US reports are most frequently reported from France (1.2%), the United Kingdom (3.2%), Germany (0.6%), Australia (0.3%), Brazil (0.4%), South Africa (0.7%), and Sweden (0.2%).

Antiretroviral Exposure

Of the 9889 evaluable prospective reports, 4458 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 9889 pregnancies reported, there were 10065 outcomes of pregnancy including 178 multiple births): 9397 live births, 218 spontaneous abortions, 125 stillbirths, and 325 induced abortions. Of the 9397 live births, 3951 had a maternal exposure to antiretroviral therapy during the first trimester. It should be noted that there were 1195 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 2008

	Overall	
Pregnancies Enrolled	11209	
Pending Cases [1]	431	(3.8%)
Cases lost to follow-up [2]	889	(7.9%)
Reports used in analysis	9889	(88.2%)

[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 2008

	Primary Analysis	Lost to Follow-up
Pregnancies Enrolled	9889	889
Age (years)		
N	9768	771
Median (Interquartile Range)	28.0 (9.0)	28.0 (8.0)
Min - Max	13 - 55	15 - 44
Missing	121	118
CD4+ T-cell categories at start of pregnancy		
>= 500 L	3014 (30.5%)	210 (23.6%)
200-499 L	4531 (45.8%)	285 (32.1%)
< 200 L	1830 (18.5%)	101 (11.4%)
Unknown	69 (0.7%)	43 (4.8%)
N/A	71 (0.7%)	25 (2.8%)
Missing	374 (3.8%)	225 (25.3%)
Clinical categories at start of pregnancy		
HIV Infected [1]		
A. Asymptomatic, acute (primary) HIV or PGL	7219 (73.0%)	480 (54.0%)
B. Symptomatic, not (A) or (C) conditions	922 (9.3%)	34 (3.8%)
C. AIDS-indicator conditions	1208 (12.2%)	75 (8.4%)
HIV Uninfected [2]		
HIV Postexposure prophylaxis	26 (0.3%)	9 (1.0%)
Hepatitis B mono-infected	61 (0.6%)	17 (1.9%)
Unknown	77 (0.8%)	41 (4.6%)
Missing	376 (3.8%)	233 (26.2%)

[1] Includes 98 patients co-infected with HIV and Hepatitis B.
[2] Where antiretroviral drugs have been used for therapy.
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 2008

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Enrolled	4458	4012	1416	9889
NRTI	1225	1387	599	3212
NtRTI	41	0	0	41
NNRTI	36	0	2	38
PI	65	13	0	79
NRTIs/NNRTIs	808	582	216	1607
NRTIs/NtRTIs	159	21	8	188
NRTIs/NtRTIs/NNRTIs	94	19	6	119
NRTIs/PIs	1499	1835	538	3872
NNRTIs/PIs	14	1	0	15
NRTIs/NNRTIs/PIs	184	54	18	256
NRTIs/NtRTIs/PIs	266	95	27	388
NtRTIs/NNRTIs/PIs	5	0	0	5
NRTIs/NtRTIs/NNRTIs/PIs	43	5	2	50
PI(s) + NRTI(s) + NtRTI	9	0	0	9
Other combination	10	0	0	10

[1] NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, zalcitabine, and zidovudine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, telbivudine, and tenofovir disoproxil fumarate.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, and nevirapine.
PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.
[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.

Pregnancy Outcomes

Of the 3951 live birth outcomes with a 1st trimester exposure to an antiretroviral drug, there were 117 reports of defects (110 / 3841 defects in live births, 3 / 66 in stillbirths, and 4 / 315 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 109*.) Therefore, Table 4 excludes reports of only one conditional defect or defects identified in a fetal loss occurring earlier than 20 weeks gestation. See Appendix C for the list of defects reported to the Registry and classified by the Registry as defects. To facilitate the recognition of a potential signal, the Registry has developed an organ system classification system which removes some of the granularity in looking at individual defects by grouping similar defects or defects of similar etiology together (10). See Appendix E for further description of the system.

Of the 9397 live birth outcomes, 5446 are in the combined second and/or third trimester exposure group, with 143 reported birth defects (Table 4). This includes 1990 live births with a second and/or third trimester exposure in the NRTI(s) only exposure group, with 54 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 66 defects of 2381 live births; for the NRTI + NNRTI group, 17 defects of 796 births; for the PI + NRTI + NNRTI group, 3 defect of 75 births and in the other combination groups of 186 live births there were 3 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 defect evaluator with agreement by the Advisory Committee.

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, an increased risk for birth defects has been detected for didanosine only. All cases were thoroughly reviewed and no pattern was discovered. These defects are detailed on the following listing. Although no pattern of birth defects has been detected with didanosine, the Registry continues to monitor an apparent increased frequency of defects among infants exposed to didanosine in the first trimester of gestation.

For abacavir, efavirenz, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, and tenofovir, 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 lamivudine 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.

Listing 1: Listing of Birth Defect Cases with Didanosine Exposure – Prospective Registry Cases with Follow-up Data Closed Through 31 January 2008

First-Trimester Exposure to Didanosine	Exposure to other Antiretroviral Drugs by Trimester
Saccrococcygeal teratoma	Nelfinavir (1st), tenofovir (1st)
Anomaly in cardiac rhythm	Nelfinavir (1st), zidovudine (1st)
Anomaly of calf	Kaletra (1st) stavudine (1st), tenofovir (3rd), zidovudine (3rd)
Chordee and hypospadias NOS	Atazanavir (1st), stavudine (1st)
Hypospadias	Lamivudine (1st), nelfinavir (1st), zidovudine (1st), efavirenz (3rd), ritonavir (3rd)
Hypospadias	Nelfinavir (1st), stavudine (1st)
Congenital hydronephrosis	Lamivudine (1st), tenofovir (1st), combivir (2nd)
Lobulated/fused/horseshoe kidney	Indinavir (1st), stavudine (1st), zidovudine (1st)
Polydactyly NOS - hand	Efavirenz (1st), combivir (1st), nelfinavir (1st), stavudine (1st), indinavir (3rd), ritonavir (3rd), zidovudine (3rd)
SMAI*	Abacavir (1st), lamivudine (1st), nelfinavir (1st), stavudine (1st), combivir (3rd)
Hip dysplasia/dislocation	Nevirapine (1st), zidovudine (1st), abacavir (2nd), lamivudine (2nd), nelfinavir (2nd), saquinavir (2nd)
Pectus excavatum, other specified anomaly of respiratory system	Zidovudine (2nd)
Heterotaxy syndrome	Nelfinavir (1st),nevirapine (1st), combivir (2nd), lamivudine (2nd), zidovudine (2nd)
Tricuspid atresia, tiny right ventricle, and atrial septal defect	Nelfinavir (1st), nevirapine (1st)
Genetic/Chromosomal Defects	
Trisomy 21, patent ductus arterious (PDA)	Nelfinavir (1st), zidovudine (1st)
Trisomy 21, VSD, other specified anomaly of nose	Nelfinavir (1st), stavudine (1st), combivir (2nd)
Second/Third-Trimester Exposure to Didanosine	**Exposure to other Antiretroviral Drugs**
Anotia/Microtia	Combivir (1st), nelfinavir (1st), ritonavir (3rd), saquinavir (3rd)
Other and unspecified polydactyly	Combivir (2nd), nelfinavir (2nd), zidovudine (2nd)
Mild bilateral renal pelviectasis	Lamivudine (2nd), saquinavir (2nd), zidovudine (2nd)
Premature synostosis of metopic suture	Lamivudine (2nd), zidovudine (2nd)
Club foot	Lamivudine (1st), nelfinavir (2nd), stavudine (2nd)

* Spinal muscular atrophy is probably genetically based. DNA mutation study results not available.

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 10 among the 364 infants with first trimester exposure to efavirenz. A single case of myelomeningocele has been noted.

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 Metropolitan Atlanta Congenital Defects Program (MACDP) classifications and to increase the potential to identify a possible pattern or signal (10). 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 2008

	With Birth Defects[3] / Without Birth Defects[4]				
	Live Births	Spontaneous Losses	Still-birth	Induced Abortions	Overall
Number of Outcomes [5,6]	248 / 9149	0 / 218	7 / 118	5 / 320	10065
Earliest Exposure					
First Trimester	110 / 3841	0 / 199	3 / 66	4 / 315	4538
Second/Third Trimester	138 / 5308	0 / 19	4 / 52	1 / 5	5527
First Trimester:					
NRTI	32 / 1054	0 / 32	1 / 13	2 / 108	1242
NtRTI	0 / 27	0 / 3	0 / 0	0 / 12	42
NNRTI	0 / 30	0 / 2	0 / 0	0 / 4	36
PI	2 / 50	0 / 5	0 / 0	0 / 8	65
NRTIs/NNRTIs	19 / 691	0 / 56	0 / 14	0 / 44	824
NRTIs/NtRTIs	2 / 103	0 / 15	0 / 11	0 / 30	161
NRTIs/NtRTIs/NNRTIs	2 / 77	0 / 11	0 / 3	0 / 4	97
NRTIs/PIs	41 / 1348	0 / 41	2 / 17	1 / 78	1528
NtRTIs/PIs	0 / 2	0 / 0	0 / 2	0 / 1	5
NNRTIs/PIs	0 / 5	0 / 3	0 / 1	0 / 5	14
NRTIs/NNRTIs/PIs	5 / 158	0 / 15	0 / 1	1 / 5	185
NRTIs/NtRTIs/PIs	7 / 241	0 / 12	0 / 2	0 / 13	275
NtRTIs/NNRTIs/PIs	0 / 3	0 / 0	0 / 1	0 / 1	5
NRTIs/NtRTIs/NNRTIs/PIs	0 / 40	0 / 3	0 / 1	0 / 0	44
NRTIs/NtRTIs/PIs/EIs	0 / 8	0 / 0	0 / 0	0 / 1	9
Other combination	0 / 4	0 / 1	0 / 0	0 / 1	6

[1] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion ≥20 weeks gestation.
[2] NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, zalcitabine, and zidovudine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, telbivudine, and tenofovir disoproxil fumarate.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, and nevirapine.
PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium,indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.
[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 178 multiple births.
[6] Includes data from the DART Study (See page 20)
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 2008
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]	117/3951		143/5446	
Proportion of defects reported with an exposure to: [3, 4]				
Any NRTI containing regimen	115/3830		145/5506	
Any Abacavir regimen	17/512	3.3% (1.9%, 5.3%)	23/788	2.9% (1.9%, 4.4%)
Any Didanosine regimen [5]	16/353	4.5% (2.6%, 7.3%)	5/252	2.0% (0.6%, 4.6%)
Any Emtricitabine regimen	6/194		1/103	
Any Entecavir regimen	0/2		0/0	
Any Lamivudine regimen	85/2784	3.1% (2.4%, 3.8%)	120/4476	2.7% (2.2%, 3.2%)
Any Stavudine regimen	19/651	2.9% (1.8%, 4.5%)	6/188	3.2% (1.2%, 6.8%)
Any Zalcitabine regimen	2/40		0/12	
Any Zidovudine regimen	87/2808	3.1% (2.5%, 3.8%)	158/5858	2.7% (2.3%, 3.2%)
Any NtRTI containing regimen	11/515		4/308	
Any Adefovir dipivoxil regimen [6]	0/23		0/0	
Any Telbivudine regimen [6]	0/1		0/0	
Any Tenofovir regimen	11/491	2.2% (1.1%, 4.0%)	4/309	1.3% (0.4%, 3.3%)
Any NNRTI containing regimen	27/1032		28/1138	
Any Delavirdine regimen	0/11		0/2	
Any Efavirenz regimen [7]	10/364	2.7% (1.3%, 5.0%)	2/36	5.6% (0.7%, 18.7%)
Any Nevirapine regimen	18/737	2.4% (1.5%, 3.8%)	27/1141	2.4% (1.6%, 3.4%)
Any PI containing regimen	59/1912		84/3067	
Any Amprenavir regimen	1/27		0/10	
Any Atazanavir sulfate regimen	5/188		2/94	
Any Darunavir regimen	2/8		0/4	
Any Fosamprenavir calcium regimen	2/51		0/13	
Any Indinavir regimen	6/272	2.2% (0.8%, 4.7%)	3/161	1.9% (0.4%, 5.4%)
Any Lopinavir regimen	6/328	1.8% (0.7%, 3.9%)	19/815	2.3% (1.4%, 3.6%)
Any Nelfinavir regimen	33/972	3.4% (2.3%, 4.7%)	64/2159	3.0% (2.3%, 3.8%)
Any Ritonavir regimen	16/628	2.5% (1.5%, 4.1%)	26/1019	2.6% (1.7%, 3.7%)
Any Saquinavir regimen	6/142		8/184	
Any Tipranavir regimen	0/2		0/1	
Any EI containing regimen	0/11		0/4	
Any Enfuvirtide regimen	0/11		0/4	

[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 52 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] The Registry notes the high frequency of defects after first trimester exposure to didanosine compared with second/third trimester exposures. All defects were reviewed and no pattern was discovered. See Listing 1: Listing of Birth Defect Cases with Didanosine Exposure - Prospective Registry Cases with Follow-up Data Closed Through 31 January 2008 for a description of these defects.
[6] For treatment of HBV
[7] The ten infants with defects reported with first trimester exposure to efavirenz were: 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 and 6) polydactyly, and 7) long bones malformation, 8) sacral myelomeningocele and hydrocephalus, 9) shortening of right leg, and 10) cutis aplasia (scalp).
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.

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 2008

	Earliest Antiretroviral Therapy (ART) Exposure in First Trimester						
	Any NRTI(s)	Any NtRTI(s)	Any NNRTI(s)	Any PI(s)	Any EI(s)	Overall First Trimester Exposure	Earliest ART Exposure in Second and/or Third Trimester
Pregnancies Identified	4290	624	1185	2093	14	4457	5428
Number of Pregnancies with Multiple Gestations	78	17	21	41	0	80	98
Number of Outcomes [2]	4369	641	1207	2134	14	4538	5527
Number of Live Births	3830	515	1032	1912	11	3951	5446
Number of Outcomes with Defects [1,2]	115	11	27	59	0	117	143
CNS	7	2	3	3	0	7	11
Eye, ear, face and neck	13	1	1	9	0	13	21
Cleft lip and/or palate	4	1	0	1	0	4	11
Conotruncal heart defects	4	1	0	3	0	4	5
Obstructive heart defects - right sided	2	0	2	2	0	3	7
Obstructive heart defects - left sided	1	0	0	0	0	1	2
Heart - other defects	15	0	4	9	0	15	28
Other circulatory system	5	1	3	1	0	5	6
Respiratory system	1	0	0	0	0	1	0
Upper gastrointestinal system	3	0	0	1	0	3	2
Lower gastrointestinal system	3	0	0	2	0	4	6
Female genitalia	2	0	0	0	0	2	0
Male genitalia	15	0	0	10	0	16	8
Renal and urinary system	16	3	4	9	0	16	10
Limb reduction/addition defects	13	3	3	7	0	13	23
Other musculoskeletal defects	27	1	8	11	0	27	28
Skin and skin derivatives	4	0	2	2	0	4	2
Chromosome anomaly	9	1	0	7	0	9	12
Other organs and organ systems	6	2	2	4	0	6	6
Specified syndromes/sequences/associations	9	2	1	6	0	9	6

[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.
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:NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, zalcitabine, and zidovudine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, telbivudine, and tenofovir disoproxil fumarate.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, and nevirapine.
PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.

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 117 outcomes with defects of 3951 live births or 3.0% (95% CI: 2.5 - 3.5). Measured against 9400 live births with exposure at any time during pregnancy, there were 261 outcomes with birth defects, a prevalence of 2.8 birth defects per 100 live births (95% CI: 2.5 - 3.1). This proportion is not substantially higher than the CDC's population-based birth defects surveillance system (MACDP) [†] (5, 6, 7, 8) 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. Additionally, the prevalence of defects among offspring of women with first trimester exposure to antiretroviral medications (3.0 per 100 live births) is not significantly different from the prevalence of defects among women with the first exposure during the second and/or third trimester (2.6 per 100 live births) (prevalence ratio: 1.13, 95% CI: 0.89, 1.43).

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 2008

	Overall
Number of Live Births	9400
Number of Outcomes with at least one defect [2]	261 (2.8%)
95% Confidence Intervals for prevalence [3] of Birth Defects [4] for exposures in:	
First Trimester	117/3951 (3.0%) 2.5% - 3.5%
Second/Third Trimester	143/5446 (2.6%) 2.2% - 3.1%
Any Trimester	261/9400 (2.8%) 2.5% - 3.1%
Risk of defects for first trimester exposures relative to second/third trimester exposures	1.13 (0.89, 1.43)

[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 ≥20 weeks gestation.
Note: Only upper confidence limits are presented when no defects were observed.
Note: See Table 4 for the other pregnancy outcomes.

[†]MACDP, the Metropolitan Atlanta Congenital Defects Program actively searches for birth defects amonth all births in five counties of the metropolitan Atlanta area with approximately 50,000 annual births in a population of about 2.9 million. For more information, see references 5, 6, and 7. 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 (8).

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 defect evaluator with agreement by the Advisory Committee. Because of animal data, particular emphasis is placed on review of central nervous system (CNS) defects. To date, the Registry has received retrospective reports of five myelomeningocele (neural tube) defects, three with efavirenz exposure and in addition two Dandy Walker defects 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 (8). 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. 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.

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.

Data from two observational studies (ACTG 367 and WITS (Women and Infants Transmission Study)), formerly included in this section, have been moved to the primary Registry analysis. The WITS study has ended and all data have been provided to the Registry. The rationale for moving 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. Data from several clinical studies (ACTG 082, PACTG 326, ACTG 5084, NIH 00861) as well as data from a German multi-site clinical study with intensive follow-up of infants for 18 months were moved from the primary analysis to this section.

To date the Registry has received 173 cases from a prospective clinical study in Africa (the Development of AntiRetroviral Therapy in Africa study – DART), which is a 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.

In a published analysis from the Women and Infants Transmission Study, an elevated rate of hypospadias after first trimester zidovudine exposure was detected. 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. In the current analysis, no additional cases of hypospadias have been received. The Registry continues to monitor this defect closely.

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 (VIRACEPT®) 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 in 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#Viracept 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 Viracept®) and to provide guidance on the use of Viracept® in patients. Effective March 31, 2008, all Viracept® 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 Viracept® manufactured by Pfizer for the US and Puerto Rico, is available at: http://www.pfizerpro.com.

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

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

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

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 31 January 2008

	Clinical Studies in Pregnancy
Pregnancies Reported	1230
Age (years)	
N	1222
Median (Interquartile Range)	26.0 (9.0)
Min - Max	13 - 43
Missing	8
CD4+ T-cell categories at start of pregnancy	
>= 500 L	255 (20.7%)
200-499 L	742 (60.3%)
< 200 L	219 (17.8%)
Unknown	3 (0.2%)
N/A	0 (0.0%)
Missing	11 (0.9%)
Clinical categories at start of pregnancy *	
A. Asymptomatic, acute (primary) HIV or PGL	386 (31.4%)
B. Symptomatic, not (A) or (C) conditions	40 (3.3%)
C. AIDS-indicator conditions	38 (3.1%)
Unknown	343 (27.9%)
Missing	423 (34.4%)

* Includes 1 patient co-infected with HIV and Hepatitis B

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 2008

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Reported	262	511	457	1230
NRTI	160	382	416	958
NRTIs/NNRTIs	27	33	24	84
NRTIs/PIs	58	95	13	166
NRTIs/NNRTIs/PIs	8	0	1	9
NRTIs/NtRTIs/PIs	6	0	1	7
Other combination	3	1	2	6

[1] NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, zalcitabine, and zidovudine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, telbivudine, and tenofovir disoproxil fumarate.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, and nevirapine.
PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
EI=entry inhibitor, which includes enfuvirtide, and maraviroc.
[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.

Table 10 presents a pooled summary of pregnancy exposures and outcome data from all reported studies. Among the 1249 (Table 10) prospectively reported outcomes in this group, there were 269 live births with a first trimester exposure, with 17 / 252 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 6.3 (95% CI: 3.7 - 9.9) (Table 12). The number of defects identified with a first exposure in the second or third trimester was 24/971. The prevalence of birth defects per 100 live births among women in this group was 2.5 (95% CI: 1.6 - 3.7). The prevalence of defects among offspring of women with first trimester exposure to antiretroviral medications (6.3 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 (2.5 per 100 live births) [prevalence ratio: (2.56, 95% CI: 1.39, 4.69)]. 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.

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 is conducting a thorough evaluation of these cases.

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 2008

	With Birth Defects[3] / Without Birth Defects[4]				
	Live Births	Spontaneous Losses	Still-birth	Induced Abortions	Overall
Number of Outcomes [5]	41 / 1199	0 / 1	0 / 8	0 / 0	1249
Earliest Exposure					
First Trimester	17 / 252	0 / 1	0 / 0	0 / 0	270
Second/Third Trimester	24 / 947	0 / 0	0 / 8	0 / 0	979
First Trimester:					
NRTI	8 / 156	0 / 0	0 / 0	0 / 0	164
NRTIs/NNRTIs	2 / 28	0 / 1	0 / 0	0 / 0	31
NRTIs/PIs	6 / 52	0 / 0	0 / 0	0 / 0	58
NRTIs/NNRTIs/PIs	1 / 7	0 / 0	0 / 0	0 / 0	8
NRTIs/NtRTIs/PIs	0 / 6	0 / 0	0 / 0	0 / 0	6
Other combination	0 / 3	0 / 0	0 / 0	0 / 0	3

[1] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion ≥20 weeks gestation.
[2] NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, zalcitabine, and zidovudine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, telbivudine, and tenofovir disoproxil fumarate.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, and nevirapine.
PI=protease inhibitor, which includes amprenavir, atazanavir, datunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
EI=entry inhibitor, which includes enfuvirtide, maraviroc.
[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 19 multiple births.
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 2008

	Earliest Antiretroviral Therapy (ART) Exposure in First Trimester						
	Any NRTI(s)	Any NtRTI(s)	Any NNRTI(s)	Any PI(s)	Any EI(s)	Overall First Trimester Exposure	Earliest ART Exposure in Second and/or Third Trimester
Pregnancies Enrolled	261	8	37	73	0	262	968
Number of Pregnancies with Multiple Gestations	8	0	4	0	0	8	11
Number of Outcomes [2]	269	8	41	73	0	270	979
Number of Live Births	268	8	40	73	0	269	971
Number of Outcomes with Defects [1,2]	17	0	3	7	0	17	24
CNS	0	0	0	0	0	0	0
Eye, ear, face and neck	0	0	0	0	0	0	1
Cleft lip and/or palate	0	0	0	0	0	0	1
Conotruncal heart defects	0	0	0	0	0	0	0
Obstructive heart defects - right sided	1	0	0	1	0	1	1
Obstructive heart defects - left sided	0	0	0	0	0	0	0
Heart - other defects	12	0	2	4	0	12	7
Other circulatory system	2	0	1	1	0	2	1
Respiratory system	0	0	0	0	0	0	1
Upper gastrointestinal system	0	0	0	0	0	0	0
Lower gastrointestinal system	0	0	0	0	0	0	0
Female genitalia	0	0	0	0	0	0	1
Male genitalia	2	0	1	2	0	2	1
Renal and urinary system	0	0	0	0	0	0	0
Limb reduction/addition defects	1	0	0	1	0	1	7
Other musculoskeletal defects	3	0	0	0	0	3	9
Skin and skin derivatives	2	0	0	0	0	2	0
Chromosome anomaly	1	0	0	0	0	1	1
Other organs and organ systems	0	0	0	0	0	0	1
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.
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: NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, zalcitabine, and zidovudine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, telbivudine, and tenofovir disoproxil fumarate.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, and nevirapine.
PI=protease inhibitor, which includes amprenavir, atazanavir, datunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir
EI=entry inhibitor, which includes enfuvirtide, maraviroc.

Table 12: Confidence Intervals for Birth Defects [1] - Reports from Clinical Studies in Pregnancy with Follow-up Data Closed Through 31 January 2008

	Overall
Number of Live Births	1240
Number of Outcomes with at least one defect [2]	41 (3.3%)
95% Confidence Intervals for prevalence [3] of Birth Defects [4] for exposures in:	
First Trimester	17/269 (6.3%) 3.7% - 9.9%
Second/Third Trimester	24/971 (2.5%) 1.6% - 3.7%
Any Trimester	41/1240 (3.3%) 2.4% - 4.5%
Risk of defects for first trimester exposures relative to second/third trimester exposures	2.56 (1.39, 4.69)

[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 ≥20 weeks gestation.
Note: Only upper confidence limits are presented when no defects were observed.

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. Infants are followed for at least 18 months. In a 2001 publication (11), the European Collaborative Study reported on infants born to 2876 HIV-infected pregnant women. There were 37 infants with reported birth defects. Among the 800 exposed to antiretroviral drugs in utero, there were 10 (1.25%) with reported birth defects; four with ventricular septal defects, two with Trisomy 21, and one each with cataract, hydrocephalus, polycystic kidney, and unspecified familial anomaly. A similar proportion of infants not exposed to antiretroviral drugs in utero had reported birth defects (1.40%, 27/2283). The pattern of defects was also similar in the two groups. In a 2003 publication (12), the European Collaborative Study reported on 2414 uninfected infants born to HIV-infected women. Among these infants, 37 were reported to have birth defects. The prevalence of birth defects among infants exposed to antiretroviral therapy in utero (13/906, 1.4%) was similar to those not exposed (24/1508, 1.6%). Of the 13 exposed infants, 7 were exposed in the first trimester; 1 had Trisomy 21, 1 hydronephrosis, 2 ventricular septal defects, and 3 had unspecified anomalies. Of the 6 who were exposed later in pregnancy, 2 had Trisomy 21, 1 had ventricular septal defects, 1 had polycystic kidney, 1 had polydactyly, and 1 had unspecified anomalies. Presumably there is overlap of the infants reported in these two publications.

In March 2007, the European Collaborative Study coordinating center produced Tables 13 and 14 specifically for the Registry. Additionally, the National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland produced Tables 15 and 16 specifically for the Registry (13). For comparison purposes, they both used the same format as Registry tables 11 and 12.

* 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.

Table 13: 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: The cardiovascular organ systems reflect separate types of structural heart defects; therefore, it is not appropriate to add them together.

Table 14: European Collaborative Study Data: Confidence Intervals for Birth Defects by Organ System and Treatment Regimen. 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.

Newschaffer and colleagues (14) 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.

Bussmann and colleagues (15) 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.

Other Studies: 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. Following is a list of these studies (15, 17,18). It is inappropriate to attempt to calculate rates of birth defects from these studies due to the small number of cases.

Table 15: United Kingdom and Ireland Surveillance Data: Summary of Birth Defects by Organ System and Treatment Regimen – First Trimester Exposures. Data Reporting Period December 1984 – March 2007

Summary of birth defects by organ system and treatment regimen
Pregnancies with delivery/outcome 1990-2005, reported by the end of 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 [3]	Earliest ART Exposure in 2nd or 3rd Trimester
Pregnancies Reported	1243	181	743	447	3	1262	4151
Number of Pregnancies with Multiple Gestations	28	4	18	11	0	28	58
Number of Outcomes	1271	185	761	458	3	1290	4209
Number of Live Births	1217	179	727	441	1	1236	4162
Number of Outcomes with Defects [1,2]	44	7	22	16	0	45	114
CNS	6	2	4	1	0	6	9
Eye, ear, face and neck	1	0	0	0	0	1	4
Cleft lip and/or palate	0	0	0	0	0	0	5
Conotruncal heart defects	1	0	1	0	0	1	1
Obstructive heart defects, right-sided	2	0	2	1	0	2	2
Obstructive heart defects, left-sided	0	0	0	0	0	0	1
Heart - other defects	5	0	2	2	0	5	9
Other circulatory system	1	0	0	1	0	1	2
Respiratory system	1	0	0	0	0	1	3
Upper gastrointestinal system	1	0	1	0	0	1	1
Lower gastrointestinal system	3	1	2	0	0	4	7
Female genitalia	0	0	0	0	0	0	0
Male genitalia	3	0	2	1	0	3	9
Renal and urinary system	5	0	4	1	0	5	9
Limb reduction/addition	2	0	2	0	0	2	18
Other musculoskeletal defects	9	1	3	3	0	9	22
Skin and skin derivatives	3	1	1	2	0	3	7
Chromosome anomaly	3	2	1	1	0	3	11
Other organ systems - specified	1	0	0	1	0	1	0
Specified syndromes	1	0	0	1	0	1	1
Unspecified abnormality	1	1	0	1	0	1	4

[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 $\geq$20 weeks gestation
[3] Seven cases had first trimester exposure to unspecified antiretroviral drugs, one with an abnormality reported (other musculoskeletal defect).
NB Pregnancies/outcomes with no exposure to ART are excluded.

Table 16: United Kingdom and Ireland Surveillance Data: Confidence Intervals for Birth Defects by Organ System and Treatment Regimen. Data Reporting Period December 1984 – March 2007

	Overall
Number of live births	5398
Number of outcomes with at least one defect	159 (2.9%)
95% confidence intervals for % birth defects for exposures in:	
First Trimester	45/1236 (3.6%)
	2.7 - 4.9
Second/Third Trimester	114/4162 (2.7%)
	2.3 - 3.3
Any Trimester	159/5398 (2.9%)
	2.5 - 3.4
Risk of defects for first trimester exposures relative to second/third trimester exposures	1.3 (0.9 - 1.9)

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

Citations of Other Studies Reviewed by the Registry

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.

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

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.

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

SUMMARY AND ADVISORY COMMITTEE CONSENSUS

Primary Registry Analysis (Prospective Reports)

The Registry's analytic approach is to evaluate drugs in all specific classes of antiretroviral therapies. The following specific drugs have large enough groups of exposed women to warrant a separate analysis: abacavir, didanosine, efavirenz, indinavir, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, tenofovir, and zidovudine.

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, an increased frequency for birth defects has been detected for didanosine only. Although no pattern of birth defects has been detected with didanosine, the Committee continues to monitor this increase.

For abacavir, efavirenz, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, and tenofovir, 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 lamivudine 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.

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.

Supplemental Analyses

Retrospective Reports: Retrospective reports are those reported to the Registry after the outcome or perceived outcome of pregnancy is known. 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.

Reports from Clinical Studies in Pregnancy: 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. The Registry will continue to examine data as available from further studies. A published analysis from the Women and Infants Transmission Study (WITS) detected a statistically significant elevated rate of hypospadias after first trimester exposure to zidovudine. The signal has not appeared in the primary analysis of the Registry. The WITS data have been incorporated into the primary analysis beginning with the January 2008 Interim Report. The Registry will continue to monitor hypospadias closely.

Reports from the Published Literature: The registry has not identified a signal in any of the published studies reviewed to date.

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GLOSSARY AND ABBREVIATIONS

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.

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.

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 raltegravir.)

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.

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

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

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

PI – Protease inhibitor. (Represented in this Registry by amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, 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 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 – A fetal loss occurring <20 weeks gestation.

Stillbirth – A fetal death occurring ≥20 weeks gestation, the fetus weighs 500 gms or more, or is designated as such by the reporter.

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.

APPENDICES

Appendix A: Prevalence of Birth Defects

Prevalence of Birth Defects, 95% 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
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

Appendix B: Summary of Treatment Regimens

Summary of Antiretroviral Treatments by Trimester of Earliest Exposure* Prospective Registry Cases with Follow-up Data Closed Through 31 January 2008

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Enrolled	4458	4012	1416	9889
3TC	3082	3212	980	7275
ABC	565	484	150	1199
ADV	36	0	0	36
APV	30	2	0	32
ATV	202	53	8	263
D4T	748	72	19	839
DDC	61	4	0	65
DDI	402	86	16	504
DLV	13	1	0	14
DRV	11	0	0	12
EFV	454	12	7	473
ETV	5	0	0	6
FOS	60	5	3	68
FTC	223	53	20	296
IDV	318	80	19	417
LdT	1	0	0	1
LPV	365	441	153	959
NFV	1025	1398	390	2813
NVP	821	648	237	1707
RTV	688	530	175	1393
SQV	164	63	22	249
T20	14	0	0	14
TDF	587	140	43	770
TPV	2	0	0	2
ZDV	3098	3860	1383	8342

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Enrolled	4458	4012	1416	9889
3TC & NFV & ZDV	555	1234	351	2140
ZDV	541	644	377	1562
3TC & NVP & ZDV	371	528	176	1076
3TC & ZDV	281	345	97	723
ABC & 3TC & ZDV	179	363	120	662
3TC & LPV & RTV & ZDV	99	305	107	511
IDV & 3TC & ZDV	134	58	17	209
3TC & TDF & ZDV	120	10	6	136
3TC & NFV & d4T	93	8	0	101
3TC & NVP & d4T	83	10	3	96
EFV & 3TC & ZDV	76	1	4	81
ATV & FTC & RTV & TDF	55	12	1	68
3TC & NFV & NVP & ZDV	16	28	10	54
3TC & RTV & SQV & ZDV	11	32	11	54
3TC	43	8	2	53
ABC & 3TC & LPV & RTV & ZDV	18	27	7	52
ABC & 3TC & NVP & ZDV	24	15	10	49
3TC & SQV & ZDV	31	11	5	47
3TC & d4T	37	5	0	42

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
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Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

	First Trimester	Second Trimester	Third Trimester	Overall
FTC & LPV & RTV & TDF	21	11	10	42
ABC & 3TC & NFV & ZDV	12	21	5	38
ddI & NFV & ZDV	18	14	5	37
ddI & NFV & d4T	32	4	1	37
EFV & 3TC & NVP & ZDV	35	0	0	35
IDV & 3TC & d4T	32	1	0	33
EFV & 3TC & d4T	32	0	0	32
ADV	31	0	0	31
EFV & FTC & TDF	24	6	0	30
NFV	22	6	0	28
ATV & 3TC & ZDV	18	7	2	27
IDV	24	3	0	27
3TC & LPV & RTV & TDF & ZDV	12	10	4	26
ddI & ZDV	15	9	2	26
3TC & LPV & NFV & RTV & ZDV	5	16	4	25
EFV & 3TC & NFV & ZDV	25	0	0	25
ABC & 3TC & TDF & ZDV	16	6	2	24
ATV & 3TC & RTV & ZDV	9	12	1	22
EFV	22	0	0	22
ddC & ZDV	20	2	0	22
ddI & NVP & d4T	14	6	0	20
3TC & NFV & d4T & ZDV	13	4	2	19
NVP & ZDV	2	0	17	19
3TC & RTV & ZDV	13	4	1	18
ABC & 3TC & NVP	16	2	0	18
3TC & LPV & RTV & d4T	13	2	2	17
ddI	15	1	1	17
3TC & NFV & TDF & ZDV	6	8	2	16
3TC & NVP & TDF	15	1	0	16
3TC & NVP & d4T & ZDV	5	7	3	15
ABC & 3TC & LPV & RTV	10	4	1	15
EFV & 3TC & TDF	15	0	0	15
FTC & NFV & TDF	10	5	0	15
ddI & NVP & ZDV	12	2	1	15
IDV & 3TC & RTV & ZDV	10	4	0	14
NVP	12	0	2	14
d4T	14	0	0	14
IDV & 3TC & NFV & ZDV	9	3	1	13
ddI & 3TC & ZDV	6	7	0	13
3TC & LPV & RTV & TDF	9	3	0	12
ABC & EFV & 3TC & ZDV	12	0	0	12
LPV & RTV	8	4	0	12
ddI & LPV & RTV & TDF	9	3	0	12
3TC & d4T & TDF	11	0	0	11
ABC & 3TC & d4T	10	1	0	11
ABC & EFV & 3TC	11	0	0	11
ABC & FOS & 3TC & RTV	11	0	0	11
LPV & RTV & TDF & ZDV	6	4	1	11
3TC & LPV & NVP & RTV & ZDV	0	6	4	10
EFV & 3TC & NVP & d4T	10	0	0	10
FTC & NVP & TDF	9	1	0	10
IDV & 3TC & RTV & d4T	10	0	0	10
3TC & NFV & NVP & d4T & ZDV	7	2	0	9
ABC & ATV & 3TC & RTV	9	0	0	9
ABC & EFV & d4T	9	0	0	9
EFV & 3TC & NFV & d4T	9	0	0	9
LPV & RTV & ZDV	4	3	2	9

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
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Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

	First Trimester	Second Trimester	Third Trimester	Overall
SQV & ddC & ZDV	9	0	0	9
TDF	9	0	0	9
ddI & EFV & d4T	9	0	0	9
ddI & SQV & ZDV	3	5	1	9
3TC & NFV	5	2	1	8
3TC & RTV & SQV & d4T	7	1	0	8
3TC & d4T & ZDV	8	0	0	8
ABC & ATV & 3TC & ZDV	6	2	0	8
ATV & 3TC & RTV & TDF	8	0	0	8
ATV & RTV & TDF & ZDV	3	4	1	8
EFV & 3TC & LPV & RTV & ZDV	7	1	0	8
ddC	8	0	0	8
ddI & 3TC & NFV	4	3	1	8
3TC & NVP & TDF & ZDV	3	2	2	7
ABC & FTC & d4T	7	0	0	7
FTC & FOS & RTV & TDF	7	0	0	7
IDV & 3TC & d4T & ZDV	7	0	0	7
ddI & 3TC & NFV & d4T & ZDV	7	0	0	7
ddI & 3TC & NVP	4	3	0	7
ddI & IDV & d4T	7	0	0	7
3TC & NFV & TDF	4	2	0	6
3TC & SQV & d4T	6	0	0	6
ABC & 3TC & NFV	4	2	0	6
ABC & LPV & RTV & TDF	5	1	0	6
ABC & NVP & ZDV	5	1	0	6
ATV & FTC & TDF	5	1	0	6
ATV & ddI & RTV & TDF	6	0	0	6
EFV & IDV	6	0	0	6
ENT	5	0	0	6
FOS & 3TC & RTV & ZDV	4	2	0	6
FTC & d4T	6	0	0	6
IDV & ZDV	5	1	0	6
SQV & ZDV	6	0	0	6
ddI & 3TC & LPV & RTV	4	2	0	6
ddI & 3TC & NFV & ZDV	4	2	0	6
ddI & 3TC & NVP & d4T & ZDV	5	1	0	6
ddI & EFV & NVP & ZDV	6	0	0	6
ddI & LPV & RTV & d4T	6	0	0	6
3TC & LPV & RTV & d4T & ZDV	1	3	1	5
3TC & NFV & SQV & d4T	5	0	0	5
ABC & 3TC & LPV & RTV & TDF	3	2	0	5
ABC & ATV & 3TC	4	1	0	5
ABC & NFV & d4T	5	0	0	5
ABC & NVP & d4T	2	2	1	5
EFV & 3TC & NVP & d4T & ZDV	5	0	0	5
EFV & FTC & 3TC & NFV & TDF & ZDV	4	1	0	5
NVP & TDF & ZDV	1	3	1	5
ddI & 3TC & LPV & RTV & ZDV	4	1	0	5
ddI & EFV & NVP & d4T	5	0	0	5
ddI & EFV & ZDV	5	0	0	5
ddI & LPV & RTV & ZDV	1	4	0	5
ddI & NFV & d4T & ZDV	4	0	1	5
3TC & NFV & NVP	4	0	0	4
3TC & NFV & SQV & ZDV	3	1	0	4
ABC & 3TC & LPV & RTV & TDF & ZDV	2	2	0	4
ABC & ATV & 3TC & RTV & ZDV	4	0	0	4
ABC & EFV & 3TC & NFV & ZDV	4	0	0	4

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
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Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

	First Trimester	Second Trimester	Third Trimester	Overall
ABC & FOS & 3TC	4	0	0	4
ABC & NFV & TDF	3	1	0	4
ABC & ddI & LPV & RTV	4	0	0	4
ABC & ddI & NFV	4	0	0	4
ATV & 3TC & RTV & TDF & ZDV	3	1	0	4
ATV & 3TC & d4T	4	0	0	4
ATV & FTC & 3TC & NFV & RTV & TDF & ZDV	4	0	0	4
ATV & ddI & 3TC & RTV	4	0	0	4
DRV & FTC & RTV & TDF	4	0	0	4
EFV & 3TC & NFV & d4T & ZDV	4	0	0	4
EFV & FTC & 3TC & LPV & RTV & TDF & ZDV	4	0	0	4
EFV & FTC & LPV & RTV & TDF	4	0	0	4
FOS & 3TC & ZDV	4	0	0	4
FTC & LPV & RTV & TDF & ZDV	2	0	2	4
ddI & EFV & LPV & RTV	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 & TDF	3	0	0	3
3TC & ddC & ZDV	3	0	0	3
ABC & 3TC & LPV & NFV & RTV & ZDV	0	3	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 & DRV & T20 & 3TC & RTV & TDF & ZDV	3	0	0	3
ABC & EFV & 3TC & NVP & d4T & ZDV	3	0	0	3
ABC & FOS & 3TC & RTV & ZDV	2	0	1	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
ADV & 3TC	3	0	0	3
APV & 3TC & d4T	3	0	0	3
ATV & ddI & FTC	3	0	0	3
EFV & 3TC & NFV & TDF & ZDV	3	0	0	3
EFV & 3TC & TDF & ZDV	3	0	0	3
EFV & FTC & TDF & ZDV	0	0	3	3
FOS & 3TC & RTV & TDF	2	0	1	3
FTC	3	0	0	3
FTC & 3TC & LPV & RTV & TDF & ZDV	2	1	0	3
FTC & 3TC & NFV & TDF & ZDV	0	3	0	3
FTC & 3TC & NVP & TDF & ZDV	3	0	0	3
FTC & 3TC & NVP & d4T	3	0	0	3
FTC & NVP & d4T	3	0	0	3
IDV & 3TC & NFV & d4T & ZDV	3	0	0	3
IDV & 3TC & NVP & ZDV	1	2	0	3
IDV & NVP & ZDV	2	1	0	3
IDV & d4T & ZDV	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
SQV	3	0	0	3
ddI & 3TC	3	0	0	3
ddI & 3TC & SQV & ZDV	1	2	0	3

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
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Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

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

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
w:_tables.sas... (JElder)

Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

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

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
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Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

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

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
w:_tables.sas... (JElder)

Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

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

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
w:_tables.sas... (JElder)

Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

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

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
w:_tables.sas... (JElder)

Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

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

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
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Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

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

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
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Appendix B: (cont.)
Summary of Treatment Regimens Taken During the Trimester of Earliest Exposure*
by Trimester of Earliest Exposure
All Registry Cases with Follow-up Data Closed Through 31 January 2008

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

*Includes only the earliest exposure; does not include exposure to drugs taken subsequently in pregnancy.
Note: 3TC=lamivudine, ABC=abacavir, ADV=adefovir dipivoxil, APV=amprenavir, ATV=atazanavir sulfate, d4T=stavudine, ddC=zalcitabine, ddI=didanosine, DLV=delavirdine mesylate, EFV=efavirenz, ENT=entecavir, FOS=fosamprenavir calcium, FTC=emtricitabine, IDV=indinavir, LPV/r=lopinavir/ritonavir, MVC=maraviroc, NFV=nelfinavir, NVP=nevirapine, RAL=raltegravir, RTV=ritonavir, SQV=saquinavir mesylate or saquinavir, TDF=tenofovir disporoxil fumatrate, TPV=tipranavir, ZDV=zidovudine.
Occurrences of 3TC & ZDV may represent the combination product.
Source: Kendle 9:07:44 on FRI, 09MAY2008 ::
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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.	Tracheomalacia, pectus excavatum	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.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association[1]
	16.	Heart arrhythmia	Temporality: Cannot rule out a possible association[1]
*	17.	Congenital hydronephrosis	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) ф literature reports

[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.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association[1]
	27.	Fetal alcohol syndrome	Temporality: Cannot rule out a possible association [1]
	28.	Pyloric stenosis	Temporality: Unable to assess [2]
	29.	Club Foot	Temporality: Unable to assess[2]
*	30.	Club Foot	Temporality: Unable to assess[2]
*	31.	Hip dysplasia/dislocation	Temporality: Unable to assess [2]
*‡	32.	Club Foot	Temporality: Unable to assess[2]
*	33.	Pyloric stenosis, hydrocephaly, hepatomegaly, hydrocele	Temporality: Unable to assess [2]
*	34.	Club Foot	Temporality: Unable to assess[2]
*	35.	Club foot	Temporality: Unable to assess[2]
	36.	Congenital adrenal hyperplasia	Temporality: No temporal association [3]
	37.	Truncus arteriosis	Temporality: No temporal association [3]
*	38.	Hypoplastic left ventricle	Temporality: No temporal association [3]
*	39.	Polydactyly	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 NRTI(s) + PI(s) Regimen:

	1.	Transposition of the great vessels, right malformed pinna/atretic canal, hepatosplenomegaly, atrial septal defect	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 dyplastic kidney	Temporality: Cannot rule out a possible association[1]
	6.	Hearing deficit	Temporality: Cannot rule out a possible association[1]
¥	7.	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 (aborted <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 with atrial wall aneurysm	Temporality: Cannot rule out a possible association[1]
	13.	Cardiac arrythmia	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) ф literature reports

[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

	14.	Bilateral club feet	Temporality: Cannot rule out a possible association[1]
¥	15.	Bilateral ankle anomaly. Lateral medialus positioned toward achilles tendon. Does not hinder movement	Temporality: Cannot rule out a possible association[1]
	16.	Trisomy 21	Temporality: Cannot rule out a possible association[1]
¥	17.	Chordee and hooded penis (hypospadias)	Temporality: Cannot rule out a possible association[1]
¥	18.	Bigeminy- fetal bradyarrhythmia	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.	Down Syndrome, patent ductus arterious (PDA)	Temporality: Cannot rule out a possible association[1]
¥	21.	Down Syndrome, ventricular septal defect (VSD), hypoplastic nasal bone	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.	Malformed left external ear with non-patent ear canal	Temporality: Cannot rule out a possible association[1]
	25.	Hydrocephalus, smooth philtrum, lowest ears, accessory nipple, bilateral club feet, undescended testes, and polycystic kidney disease	Temporality: Cannot rule out a possible association[1]
	26.	Brain growth retardation, Microcephaly, Micropenis, 2 vessel cord	Temporality: Cannot rule out a possible association[1]
	27.	Right hydronephrosis	Temporality: Cannot rule out a possible association[1]
	28.	Hypospadias	Temporality: Cannot rule out a possible association[1]
	29.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
	30.	Hypospadias on the glans	Temporality: Cannot rule out a possible association[1]
¥	31.	Trisomy 21 (induced abortion <20 weeks gestation)	Temporality: Cannot rule out a possible association [1]
* ¥	32.	Hypospadias	Temporality: Cannot rule out a possible association [1]
* ¥	33.	Hypospadias	Temporality: Cannot rule out a possible association [1]
	34.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
*	35.	Pyloric stenosis	Temporality: Cannot rule out a possible association [1]
*	36.	Tetralogy of Fallot	Temporality: Cannot rule out a possible association [1]
*	37.	Single kidney	Temporality: Cannot rule out a possible association [1]
*	38.	Micrognathia	Temporality: Cannot rule out a possible association [1]
*	39.	Syndactyly, polydactyly	Temporality: Cannot rule out a possible association [1]
*	40.	Congenital myotonic dystrophy	Temporality: Unable to assess[2]
	41.	Long thin toes	Temporality: Cannot rule out a possible association[1]
		Benign external hydrocephalus, frontal bossing	Temporality: Unable to assess[2]

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

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

[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

	42.	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, Qustionalble septo-optic dysplasia	Temporality: Unable to assess[2]
	43.	Chromosomic aberration, no karyotype done (aborted <20 weeks gestation)	Temporality: Unable to assess[2]
	44.	Developmental hip dysplasia	Temporality: Unable to assess[2]
	45.	Muscular ventricular septal defect (VSD)	Temporality: Unable to assess[2]
*	46.	Club foot	Temporality: Unable to assess[2]
*	47.	Trisomy 21	Temporality: Cannot rule out a possible association [1]
		AV Canal	Temporality: No temporal association [3]
*	48.	Hypospadias	Temporality: No temporal association [3]
*	49.	Epispadias	Temporality: No temporal association [3]
	50.	Hirschprung's disease	Temporality: No temporal association [3]

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

	1.	Hydrocephalus, holoprosencephaly	Temporality: Cannot rule out a possible association[1]
	2.	Patent foramen ovale (or possible small secundum atrial septal defect), small patent ductus arteriosis (PDA)	Temporality: Cannot rule out a possible association[1]
	3.	Mild hydronephrosis	Temporality: Cannot rule out a possible association[1]
	4.	Talipes (positional, both feet)	Temporality: Cannot rule out a possible association[1]
	5.	Hypoplastic right ventricle, Pulmonary atresia	Temporality: Cannot rule out a possible association[1]
	6.	Urinary obstruction, duplicated right collecting system with obstructed upper pole moiety, possibly with associated vesicoureteral reflux	Temporality: Cannot rule out a possible association[1]
	7.	Atrial septal defect (ASD), biventricular hypertrophy, dilated renal pelvis, and dilated cerebral ventricle	Temporality: Cannot rule out a possible association[1]
	8.	Small muscular ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association[1]
¥	9.	Long bones malformation	Temporality: Cannot rule out a possible association[1]
	10.	Congenital hydronephrosis	Temporality: Cannot rule out a possible association[1]
	11.	Hearing loss, congenital CMV	Temporality: Cannot rule out a possible association[1]
*	12.	AV canal	Temporality: Cannot rule out a possible association[1]
	13.	Polydactyly	Temporality: Cannot rule out a possible association[1]
¥	14.	Shortening of right leg	Temporality: Cannot rule out a possible association[1]
	15.	Umbilical hernia with a small granuloma	Temporality: Cannot rule out a possible association[1]
	16.	Bilateral hip dislocation	Temporality: Unable to assess[2]
¥	17.	Subluxation of bilateral hips, hip dislocation	Temporality: Unable to assess[2]
	18.	Bilateral congenital dislocation of hips	Temporality: Unable to assess[2]
	19.	Hemangioma on nostril	Temporality: Unable to assess [2]

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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

	20.	Congenital talipies	Temporality: Unable to assess [2]

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

¥	1.	Left kidney mild to moderate hydronephrosis	Temporality: Cannot rule out a possible association[1]
	2.	Polydactyly (postaxial - bilateral hands)	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.	Transposed organs	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 (hand)	Temporality: Cannot rule out a possible association[1]
¥	4.	Tricuspid atresia, tiny right ventricle, and atrial septal defect	Temporality: Cannot rule out a possible association[1]
	5.	Polydactyly	Temporality: Cannot rule out a possible association[1]
*	6.	Incomplete formation of scalp tissue	Temporality: Cannot rule out a possible association[1]
*	7.	Tuberous sclerosis	Temporality: Cannot rule out a possible association[1]
*	8.	Mild retromicrognathia	Temporality: Cannot rule out a possible association[1]
*	9.	Polydactyly	Temporality: No temporal association [3]
*	10.	Polydactyly	Temporality: No temporal association [3]

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

¥	1.	Trisomy 8	Temporality: Cannot rule out a possible association[1]
	2.	Dilated right pyelum	Temporality: Cannot rule out a possible association[1]
	3.	Tetralogy of Fallot, Cleft palate, bilateral small kidneys, DiGeorge Syndrome, 22q11.2 deletion positive	Temporality: Cannot rule out a possible association[1]
¥	4.	Sacrococcygeal teratoma	Temporality: Cannot rule out a possible association[1]

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

	1.	Kyphosis, microcephaly, hydrops, 2 vessel cord	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.	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]
*	2.	Sacral meningomyelocele+hydrocephalus	Temporality: Cannot rule out a possible association[1]

Birth Defects from Pregnancies with First-Trimester Exposure to Unspecified Antiretroviral Regimen:

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

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

[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

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; intrauterine growth retardation (IUGR).	Temporality: Cannot rule out a possible association[1]
	5.	Patent ductus arteriosus (PDA), patent foramen ovale (PFO), cardiomyopathy	Temporality: Cannot rule out a possible association[1]
	6.	Ventricular septal defect (VSD) (muscular)	Temporality: Cannot rule out a possible association[1]
	7.	Dacryocystocele	Temporality: Cannot rule out a possible association[1]
	8.	Trisomy 21	Temporality: Cannot rule out a possible association[1]
	9.	Bilateral polydactyly	Temporality: Cannot rule out a possible association[1]
*‡	10.	Metopic craniosynostosis	Temporality: Cannot rule out a possible association[1]
	11.	Down syndrome	Temporality: Cannot rule out a possible association [1]
*	12.	Micrognathia	Temporality: Cannot rule out a possible association [1]
*	13.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]
*	14.	Congenital hydrocephalus	Temporality: Cannot rule out a possible association [1]
*	15.	Multicystic left kidney	Temporality: Cannot rule out a possible association [1]
*	16.	Premature synostosis of metopic suture	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.	Syndactyly fingers and toes,	Temporality: Cannot rule out a possible association[1]
		Club feet, severe arthrogryposis,	Temporality: Unable to assess[2]
*	20.	Right hip dislocation	Temporality: Unable to assess[2]
	21.	Hydrocephalus of anterior lateral ventricle	Temporality: Unable to assess[2]
	22.	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]
	23.	Secundum atrial septal defect	Temporality: Cannot rule out a possible association[1]
		Chondrodystrophy, Ventricular septal defect (VSD), imperforate pulmonary valve, aortic stenosis, cardiomegaly, tricuspid regurgitation, aneurysm of septum primum	Temporality: No temporal association [3]
	24.	Bilateral hydronephrosis	Temporality: Cannot rule out a possible association[1]
		Hypoplastic public bone, 2 vessel umbilical cord	Temporality: No temporal association [3]

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	25.	Trisomy 13	Temporality: Cannot rule out a possible association[1]
		Dysmorphic eyes, patent ductus arteriosus, atrial septal defect, ventricular septal defect, duodenal atresia, rocker-bottom feet	Temporality: No temporal association [3]
	26.	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]
	27.	Cardiac axis abnormality	Temporality: Unable to assess[2]
		Dandy Walker Malformation, ventriculomegaly	Temporality: No temporal association [3]
	28.	Atrial septal defect (ASD)	Temporality: No temporal association [3]
	29.	Micrognathia, left ear low set pinna microtia, right ear malformation, small muscular ventricular septal defect	Temporality: No temporal association [3]
	30.	Microphthalmos of right eye with a possible coexistent cataract	Temporality: No temporal association [3]
	31.	Small cleft in front gum – very benign	Temporality: No temporal association [3]
	32.	Hand defect, missing digits	Temporality: No temporal association [3]
	33.	Bicuspid aortic valve, abnormal pulmonic valve and possibly abnormal aorta but no gross aortic coarctation	Temporality: No temporal association [3]
	34.	Polydactyly	Temporality: No temporal association [3]
	35.	Syndactyly, right hand	Temporality: No temporal association [3]
	36.	Hypospadias, mild	Temporality: No temporal association [3]
	37.	Ventricular septal defect (VSD) - membranous; diagnosed at 2 months of age	Temporality: No temporal association [3]
	38.	Polydactyly (bilateral hands and feet, postaxial)	Temporality: No temporal association [3]
	39.	Absence of mouth and esophagus, transversed organs	Temporality: No temporal association [3]
	40.	Cleft palate and lip	Temporality: No temporal association [3]
	41.	Hypospadias	Temporality: No temporal association [3]
	42.	Alobar holoprosencephaly (stillbirth), hypotelorism, proboscis	Temporality: No temporal association [3]
	43.	Polydactyly (bilateral)	Temporality: No temporal association [3]
*	44.	Hypospadias	Temporality: No temporal association [3]
*	45.	Cleft lip & palate	Temporality: No temporal association [3]
*	46.	Sacrococcygeal teratoma	Temporality: No temporal association [3]
*	47.	Cleft lip and palate	Temporality: No temporal association [3]
*	48.	Choanal atresia	Temporality: No temporal association [3]
*	49.	Cleft lip	Temporality: No temporal association [3]
*	50.	Sacral tissue mass, tethered spinal cord	Temporality: No temporal association [3]
*	51.	Cardiomegaly, Ebstein anomaly/dysplastic tricuspid valve, pulmonary atresia	Temporality: No temporal association [3]
*	52.	Urethral stricture	Temporality: No temporal association [3]
*	53.	Polydactyly	Temporality: No temporal association [3]
*	54.	Bilateral cleft lip	Temporality: No temporal association [3]
	55.	Choanal atresia	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]

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	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 – OU	Temporality: Cannot rule out a possible association[1]
	10.	Congenital adrenal hyperplasia	Temporality: Cannot rule out a possible association [1]
	11.	Anomaly of Myocardium	Temporality: Cannot rule out a possible association[1]
	12.	Abdominal mass	Temporality: Cannot rule out a possible association[1]
	13.	Trisomy 18, ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association[1]
*‡	14.	Mild bilateral renal pelviectasis	Temporality: Cannot rule out a possible association[1]
*	15.	Cataracts, umbilical hernia	Temporality: Cannot rule out a possible association[1]
*	16.	Arrhythmia	Temporality: Cannot rule out a possible association[1]
*	17.	Congenital icthyosis	Temporality: Cannot rule out a possible association[1]
	18.	Right Cryptorchism	Temporality: Cannot rule out a possible association[1]
		Hypospadias	Temporality: No temporal association [3]
	19.	Polydactyly	Temporality: No temporal association [3]
	20.	Tethered cord, lipomeningocele, right kidney duplicated collecting system	Temporality: No temporal association [3]
	21.	Cleft palate, micrognathia	Temporality: No temporal association [3]
‡	22.	Polydactyly (bilateral)	Temporality: No temporal association [3]
	23.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
	24.	Congenital toxoplasmosis	Temporality: No temporal association [3]
	25.	Hydronephrosis of the left kidney with mild pelviectasis of the right collecting system	Temporality: No temporal association [3]
	26.	Gastroschisis	Temporality: No temporal association [3]
	27.	Omphalocele	Temporality: No temporal association [3]
	28.	Polydactyly (foot), long fingers, short ears with folded helices, low hairline front and posterior	Temporality: No temporal association [3]
	29.	Polydactyly (Extra digit left hand)	Temporality: No temporal association [3]
	30.	Polydactyly	Temporality: No temporal association [3]
	31.	Mild hypospadius	Temporality: No temporal association [3]
	32.	Diaphragmatic hernia	Temporality: No temporal association [3]
	33.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
	34.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
	35.	Cleft lip and palate	Temporality: No temporal association [3]
	36.	Cleft lip on the left	Temporality: No temporal association [3]
	37.	Missing artery in heart	Temporality: No temporal association [3]

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[3] No temporal association

*	38.	Branchial cleft cyst	Temporality: No temporal association [3]
*	39.	Polydactyly	Temporality: No temporal association [3]
*	40.	S1-2 hemivertebra	Temporality: No temporal association [3]
*	41.	Polydactyly	Temporality: No temporal association [3]
*	42.	Small perimembranous Ventricular septal defect (VSD), mild tricuspid regurgitation	Temporality: No temporal association [3]
*	43.	Ears mildly low set	Temporality: No temporal association [3]
		Ambiguous sexuality (spontaneous abortion >20 weeks)	Temporality: Unable to assess[2]
	44.	Hirschprung Disease	Temporality: Cannot rule out a possible association[1]
	45.	Midmuscular ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association[1]
	46.	Frontal ventricular septal defect (VSD), hearing loss	Temporality: Cannot rule out a possible association[1]
	47.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association[1]
	48.	Secundum atrial septal defect (ASD)/Stretched patent foramen ovale (PFO)	Temporality: Cannot rule out a possible association[1]
	49.	Undescended testes	Temporality Cannot rule out a possible association[1]
		Polydactyly (hand), Tetrology of Fallot	Temporality: No temporal association [3]
*	50.	Trisomy 17	Temporality: Cannot rule out a possible association[1]
	51.	Cleft palate	Temporality: No temporal association [3]
	52.	Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association[1]
		Double outlet right ventricle	Temporality: No temporal association [3]
	53.	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]
	54.	Hydrocephalus NOS	Temporality: Cannot rule out a possible association[1]
		Dandy Walker	Temporality: No temporal association [3]
	55.	Patent ductus arteriosus (PDA), suspect ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association[1]
		Lowset/widespread thumb, hypoplastic left leg	Temporality: No temporal association [3]
		Left club foot, spine curvature	Temporality: Unable to assess[2]
	56.	Bilateral club feet	Temporality: Unable to assess[2]
	57.	Right club foot	Temporality: Unable to assess[2]
	58.	Umbilical cord anomaly	Temporality: Unable to assess[2]
	59.	Failed right ear hearing test	Temporality: Unable to assess[2]
	60.	Left club foot	Temporality: Unable to assess [2]
	61.	Congenital dislocated hips	Temporality: Unable to assess [2]
*	62.	Hypoplastic kidneys	Temporality: Unable to assess [2]
*	63.	Trisomy NOS	Temporality: Cannot rule out a possible association [1]
	64.	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]
	65.	Trisomy 18, Ventricular septal defect (VSD)	Temporality: Cannot rule out a possible association [1]
		Overriding aorta	Temporality: No temporal association [3]

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	66.	Bilateral polydactyly – postaxial	Temporality: No temporal association [3]

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]
	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.	Congenital heart disease	Temporality: Unable to assess[2]
	10.	Flattened wide nasal ridge, wide set eyes, borderline low set ears, short neck, and widespread nipples	Temporality: No temporal association [3]
	11.	Pulmonary valve stenosis	Temporality: No temporal association [3]
	12.	II/VI systolic murmur, polydactyly (bilateral hands)	Temporality: No temporal association [3]
	13.	Clubfoot	Temporality: No temporal association [3]
	14.	Cleft palate	Temporality: No temporal association [3]
	15.	Dysplastic toes	Temporality: No temporal association [3]
	16.	Renal agenesis, left	Temporality: No temporal association [3]
	17.	Polydactyly	Temporality: No temporal association [3]

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

	1.	Skull ossification defect	Temporality: No temporal association [3]

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

	1.	Down Syndrome, patent foramen ovale (PFO) vs. secundum atrial septal defect (ASD), patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association[1]
	2.	Polydactyly (right hand)	Temporality: No temporal association [3]

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

	1.	Left hand 2nd & 3rd finger web	Temporality: No temporal association [3]
	2.	Truncus arteriosus	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]

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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 on neonatal echo, intrauterine growth retardation	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]
19.	Holoprosencephaly, facial anomaly	Temporality: Cannot rule out a possible association[1]
20.	Lung valve dysplasia, minor	Temporality: Cannot rule out a possible association[1]
21.	Abnormal macula	Temporality: Cannot rule out a possible association[1]

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[3] No temporal association

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.	Hydrocephalus	Temporality: Cannot rule out a possible association[1]
32.	Plagiocephaly	Temporality: Unable to assess[2]
33.	Aortic coarctation, atrial septal defect (ASD), ventricular septal defect (VSD), hearing impairment	Temporality: Unable to assess[2]
34.	Prognathism, genu valgum	Temporality: Unable to assess[2]
35.	Agenesis of right nostril	Temporality: Unable to assess[2]
36.	Albinism	Temporality: No temporal association [3]
37.	Hepatosplenomegaly, enlarged tongue, mongoloid appearance. Chromosomal evaluation showed no abnormalities	Temporality: No temporal association [3]
38.	Cleft lip and palate	Temporality: No temporal association [3]
39.	Large omphalocele including liver, spleen, and intestine (aborted <20 weeks gestation)	Temporality: No temporal association [3]
40.	Congenital exomphalos	Temporality: No temporal association [3]
41.	Dysmorphogenesis, bilateral deformity of feet, left hip dislocation, vertical talus of left foot	Temporality: No temporal association [3]
42.	Transposition of great vessels	Temporality: No temporal association [3]

Birth Defects from Pregnancies with First-Trimester Exposure to NNRTI(s) + PI(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 (aborted <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]

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[3] No temporal association

	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	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. (aborted <20 weeks gestation)	Temporality: Cannot rule out a possible association[1]
	15.	Skin rash over torso, face and head, bilateral talipes equinovarus, omphalocele	Temporality: Cannot rule out a possible association[1]
	16.	Extrahepatic biliary atresia, one month after birth	Temporality: Cannot rule out a possible association[1]
	17.	Tricuspid insufficiency, patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association[1]
	18.	CMV hepatitis	Temporality: Cannot rule out a possible association[1]
	19.	Atrial septal defect (ASD)	Temporality: Cannot rule out a possible association[1]
	20.	At 19th month internal rotation of left lower limb, asymmetry between both hands: left smaller than right	Temporality: Cannot rule out a possible association[1]
	21.	Bilateral choroid plexus cysts	Temporality: Cannot rule out a possible association[1]
	22.	Ascites, left ventricular dilatation	Temporality: Cannot rule out a possible association[1]
	23.	Retraction of eyelid, pulmonary valvular stenosis	Temporality: Cannot rule out a possible association[1]
	24.	Polycystic dysplasia of right kidney	Temporality: Cannot rule out a possible association[1]
	25.	Hydrocephalus, strabismus	Temporality: Cannot rule out a possible association[1]
	26.	Cardiomegaly, tricuspid insufficiency, and hepatomegaly	Temporality: Cannot rule out a possible association[1]
	27.	Meconium peritonitis, ascites	Temporality: Cannot rule out a possible association[1]
	28.	One kidney	Temporality: Cannot rule out a possible association[1]
¥	29.	Mild hydronephrosis, hypospadias (3rd degree)	Temporality: Cannot rule out a possible association[1]
	30.	Myelomeningocele, Arnold-Chiari Malformation, membranous ventricular septal defect (VSD), atrial septal defect (ASD)	Temporality: Cannot rule out a possible association[1]
	31.	Polydactyly (right hand)	Temporality: Cannot rule out a possible association[1]
	32.	Coarctation of the aorta, ventricular septal defect (VSD), patent ductus arteriosus (PDA), complete heart block	Temporality: Cannot rule out a possible association[1]
*	33.	Pulmonary atresia, tricuspid insufficiency	Temporality: Cannot rule out a possible association[1]
	34.	Craniostenosis	Temporality: Cannot rule out a possible association[1]

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Retrospective Reports (continued)

35.	Abdominal hernia, congenital anomaly	Temporality: Unable to assess[2]
36.	Metatarsus varus on right foot at 6.5 months	Temporality: Cannot rule out a possible association[1]
37.	Genu valgum developed at 3 years 8 months	Temporality: Unable to assess[2]
38.	Congenital heart malformation	Temporality: Cannot rule out a possible association[1]
39.	Suspected Trisomy 18	Temporality: Unable to assess[2]
40.	Abdominal hernia, cryptorchism Murmur	Temporality: Cannot rule out a possible association[1]
41.	Congenital talipes (talus valgus)	Temporality: Unable to assess [2]
42.	Talus Valgus, craniostenosis	Temporality: Unable to assess[2]
43.	Congenital anomaly, abdominal hernia	Temporality: Unable to assess[2]
	cryptorchism	Temporality: Cannot rule out a possible association[1]
44.	Hypospadias	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 (aborted ≥ 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 (aborted <20 weeks gestation)	Temporality: Cannot rule out a possible association[1]
5.	Left kidney oligohydramnios (severe), abnormally enlarged with pyelectasis, severe intrauterine growth retardation (IUGR)	Temporality: Cannot rule out a possible association[1]
6.	Trisomy 21	Temporality: Cannot rule out a possible association[1]
7.	Single ventricle, pulmonary atresia, discontinuous pulmonary arteries, dextrocardia, asplenia, situs inversus, heterotaxia syndrome	Temporality: Cannot rule out a possible association[1]
8.	Extended lumbosacral meningomyelocele	Temporality: Cannot rule out a possible association[1]
9.	Hydrocephalic, patent ductus arteriosus (PDA)	Temporality: Cannot rule out a possible association[1]
10.	Congenital torticollis	Temporality: Cannot rule out a possible association[1]
11.	Trisomy 21 (questionable, aborted <20 weeks gestation)	Temporality: Cannot rule out a possible association[1]
12.	Frontal osteoma, deviated right 3-4 fingers, asymmetric feet	Temporality: Cannot rule out a possible association[1]
13.	Bilateral absent kidney, dysplastic kidney	Temporality: Cannot rule out a possible association[1]
14.	Ependymal cyst	Temporality: Cannot rule out a possible association[1]
15.	Atrioventricular septal defect with double outlet right ventricle, transposition of great arteries, coarctation of aorta, ventriculomegaly of brain, situs inversus (liver and spleen)	Temporality: Cannot rule out a possible association[1]
16.	Defective hearing in one ear	Temporality: Cannot rule out a possible association[1]
17.	Dandy Walker malformation, cystic hygroma/ nuchal edema (aborted <20 weeks gestation)	Temporality: Cannot rule out a possible association[1]
18.	Cleft palate	Temporality: Cannot rule out a possible association[1]

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Retrospective Reports (continued)

	19.	Bilateral clubfeet, hydrocephalus, lumbosacral meningomyelocele with Arnold-Chiari malformation (aborted ≥ 20 weeks gestation)	Temporality: Cannot rule out a possible association[1]
	20.	Abnormal right auditory evoked potentials were evidenced at 22 months	Temporality: Cannot rule out a possible association[1]
	21.	Central cleft palate	Temporality: Cannot rule out a possible association[1]
	22.	Congenital hernia, ventricular septal defect (VSD), labial fissure	Temporality: Cannot rule out a possible association[1]
	23.	Interventricular septal defect, persistent ductus botalli	Temporality: Cannot rule out a possible association[1]
	24.	Agenesis of the corpus callosum	Temporality: Cannot rule out a possible association[1]
	25.	Septo-optic dysplasia, hypoplasia of cerebellum	Temporality: Cannot rule out a possible association[1]
	26.	Possible spinal defect	Temporality: Cannot rule out a possible association[1]
	27.	Trisomy 18	Temporality: Cannot rule out a possible association [1]
	28.	Omphalocele	Temporality: Cannot rule out a possible association[1]
	29.	Left eye ptosis, left hydrocele	Temporality: Cannot rule out a possible association[1]
	30.	Abnormal urethral meatus	Temporality: Cannot rule out a possible association[1]
*	31.	Agenesis of left hand below wrist	Temporality: Cannot rule out a possible association[1]
¥	32.	Atrial septal defect	Temporality: Cannot rule out a possible association[1]
	33.	Umbilical hernia, hypopigmentation	Temporality: Cannot rule out a possible association[1]
¥	34.	Slightly flattened bridge of nose, bifid femur	Temporality: Cannot rule out a possible association[1]
	35.	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]
	36.	Posterior cervical hygroma, hydrops (aborted <20 weeks gestation), bilateral club feet	Temporality: Unable to assess[2]
	37.	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]

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.	Angioma	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]

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

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

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	2.	Light hydronephrosis at both sides	Temporality: Cannot rule out a possible association[1]
	3.	Partial trisomy 15	Temporality: Cannot rule out a possible association [1]
	4.	Distinctive hernia diaphragmatica	Temporality: Cannot rule out a possible association [1]
*	5.	Bilateral arthrogryposis plus arthrogryposis multiplex congenital, bilateral club feet	Temporality: Cannot rule out a possible association [1]
	6.	Polydactyly	Temporality: No temporal association [3]

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

	1.	Cleft palate	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.	Varus (inward) anomaly of foot	Temporality: Unable to assess[2]

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.	Appearance consistent with Down Syndrome, chromosomes confirm 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]

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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]
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.	Macroglossia, oblique palpebral fissures	Temporality: Cannot rule out a possible association[1]
24.	Hypertrophic cardiomyopathy	Temporality: Cannot rule out a possible association[1]
25.	Hepatosplenomegaly	Temporality: Cannot rule out a possible association[1]
26.	Hernia (left ovary)	Temporality: Cannot rule out a possible association[1]
27.	Macrocephaly	Temporality: Cannot rule out a possible association[1]
28.	Cardiac arrhythmia	Temporality: Cannot rule out a possible association[1]
29.	Hepatomegaly, cardiac rhythm disorder	Temporality: Cannot rule out a possible association[1]
30.	Convergent strabismus, torticollis, pedipes valgus	Temporality: Cannot rule out a possible association[1]
31.	Hollow feet, twisted right foot	Temporality: Cannot rule out a possible association[1]
32.	Albinism, nystagmus	Temporality: Cannot rule out a possible association[1]
33.	Multiple exostosis	Temporality: Cannot rule out a possible association[1]
34.	Inguinal hernia, hydrocele, strabismus	Temporality: Cannot rule out a possible association[1]
35.	Renal dilatation (left)	Temporality: Cannot rule out a possible association[1]
36.	Skeletal dysplasia (with bowed femurs)	Temporality: Cannot rule out a possible association[1]
37.	Patent foramen ovale (PFO)	Temporality: Cannot rule out a possible association[1]
38.	Hypertrophic cardiomyopathy	Temporality: Unable to assess[2]
39.	Genu valgum	Temporality: Unable to assess[2]
40.	Ventricular septal defect (VSD)	Temporality: Unable to assess[2]
41.	Left ventricular hypertrophy	Temporality: Unable to assess[2]
	Scaphocephaly	Temporality: No temporal association [3]
42.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
43.	Asymptomatic ventricular septal defect (VSD)	Temporality: No temporal association [3]
44.	Diaphragmatic hernia	Temporality: No temporal association [3]
45.	Two-vessel cord, hypoplastic left heart and mitral atresia	Temporality: No temporal association [3]

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46.	Mitral valve atresia	Temporality: No temporal association [3]
47.	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]
48.	Ventricular septal defect (VSD), diaphragmatic hernia	Temporality: No temporal association [3]
49.	Polydactyly (left hand)	Temporality: No temporal association [3]
50.	Enlarged penis (>97 percentile)	Temporality: No temporal association [3]
51.	Double-outlet right ventricle and ventricular septal defect (VSD)	Temporality: No temporal association [3]
52.	Ventricular septal defect (VSD), atrial septal defect (ASD)	Temporality: No temporal association [3]
53.	Cleft palate	Temporality: No temporal association [3]
54.	Acrania, sacral neural tube defect, bilateral cleft upper palate, contracted lower limbs	Temporality: No temporal association [3]
55.	Atrial septal defect (ASD)	Temporality: No temporal association [3]
56.	Hypospadias	Temporality: No temporal association [3]
57.	Missing/depressed right angularis muscle and absent orbicularis muscle, small patent ductus arteriosus (PDA)	Temporality: No temporal association [3]
58.	Congenital obstructive defect of renal pelvis and ureter	Temporality: No temporal association [3]
59.	Congenital subluxation of hip (unilateral)	Temporality: No temporal association [3]
60.	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]
61.	Congenital anomalies of larynx, trachea, and bronchus (congenital anterior subglottis web)	Temporality: No temporal association [3]
62.	Cardiac murmurs, congenital anomalies of brain (right choroid plexus cyst)	Temporality: No temporal association [3]
63.	Congenital musculoskeletal deformities of skull, face and jaw. Microcephalus seizures	Temporality: No temporal association [3]
64.	Polydactyly (left foot)	Temporality: No temporal association [3]
65.	Polydactyly (left hand)	Temporality: No temporal association [3]
66.	Nonspecific abnormality of skull/head, questionable click of left hip	Temporality: No temporal association [3]
67.	Congenital heart disease (biventricular hypertrophy), cardiomegaly	Temporality: No temporal association [3]
68.	Cardiac murmurs	Temporality: No temporal association [3]
69.	Cardiac murmur	Temporality: No temporal association [3]
70.	Cardiac murmur	Temporality: No temporal association [3]
71.	Potter's syndrome	Temporality: No temporal association [3]
72.	Polydactyly (bilateral hands)	Temporality: No temporal association [3]
73.	Congenital anomaly of genital organs (ambiguous genitalia)	Temporality: No temporal association [3]
74.	Atrial septal defect (ASD)	Temporality: No temporal association [3]
75.	Polydactyly (hand)	Temporality: No temporal association [3]
76.	Congenital subluxation of hip (unilateral), toxic erythema	Temporality: No temporal association [3]
77.	Polydactyly (hand)	Temporality: No temporal association [3]
78.	Hypospadias, epispadias	Temporality: No temporal association [3]
79.	Abnormal left ventricle	Temporality: No temporal association [3]
80.	Atrial septal defect (ASD)	Temporality: No temporal association [3]
81.	Hypospadias, microphallus	Temporality: No temporal association [3]
82.	Microcephalus	Temporality: No temporal association [3]
83.	Congenital stenosis of pulmonary valve, congenital anomaly of biliary tract	Temporality: No temporal association [3]
84.	Amniotic band syndrome right ankle	Temporality: No temporal association [3]

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85.	Polydactyly (left hand)	Temporality: No temporal association [3]
86.	Hypoplastic left ventricle/atresic aortic arch	Temporality: No temporal association [3]
87.	Finger tag, heart murmur	Temporality: No temporal association [3]
88.	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]
89.	Talipes varus	Temporality: No temporal association [3]
90.	Fetal hydronephrosis	Temporality: No temporal association [3]
91.	Hypospadias	Temporality: No temporal association [3]
92.	Congenital megacolon	Temporality: No temporal association [3]
93.	Congenital megacolon	Temporality: No temporal association [3]
94.	Complex heart disease, aortic outflow obstruction	Temporality: No temporal association [3]
95.	Syndactyly of right 3-4 fingers, syndactyly of left 3-4 toes, left cleft lip	Temporality: No temporal association [3]
96.	Left chonal atresia, possible flattened facies, possible positional plagiocephaly	Temporality: No temporal association [3]
97.	Congenital dislocated hip (left)	Temporality: No temporal association [3]
98.	Duodenal atresia, cardiac malformation	Temporality: No temporal association [3]
99.	Mild strabismus, abnormal left ear	Temporality: No temporal association [3]
100.	Pulmonary atresia	Temporality: No temporal association [3]
101.	Microcephaly, dilated left cerebral ventricle	Temporality: No temporal association [3]
102.	Malrotation of small intestine	Temporality: No temporal association [3]
103.	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]
104.	Pulmonary stenosis, umbilical hernia, brown nevus	Temporality: Cannot rule out a possible association [1]
	Hyperbilirubinemia, neonatal cholestasis	Temporality: Unable to assess[2]
	Supernumerary nipple	Temporality: No temporal association [3]
105.	Angioma (nape of neck)	Temporality: Cannot rule out a possible association[1]
	Umbilical hernia	Temporality: No temporal association [3]
106.	Ptosis, strabismus, nystagmus	Temporality: Cannot rule out a possible association[1]
	Epicanthal folds	Temporality: No temporal association [3]
107.	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) + 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, question chromosomal or dwarfism	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), ф literature reports

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[2] Insufficient data to assess temporality

[3] No temporal association

	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.	Left hydronephrosis	Temporality: Cannot rule out a possible association [1]
*	14.	Trisomy 18	Temporality: Cannot rule out a possible association [1]
		Congenity gastric anomaly (“small stomach”), esophageal atresia, ventricular septal defect (VSD)	Temporality: Unable to assess[2]
	15.	Craniosynostosis	Temporality: Unable to assess[2]
	16.	Sickle cell disease	Temporality: Cannot rule out a possible association[1]
		Polydactyly (hand)	Temporality: No temporal association [3]
	17.	Omphalocele with bowel gangrene	Temporality: No temporal association [3]
	18.	Hypoplastic left heart ventricle	Temporality: No temporal association [3]
	19.	Coarctation of the aorta and patent ductus arteriosus (PDA)	Temporality: No temporal association [3]
	20.	Polycystic kidney, hypoplastic lungs	Temporality: No temporal association [3]
	21.	Prognathism	Temporality: No temporal association [3]
	22.	Anencephaly (aborted <20 weeks gestation)	Temporality: No temporal association [3]
	23.	Polydactyly (bilateral hands), accessory auricle left ear	Temporality: No temporal association [3]
	24.	Trisomy 21, atrioventricular canal defect	Temporality: No temporal association [3]
	25.	Polydactyly both hands	Temporality: No temporal association [3]
*	26.	Polydactyly postaxial hand and foot	Temporality: No temporal association [3]
	27.	Ebstein’s Anomaly	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]
	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]

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[2] Insufficient data to assess temporality

[3] No temporal association

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 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]

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

1.	Pyelectasis, Down syndrome	Temporality: Cannot rule out a possible association[1]
	Tetralogy of Fallot	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]
5.	Hypospadias (presumed male)	Temporality: Unable to assess[2]
6.	Short segment Hirschsprung 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]
ф 15.	Mitochondriopathy	Temporality: Cannot rule out[1]
	White matter degeneration	Temporality: Unable to assess[2]
	Corpus callosum hypoplasia	Temporality: No temporal association [3]

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]

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

	2. Talipes equines (bilateral)	Temporality: Unable to assess[2]
	3. Malrotation, incomplete obstruction of intestines	Temporality: Unable to assess[2]
	4. Patent foramen ovale (PFO), patent ductus arteriosus (PDA), mild TI, apical muscular ventricular septal defect (VSD)	Temporality: Unable to assess[2]
	5. Hepatomegaly, hypertrophic cardiomyopathy	Temporality: Unable to assess[2]
	6. Multiple congenital anomalies	Temporality: Unable to assess[2]
	7. Congenital club foot	Temporality: Unable to assess[2]
	8. Unspecified fetal abnormalities	Temporality: Unable to assess[2]
	9. Unilateral deafness	Temporality: Unable to assess[2]
	Glaucoma (right eye), café au lait spots: Recklinghausen disease	Temporality: No temporal association [3]

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

	1. Tetralogy of Fallot	Temporality: Unable to assess[2]

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

	1. Congenital deafness	Temporality: Unable to assess[2]

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]
	3. Omphalocele	Temporality: Unable to assess[2]

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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]

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

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.	Hypospadias	Temporality: No temporal association [3]
14.	Polydactyly	Temporality: No temporal association [3]
15.	Polydactyly (bilateral)	Temporality: No temporal association [3]
16.	Polydactyly (bilateral)	Temporality: No temporal association [3]
17.	Polydactyly (bilateral)	Temporality: No temporal association [3]
18.	Thyroglossal cysts	Temporality: No temporal association [3]
19.	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)	Temporality: No temporal association [3]
	Membranous ventricular septal defect (VSD)	Temporality: No temporal association [3]

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

1.	Ventricular septal defect (VSD), patient foramen ovale (PFO)	Temporality: Cannot rule out a possible association[1]
2.	Inguinal herniation (right)	Temporality: Cannot rule out a possible association[1]
	Herniation of umbilicus	No temporal association [3]

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

1.	Hypospadias	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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[3] No temporal association

Appendix D: Index

Appendix D: 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 is 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 the 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.

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. 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.

Abacavir is assigned FDA Pregnancy Category C status. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. 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 35 times the human exposure, based on AUC. In a fertility study, evidence of toxicity to the

developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 500 mg/kg per day. 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). There are no adequate and well-controlled studies in pregnant women. ZIAGEN should be used during pregnancy only if the potential benefits outweigh the risk.

Adefovir dipivoxil (HEPSERA®, ADV)

HEPSERA® is the trade name for adefovir dipivoxil, a diester prodrug of adefovir. Adefovir is an acyclic nucleotide analog with activity against human hepatitis B virus (HBV).

HEPSERA® is indicated for the treatment of chronic hepatitis B 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 histological, virological, biochemical, and serological responses in adult patients with HBeAg+ and HBeAg- chronic hepatitis B with compensated liver function, and in adult patients with clinical evidence of lamivudine-resistant hepatitis B virus with either compensated or decompensated liver function.

HEPSERA® is assigned FDA Pregnancy Category C status. Reproduction studies conducted with adefovir dipivoxil administered orally have shown no embryotoxicity or teratogenicity in rats at doses producing systemic exposures approximately 23 times that achieved in humans at the therapeutic dose of 10 mg/day, or in rabbits at systemic exposures 40 times that in the human.

When adefovir was administered intravenously to pregnant rats at doses associated with notable maternal toxicity (systemic exposure 38 times that in the human), embryotoxicity and an increased incidence of fetal malformations (anasarca, depressed eye bulge, umbilical hernia and kinked tail) were observed. No adverse effects on development were seen with adefovir administered intravenously to pregnant rats at a systemic exposure 12 times that in the human.

There are no adequate and well-controlled studies in pregnant women. Since animal reproduction studies are not always predictive of human response, HEPSERA® should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits.

There are no studies in pregnant women and no data on the effect of HEPSERA® on transmission of HBV 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®.

Safety and effectiveness in pediatric patients have not been established.

Long-term oral carcinogenicity studies of adefovir dipivoxil in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the therapeutic dose for

HBV infection. In both mouse and rat studies, adefovir dipivoxil was negative for carcinogenic findings. Adefovir dipivoxil was mutagenic in the in vitro mouse lymphoma cell assay (with or without metabolic activation). Adefovir induced chromosomal aberrations in the in vitro human peripheral blood lymphocyte assay without metabolic activation. Adefovir dipivoxil was not clastogenic in the in vivo mouse micronucleus assay and adefovir was not mutagenic in the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli* strains in the presence or absence of metabolic activation. In reproductive toxicology studies, no evidence of impaired fertility was seen in male or female rats at systemic exposure approximately 19 times that achieved in humans at the therapeutic dose.

Patients should be advised to tell their physician if they are pregnant or breast-feeding. It is not known if HEPSERA® can harm unborn children. A pregnant patient and her physician must decide together if HEPSERA® is appropriate for her to take. Pregnant patients who are taking HEPSERA® should talk to their physician about enrolling in the HEPSERA® pregnancy registry. It is not known if HEPSERA® can pass into breast milk and harm nursing infants. Together the patient and her physician will need to choose either breast-feeding or taking HEPSERA®.

Amprenavir (AGENERASE®, APV)

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.

Long-term carcinogenicity studies of atazanavir in animals have not been completed. Atazanavir tested positive in an *in vitro* clastogenicity test using primary human lymphocytes, in the absence and presence of metabolic activation. Atazanavir tested negative in the *in vitro* Ames reverse-mutation assay, *in vivo* micronucleus and DNA repair tests in rats, and *in vivo* DNA damage test in rat duodenum (comet assay). Atazanavir did not produce significant effects on mating, fertility, or early embryonic development in rats at

the systemic drug exposure levels equal to (males) or two times (females) those at the human clinical dose (400 mg daily).

Atazanavir is labeled Pregnancy Category B. Atazanavir did not produce teratogenic effects at maternal doses producing systemic drug exposure levels equal to (in rabbits) or two times (in rats) those at the human clinical dose (400 mg daily). In pre- and post-natal development assessments in rats, atazanavir caused body weight loss or weight gain suppression in offspring at maternally toxic drug exposure levels two times those at the human clinical dose. Offspring were unaffected at a lower dose that produced maternal exposure equivalent to that observed in humans given 400 mg once daily.

There are no adequate and well-controlled studies of atazanavir in pregnant women. Hyperbilirubinemia occurred frequently during treatment with atazanavir. It is not known whether atazanavir administered to the mother during pregnancy will exacerbate the physiological hyperbilirubinemia of neonates and lead to kernicterus in this age group. In the prepartum period, additional monitoring and alternative therapy to atazanavir should be considered. Cases of lactic acidosis syndrome (LAS), sometimes fatal, and symptomatic hyperlactatemia have been reported in patients (including pregnant women) receiving atazanavir in combination with nucleoside analogues, which are known to be associated with increased risk of LAS. Female gender and obesity are known risk factors for LAS. The contribution of atazanavir to the risk of development of LAS has not been established. Atazanavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Darunavir (PREZISTA™, DRV)

Darunavir (Prezista™, DRV) is an inhibitor of the human immunodeficiency virus (HIV) protease.

Indications and usage: PREZISTA™, co-administered with 100 mg ritonavir (PREZISTA/rtv), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

Pregnancy: Pregnancy Category B: Reproduction studies conducted with darunavir have shown no embryotoxicity or teratogenicity in mice, rats and rabbits. Because of limited bioavailability of darunavir in animals and/or dosing limitations, the plasma exposures (AUC values) were approximately 50% in mice and rats and 5% in the 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 or mating performance of offspring was 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.

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

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: Safety and effectiveness in pediatric patients have not been established.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term carcinogenicity studies of darunavir in rodents have not been completed. Darunavir, however, was tested negative in the *in vitro* Ames reverse mutation assay and *in vitro* chromosomal aberration assay in human lymphocytes, both tested in the absence and presence of metabolic activation system. Darunavir does not induce chromosomal damage in the *in vivo* micronucleus test in mice.

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

Delavirdine mesylate (RESCRIPTOR®, DLV)

Delavirdine mesylate (RESCRIPTOR®) is a non-nucleoside reverse transcriptase inhibitor of HIV-1. 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 recommended doses. In mice, delavirdine produced significant increases in the incidence of hepatocellular adenoma/adenocarcinoma in both males and females.

A battery of genetic toxicology tests, including the Ames assay, *in vitro* unscheduled DNA synthesis assay, a chromosomal aberration assay in human peripheral lymphocytes, a mammalian mutation assay in Chinese hamster ovary cells, and the micronucleus test in mice were negative, indicating delavirdine is not mutagenic. Delavirdine did not cause impairment of fertility in male or female rats.

Delavirdine is assigned FDA Pregnancy Category C. 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 at the recommended dose. Exposure in rats, approximately 5-fold higher than the expected human exposure, resulted in marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival. Reduced pup survival on postpartum day 0 occurred at an exposure approximately equal to the expected human exposure.

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 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 the 9 pregnancies reported in premarketing clinical studies and post marketing experience, a total of 10 infants were born (including 1 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 1 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.

Didanosine (VIDEX®, VIDEX® EC, ddI)

Didanosine, a nucleoside analogue of deoxyadenosine, inhibits the *in vitro* replication of HIV in human primary cell cultures and in established cell lines. After didanosine enters the cell, it is converted by cellular enzymes to the active antiviral metabolite, dideoxyadenosine triphosphate (ddATP). The intracellular half-life of ddATP, calculated from results obtained from *in vitro* cell culture studies, varied from 8 to 24 hours.

A common feature of dideoxynucleoside (the class of compounds to which didanosine belongs) is the lack of a free 3'-hydroxyl group. In nucleic acid replication, the 3'-hydroxyl of a naturally occurring nucleoside is the acceptor for covalent attachment of subsequent nucleoside 5'-monophosphates; its presence is therefore a requisite for continued DNA chain extension. Because ddATP lacks a 3'-hydroxyl group, incorporation of ddATP into viral DNA leads to chain termination and, thus, inhibition of viral replication. In addition, ddATP further contributes to inhibition of viral replication through interference with the HIV-RNA dependent DNA polymerase (reverse transcriptase) by competing with the natural nucleoside triphosphate, dATP, for binding to the active site of the enzyme.

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.

No evidence of mutagenicity (with or without metabolic activation) was observed in Ames *Salmonella* mutagenicity assays or in a mutagenicity assay conducted with *Escherichia Coli* tester strain WP2 uvrA where only a slight increase in revertant was observed with didanosine. In a mammalian cell gene mutation assay conducted in L5178Y/TK+/- mouse lymphoma cells, didanosine was weakly positive both in the absence and presence of metabolic activation at concentrations of approximately 2000 µg/mL and above. In

an *in vitro* cytogenic study performed in cultured human peripheral lymphocytes, high concentrations of didanosine (500 µg/mL) elevated the frequency of cells bearing chromosome aberrations. Another *in vitro* mammalian cell chromosome aberration study using Chinese hamster lung cells revealed that didanosine produces chromosome aberrations at 500 µg/mL after 48 hours of exposure. However, no significant elevations in the frequency of cells with chromosome aberrations were seen at didanosine concentrations up to 250 µg/mL. In a BALB/c 3T3 *in vitro* transformation assay, didanosine was considered positive only at concentrations of 3000 µg/mL and above. No evidence of genotoxicity was observed in rat and mouse micronucleus assays.

The results from the genotoxicity studies suggest that didanosine is not mutagenic at biologically and pharmacologically relevant doses. At significantly elevated doses *in vitro*, the genotoxic effects of didanosine are similar in magnitude to those seen with natural DNA nucleosides.

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. There are no adequate and well-controlled studies in pregnant women. Since animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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.

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 should always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). 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 2005, the Antiretroviral Pregnancy Registry has received prospective reports of 282 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (277 pregnancies). Birth defects occurred in 5 of 228 live births (first-trimester exposure) and 1 of 14 live births (second/third-trimester exposure). None of these prospectively reported defects were neural tube defects. However, 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 (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®**.

ACTG 382 is an ongoing, open-label study in 57 NRTI-experienced pediatric patients to characterize the safety, pharmacokinetics, and antiviral activity of SUSTIVA® in combination with nelfinavir (20-30 mg/kg TID) and NRTIs. Mean age was 8 years (range 3-16). SUSTIVA® has not been studied in pediatric patients below 3 years of age or who weigh less than 13 kg. At 48 weeks, the type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of rash, which was reported in 46% (26/57) of pediatric patients compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric patients compared to 0.9% of adults.

The starting dose of SUSTIVA® was 600 mg once daily adjusted to body size, based on weight, targeting AUC levels in the range of 190-380 μM•h. The pharmacokinetics of efavirenz in pediatric patients was similar

to the pharmacokinetics in adults who received 600-mg daily doses of SUSTIVA®. In 48 pediatric patients receiving the equivalent of a 600-mg dose of SUSTIVA®, steady-state C_{max} was 14.2 ± 5.8 μM (mean ± SD), steady-state C_{min} was 5.6 ± 4.1 μM, and AUC was 218 ± 104 μM•h.

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 should always be used in combination with other methods of contraception, including oral or other hormonal contraception, because the effects of efavirenz on hormonal contraceptives are not fully characterized. Women should be advised to notify their physician if they 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.

Emtricitabine (EMTRIVA®, FTC)

EMTRIVA® is the brand name of emtricitabine, a synthetic nucleoside analog with activity against human immunodeficiency virus type 1 (HIV-1) reverse transcriptase.

EMTRIVA® is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in patients over three months of age. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts from controlled studies of 48 weeks duration in antiretroviral-naïve patients and antiretroviral-treatment-experienced patients who were virologically suppressed on an HIV treatment regimen. In antiretroviral-treatment-experienced patients, the use of EMTRIVA® may be considered for patients with HIV strains that are expected to be susceptible to EMTRIVA® as assessed by genotypic or phenotypic testing.

EMTRIVA® is assigned Pregnancy Category B status. The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose. There are, however, no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, EMTRIVA® should be used during pregnancy only if clearly needed.

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether emtricitabine is secreted into human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving EMTRIVA®.

Safety and effectiveness in pediatric patients below the age of 3 months have not been established.

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

In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

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

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Patients should be advised to tell their healthcare provider if they are pregnant, planning to become pregnant, or breast-feeding. It is not known if EMTRIVA® can harm unborn children. A patient and her healthcare provider must decide together if EMTRIVA® is appropriate for her to take. Patients using EMTRIVA® during pregnancy should talk to their healthcare provider about enrolling in the EMTRIVA® pregnancy registry. HIV-positive women should be advised not to breast feed because of the chance of passing HIV to the infant. Also, it is not known if EMTRIVA® can pass into breast milk and harm nursing infants. Women with HIV who have or will have babies should consult their healthcare provider on how best to feed their infants.

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. There are no results from controlled trials evaluating the effect of FUZEON® on clinical progression of HIV-1.

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 doses of up to 30 mg/kg/day administered by subcutaneous injection (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.

Entecavir (BARACLUDE®, ETV)

Entecavir (BARACLUDE®, ETV) is a guanosine nucleoside analogue with selective activity against hepatitis B virus (HBV). Entecavir inhibits HBV polymerase and 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 after one year of treatment in nucleoside-treatment- naïve and lamivudine resistant adult patients with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease and on more limited data in adult patients 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.

Entecavir is labeled Pregnancy Category C. Reproduction studies have been performed in rats and rabbits at orally administered doses of 200 and 16 mg/kg/day and showed no embryotoxicity or maternal toxicity in rat and rabbit at doses producing systemic exposures approximately 28 and 212 times those achieved at the highest recommended dose of 1 mg/day in humans. 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.

Etravirine (INTELENCE™, ETR)

Etravirine (INTELENCE™, ETR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1).

Indication and Usage: INTELENCE™, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to a NNRTI and other antiretroviral agents.

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 foetus.

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™.

Paediatric use: Safety and effectiveness in paediatric patients have not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies of etravirine in rodents are ongoing. 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.

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).

Fosamprenavir calcium (LEXIVA®, FOS)

LEXIVA® is the brand name for fosamprenavir calcium, a prodrug of amprenavir, an inhibitor of human immunodeficiency virus (HIV) protease.

Fosamprenavir calcium 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 calcium 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 (AUC0-24 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 calcium alone or similar to those seen in humans following administration of fosamprenavir calcium in combination with ritonavir. Fosamprenavir calcium did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats.

LEXIVA® 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 calcium 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 calcium. Systemic exposures (AUC0-24 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 calcium alone or 0.3 (rabbits) to 0.7 (rats) times the exposures in humans following administration of the MRHD of fosamprenavir calcium 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. The mating and fertility of the F1 generation born to female rats given fosamprenavir calcium was no different from control animals; however, fosamprenavir calcium did cause a reduction in both pup survival and body weights. Surviving F1 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 to control animals. Systemic

exposure (AUC0-24 hr) to amprenavir in the F0 pregnant rats was approximately 2 times higher than exposures in humans following administration of the MRHD of fosamprenavir calcium alone or approximately the same as those seen in humans following administration of the MRHD of fosamprenavir calcium in combination with ritonavir. There are no adequate and well-controlled studies in pregnant women. LEXIVA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 was 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.

Long-term carcinogenicity studies of lamivudine in animals have not yet been completed. 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 (approximately 65 times the recommended human dose based on body surface area comparisons). In a study of reproductive performance, lamivudine, administered to rats at doses up to 130 times the usual adult dose based on body surface area comparisons, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

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 harm to the fetus due to lamivudine. 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 130 times the usual adult dose. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. There are no adequate and well-controlled studies in pregnant women. Animal reproductive toxicity studies are not always predictive of human response; therefore lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

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. 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.

Maraviroc (CELSENTRI™, SELZENTRY™ , MVC)

Maraviroc (CELSENTRI™, SELZENTRY™) is an antagonist of the human chemokine receptor CCR5.

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.

A fertility study in rats at daily doses of 100, 300, and 1000 mg/kg, showed reductions in body weight in males and pregnant females at 1000mg/kg. This dose was also associated with an increase in pre-implantation loss and smaller numbers of implants and viable foetuses. The NOAEL in adults was 300 mg/kg; the NOAEL for fertility was 1000mg/kg.

In a 6-month carcinogenicity study in male and female ras-H2 transgenic mice, maraviroc administered up to the daily dose of 1500 mg/kg, did not induce any hyperplastic, neoplastic, inflammatory, or degenerative changes.

Maraviroc is labeled Pregnancy Category B. 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 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. There were no associated clinical signs or macroscopic findings. Treatment with maraviroc had no effect on reproductive parameters. The NOAEL was 75mg/kg for the pregnant females and 200mg/kg for the foetuses. In a pre-and post-natal development study in rats at daily doses of 100, 300, and 1000 mg/kg, the only treatment-related effect of note was a slight increase in the motor activity of F1 males born to rats treated with 1000 mg/kg.

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* rat 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.

Nevirapine (VIRAMUNE®, NVP)

VIRAMUNE® (nevirapine) is a non-nucleoside reverse transcriptase inhibitor with activity against Human Immunodeficiency Virus Type 1 (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 polymerase (such as human DNA polymerase a, b, g, or d) 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies of nevirapine in animals are currently in progress. In genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including microbial assays for gene mutation (Ames: Salmonella strains and E. coli), mammalian cell gene mutation assays (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. 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 nevirapine.

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.

Nursing Mothers: Results from a pharmacokinetic study (ACTG 250) in 10 HIV-1 infected pregnant women who were administered a single oral dose of 100 or 200 mg nevirapine at a median of 5.8 hours before delivery, indicate that nevirapine readily crosses the placenta and is found in breast milk. Consistent with the recommendation by the U.S. Public Health Service Centers for Disease Control and Prevention that HIV-

infected mothers not breast-feed their infants to avoid postnatal transmission of HIV, mothers should discontinue nursing if they are receiving nevirapine.

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

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 counts at initiation of therapy place patients at increased risk; women with CD4 counts >250 cells/mm^3, including pregnant women receiving VIRAMUNE® in combination with other antiretrovirals for the treatment of HIV infection, are at the greatest risk. However, hepatotoxicity associated with VIRAMUNE® use can occur in both genders, all CD4 counts and at any time during treatment. 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 (see WARNINGS). 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 (see WARNINGS).

It is essential that patients 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. In addition, the 14-day lead-in period with VIRAMUNE® 200 mg daily dosing must be strictly followed (see WARNINGS).

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-uninfected individuals receiving multiple doses of VIRAMUNE® in the setting of post-exposure prophylaxis, an unapproved use.

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.

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 availability 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 on 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.

Stavudine (ZERIT®, d4T)

Stavudine, a nucleoside analogue of thymidine, inhibits the replication of HIV in human cells *in vitro*. Stavudine is phosphorylated by cellular kinases to stavudine triphosphate, which exerts antiviral activity. Stavudine triphosphate has an intracellular half-life of 3.5 hours in CEM and peripheral blood mononuclear cells. Stavudine triphosphate inhibits HIV replication by two known mechanisms: 1) it inhibits HIV reverse transcriptase by competing with the natural substrate deoxythymidine triphosphate (K - 0.0083 to 0.032 µM); and 2) it inhibits viral DNA synthesis by causing DNA chain termination because virus infection and stavudine treatment, size of virus oculum, the cell type employed and the particular assay method used.

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.

This information can also be found in the official prescribing information.

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

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.

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 (a prodrug of tenofovir) which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. In vivo tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

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

VIREAD® is assigned FDA Pregnancy Category B status. Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD® should be used during pregnancy only if clearly needed.

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. With the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving VIREAD®.

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

Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

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

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on

body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

Patients should be advised to tell their healthcare provider if they are pregnant or planning to become pregnant. The effects of VIREAD® on pregnant women or their unborn children are not known. Women should not breast-feed if they are taking VIREAD® or if they have HIV. There is a chance that an infant that does not already have HIV could contract the virus through breast-feeding. Women with HIV who have or will have babies should consult their healthcare provider on how best to feed their infants.

Tipranavir (APTIVUS®, TPV)

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. Tipranavir, co-administered with 200 mg of ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term animal carcinogenicity bioassays with tipranavir and tipranavir/ritonavir are currently in progress. However, 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 tipranavir/ritonavir BID.

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®.

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 at 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.

Zidovudine (RETROVIR®, ZDV)

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. In mutagenicity assays, zidovudine was weakly positive at high concentrations in mouse lymphoma cells; dose-related structural chromosomal alterations were seen at low to moderate concentrations in cultured human lymphocytes; and BALB/c-3T3 cells were transformed at low concentrations. No effects were seen in bacterial mutagenicity assays (possibly due to bactericidal activity of zidovudine at low concentrations) or in a single dose intravenous bone marrow cytogenetic assay in rats. Positive results were noted in multidose micronucleus studies.

Zidovudine is assigned FDA Pregnancy Category C status. 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. Early embryo death did not occur in rats or rabbits in standard developmental (teratology) studies, however, pregnant New Zealand white rabbits given 500 mg/kg/day during gestation days 6-18 showed an increase in late fetal deaths. No other evidence of developmental toxicity was noted in either species, and zidovudine was not teratogenic in rats or rabbits given up to 500 mg/kg/day during the period of major organogenesis. When oral doses of 3000 mg/kg/day (near the median lethal dose of 3683 mg/kg) of zidovudine were given to pregnant rats (unpublished data) during the period of organogenesis, there was severe maternal toxicity and an increased incidence of a variety of types of fetal malformations. The area-under-the-concentration-time-curve (AUC) for zidovudine at this dose was 300-fold higher than the daily AUC in humans given 600 mg per day.

In both the reproduction/fertility study and a peri- and postnatal study in rats, there were no adverse effects of zidovudine treatment on survival, growth, or developmental measurements in live-born offspring.

In standard oral carcinogenicity bioassays, no evidence of carcinogenicity was seen in male mice or rats. In female mice, five malignant and two benign vaginal epithelial neoplasms occurred in animals given 40 mg/kg/day. A single benign vaginal epithelial tumor was seen in a mouse given 30 mg/kg/day. In rats, two malignant vaginal epithelial neoplasms were seen in animals given 300 mg/kg/day. In a subsequent lifetime carcinogenicity bioassay in which zidovudine was given intravaginally, 13 vaginal squamous cell carcinomas were seen at the highest dose tested. It was concluded that the vaginal tumors seen in the oral carcinogenicity studies were the result of chronic local exposure of the highly replicative rodent vaginal epithelium to high urine concentrations of zidovudine.

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, a transplacental

carcinogenicity study was conducted. In this study, pregnant Charles River CD-1 mice were treated with zidovudine (at doses of 20 and 40 mg/kg/day) beginning on gestation day 10, and continuing through parturition. During lactation the pups were exposed via the milk. At weaning, pups were given zidovudine in the drinking water for two weeks, at which time dosing via gavage was initiated. Treatment with zidovudine was continued for 23 months.

ZDV-related findings were limited to the vagina, where there were 11 vaginal squamous cell carcinomas in Group 4. None of the tumors metastasized. The earliest a vaginal tumor was seen was after 694 days (23 months) daily dosing. Treatment with zidovudine did not induce tumors in any tissue or organ in males. These findings are identical to those seen in the standard oral carcinogenicity study in mice. As noted above, in that study there were 7 vaginal epithelial cell tumors seen in a group of 60 mice, for an incidence rate of 12%. In this transplacental carcinogenicity study there were 11 vaginal epithelial cell tumors in a group of 70 mice, for an incidence rate of 16%. Time of onset was also unaltered by prenatal treatment with zidovudine. In the standard oral carcinogenicity study in mice, the earliest that a vaginal tumor was noted was after 19 months of daily dosing. In the transplacental study, vaginal tumors were first seen after 23 months of daily dosing. These studies support the conclusion that zidovudine is not a transplacental carcinogen.

Another transplacental carcinogenicity study was conducted by the National Cancer Institute in order to explore the carcinogenic potential of zidovudine in mice at the maximum maternal doses that were not associated with fetal death. In this NCI study, pregnant CD-1 mice were given 12.5 mg or 25 mg of zidovudine (~1000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) orally per day on gestation days 12 to 18. One year post-partum, male progeny given 25 mg per day had increased numbers of lung and liver tumors, while female progeny at this dose had increased numbers of lung and reproductive tract tumors. These findings did not show a clear dose-response relationship.

Clinical trials with zidovudine indicate that the drug can be used safely and effectively in adult and pediatric patients with HIV infection. Studies specifically concerning the safety and efficacy of zidovudine in pregnant women are ongoing.

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. 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. Abnormalities reported in infants exposed to zidovudine included systolic murmurs [3], cardiomyopathy-like hypoxia [1], seizures [2], polydactyly [3], diaphragmatic hernia [1], amniotic band syndrome [1], cleft-lip and heart disease [1], 2-vessel cord and arrhythmias [1], and dysmorphic toes [1]. Grade 2 or 3 anemia was more common in zidovudine treated infants compared to the placebo groups; however, all values recovered by 12 weeks of age. Other laboratory results were balanced between the treatment and placebo groups of infants. Women in this study did not receive zidovudine during the first trimester of pregnancy. Therapy with zidovudine reduced the risk of HIV transmission by 67.5% but did not prevent HIV infection in 8.3% of exposed infants. The Data and Safety Monitoring Board recommended that zidovudine should be made available to women who had not yet delivered and to infants who were less than 6 weeks of age in the study. It is unknown whether there are any long-term maternal or newborn adverse effects associated with exposure to zidovudine during pregnancy.

Appendix E: 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 (19, 20), the Guidelines for Good Pharmacoepidemiology Practices (GPP) (21), and the FDA Guidance on Pharmacovigilance (28).

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 quarterly interim 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 (22).

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, emtricitabine, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, 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 1-910-256-0238 or Fax 800-800-1052 or 1-910-256-0637.) For UK, Germany, France toll free call 00800-5913-1359 or Fax 00800-5812-1658. 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. 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. 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 after 20 weeks gestation or weighing more 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 (7). 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 $\geq$20 weeks, when available, have been included to increase the sensitivity of Registry monitoring. The MACDP includes major defects, as well as conditional defects in the presence of a major defect, as defect cases. The Registry considers reports of 2 or more conditional defects as a defect case so as not to miss a potential signal and to capture the instance where the combination of conditional events might constitute a major defect.

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 conditional 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 (10). 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) and the MACDP (5, 7, 27). 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 Abbott Laboratories, Augoron Pharmaceuticals/Pfizer Inc, Aurobindo Pharma Ltd, Barr Laboratories, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Gilead Sciences Inc, GlaxoSmithKline, Hetero USA, Merck & Co. Inc, Mylan Laboratories, Novartis Pharmaceuticals, Ranbaxy Inc, Roche, and Tibotec BVBA. 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 (7). 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. 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% (24). 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 (25). The overall prevalence of birth defects by year (1968-1999 ranges from 2% to 5%) (25). 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 the MACDP, a population-based birth defects surveillance system administered by the CDC. The total prevalence of birth defects identified among births from 1968 through 2003 was 2.67% and 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). The prevalence of “early diagnoses” is important for Registry comparisons since the majority of outcome reports are from obstetricians who may have limited access to diagnoses made after the day of birth. 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. As a second method of analysis, the risk of birth defects among women with first trimester exposures to antiretroviral medications are compared with the risk of birth defects among women with second or third trimester exposures to antiretroviral medications. Prevalence ratios and 95% confidence intervals 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 CDC 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.

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 (26) (monograph available upon request).

Information about the Registry can be found in other Registry publications and presentations (29 - 0).

Appendix F: 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 Abbott Laboratories; delavirdine mesylate (RESCRIPTOR®, DLV), maraviroc (SELZENTRY™, CELSENTRI™, MVC), and nelfinavir (VIRACEPT®, NFV) licensed and manufactured by Agouron Pharmaceuticals/Pfizer Inc; didanosine (generic), and zidovudine (generic) manufactured by Aurobindo Pharma Ltd; didanosine (generic) manufactured by Barr Laboratories; nevirapine (VIRAMUNE®, NVP) and tipranavir (APTIVUS®, TPV) manufactured by Boehringer Ingelheim Pharmaceuticals Inc; atazanavir (REYATAZ®, ATV), didanosine (VIDEX®, VIDEX® EC, ddI), entecavir (BARACLUDE®, ETV), and stavudine (ZERIT®, d4T) manufactured by Bristol-Myers Squibb Company; adefovir dipivoxil (HEPSERA®, ADV), emtricitabine (EMTRIVA®, FTC), tenofovir disoproxil fumarate (VIREAD®, TDF) and tenofovir disoproxil fumarate+emtricitabine (TRUVADA®, TVD) manufactured by Gilead Sciences Inc, abacavir (ZIAGEN®, ABC), abacavir+lamivudine (EPZICOM®), abacavir+ lamivudine+ zidovudine (TRIZIVIR®, TZV), amprenavir (AGENERASE®, APV), fosamprenavir calcium (LEXIVA®, FOS), lamivudine (EPIVIR®, 3TC), lamivudine+zidovudine (COMBIVIR®, ZDV+3TC), and zidovudine (RETROVIR®, ZDV) manufactured by GlaxoSmithKline Inc; zidovudine (generic) manufactured by Hetero USA; indinavir (CRIXIVAN®, IDV) and raltegravir (ISENTRESS™, RAL) manufactured by Merck & Co. Inc; stavudine (generic) and zidovudine (generic) manufactured by Mylan Laboratories; telbivudine (SEBIVO®, TYZEKA®, LdT), manufactured by Novartis Pharmaceuticals; enfuvirtide (FUZEON®, T-20), saquinavir (FORTOVASE®, SQV-SGC), saquinavir mesylate (INVIRASE®, SQV-HGC), and zalcitabine (HIVID®, ddC) manufactured by Roche; darunavir (PREZISTA™, DRV) and etravirine (INTELENCE™, ETR) manufactured by Tibotec BVBA; and efavirenz co-marketed by Bristol-Myers Squibb Company (SUSTIVA®, EFV) and Merck & Co. Inc (STOCRIN®, EFV); and efavirenz/emtricitabine/tenofovir disoproxil fumarate combination co-marketed by Bristol-Myers Squibb Company and Gilead Sciences Inc, (ATRIPLA, ATR™); and zidovudine (generic) manufactured by Ranbaxy Inc Zidovudine (generic) is also manufactured by Cipla Ltd, GlaxoSmithKline Inc (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) 1-910-256-0238
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)

- 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) 1-910-256-0238
  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)
  - 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)

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 1-910-256-0238

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 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

Patient LOG ID: The Registry assigned number for the patient assigned at registration number or Sponsor Company MCN

Date first seen: This date is only required for providers who have committed to provide all pregnancy exposures to antiretroviral drugs reports at their site.

1. Maternal Information

1.1 **Clinical Study:** Indicate if the patient is in a clinical study and if yes, whether the study is being conducted in pregnant women. If yes, please provide the study/protocol number.

1.2 **Last Menstrual Period:** Provide the date of the woman's last menstrual period.

1.3 **Corrected Estimated Date of Delivery:** If available, an 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. Preferred over the LMP.

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

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

2. Prenatal Tests

2.1 **Prenatal Test Done:** Indicate if a prenatal test was done.

- If no, move to section 3: Clinical Indicators
- If yes, continue by providing the date or gestational age when the test was done and which test was done. Go to section 2.2.

2.2 **Evidence of a Structural Defect:** Indicate if a structural defect(s) was identified on a prenatal test.

- If no, move to section 3: Clinical Indicators
- If yes, continue by providing the structural and/or chromosomal defect(s) identified and by what test the defect was identified. Go to section 3.

3. 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).

4. ANTIVIRAL THERAPY DURING PREGNANCY FORM

- **Course:** Enter the number of the course of treatment for each medication (i.e. if the patient received 2 courses of the same medication, list them separately and number each sequentially).
- **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 Gestation Week Calculated:** Indicate the date *or* the gestational age when therapy began for each course, but not both.
- **Gestation Week or Date Therapy was Discontinued or if Continued Following Delivery:** Provide date or gestation week or if therapy continues through and continuing at delivery, check "ongoing" box. Do not check the "ongoing" box if only providing registration information. This box should only be checked when providing outcome information.

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 FDA. FDA can be reached by faxing the information to 800-FDA-0178 or at http://www.fda.gov/medwatch/.

ANTIRETROVIRAL PREGNANCY REGISTRY
REGISTRATION FORM

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

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

Patient LOG ID: _____ ***Registry assigned ID number or Sponsor Manufacturer Control Number (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 _____ _____ _____
M D Y

1.3 Corrected EDD _____ _____ _____ *(e.g., by ultrasound)*
M D Y

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:
(✓) test(s)
☐ Ultrasound _____ date
☐ Ultrasound _____ date
☐ Ultrasound _____ date
☐ Amniocentesis _____ date
☐ MSAFP/serum markers _____ date
☐ Other: _____ _____ date
☐ Unknown *(go to section 3)*

2.2 Is there evidence of a structural defect from one or more of these prenatal tests?
☐ No *(go to section 3)*
☐ Yes *(complete below, then go to section 3)*
Specify structural defect _____
(✓) test(s) where defect noted
☐ Ultrasound _____ date
☐ Amniocentesis _____ date
☐ MSAFP/serum markers _____ date
☐ Other: _____ _____ date
☐ 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 _____
_____ Email _____
Alternate Contact _____
Provider's Signature _____ Date _____ _____ _____
M D Y

Phone: (US, Canada) 800-258-4263 (Toll Free) or +1-910-256-0238 (local)
Phone: (International) +1-910-256-0238
Phone: (UK, Germany, France) 00800-5913-1359 (Toll Free)
Phone: (Europe): +32-2-714-5028
Internet: www.APRegistry.com

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(Revised April 2008)

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 Company Manufacturer Control Number (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)
2. Didanosine (VIDEX®,VIDEX® EC, ddI)
2.1 Didanosine generic – Barr Labs
2.2 Didanosine generic - Aurobindo
2.99 Didanosine (unknown manufacturer)
3. Efavirenz (SUSTIVA®, EFV)
3.1 Efavirenz (STOCRIN®, EFV)
3.99 Efavirenz (unknown manufacturer)
4. Lamivudine (EPIVIR®, 3TC)
4.99 Lamivudine (unknown manufacturer)
5. Lamivudine+zidovudine (COMBIVIR®, ZDV+3TC)
5.99 Lamivudine+zidovudine (unknown manufacturer)
6. Nelfinavir (VIRACEPT®, NFV)
7. Nevirapine (VIRAMUNE®, NVP)
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
11.99 Stavudine (unknown manufacturer)
12. Zalcitabine (HIVID®, ddC)
13 Zidovudine (RETROVIR®, ZDV)
13.1 Zidovudine generic – Ranbaxy
13.2 Zidovudine generic – Teva/GSK
13.3 Zidovudine generic – Roxane/BI
13.4 Zidovudine generic – Aurobindo
13.5 Zidovudine generic – Cipla
13.6 Zidovudine generic – Mylan
13.7 Zidovudine generic – Hetero
13.99 Zidovudine (unknown manufacturer)
14. Amprenavir (AGENERASE®, APV)
15. Indinavir (CRIXIVAN®, IDV)
16. Delavirdine mesylate (RESCRIPTOR®, DLV)
17. Lopinavir+ritonavir (KALETRA®, LPV/r)
18. Abacavir+lamivudine+zidovudine (TRIZIVIR®, TZV)
19. Tenofovir disoproxil fumarate (VIREAD®, TDF)
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)

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

Course #	***Med. Code* (1-31) or if no code indicated, please write medication name Specify if Generic**	***Total Daily Dose (mg/day OR mg/kg/day) *please indicate***	***Route (enter code) 1 = oral 2 = IV 3 = sub-Q***	***Pt Taking Med. at Conception? 1 = Yes 2 = No 3 = Unknown***	***Date Treatmen tCourse Began (m/d/y) OR gestational age (0 = prior to conception)*** If calculated by gestational age: ☐ *(from LMP)* ☐ *(by corrected EDD)*	***Date Treatment Stopped (m/d/y)*** (Note: Ongoing = ongoing ***following*** delivery)
	☐ generic					or ☐ ongoing
	☐ generic					or ☐ ongoing
	☐ generic					or ☐ ongoing
	☐ generic					or ☐ ongoing
	☐ generic					or ☐ ongoing
	☐ generic					or ☐ ongoing
	☐ generic					or ☐ ongoing
	☐ generic					or ☐ ongoing

Phone: (US, Canada) 800-258-4263 (Toll Free) or +1-910-256-0238 (local)
Phone: (International) +1-910-256-0238
Phone: (UK, Germany, France) 00800-5913-1359 (Toll Free)
Phone: (Europe): +32-2-714-5028
Internet: www.APRegistry.com

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(Revised April 2008)

The Antiretroviral Pregnancy Registry
Instructions for completing the FOLLOW-UP FORM

Patient LOG ID: The Registry assigned number for the patient assigned at registration number or Sponsor Company MCN

1. Maternal Information

1.1 **Clinical Study:** Indicate if the patient is in a clinical study and if yes, whether the study is being conducted in pregnant women. If yes, please provide the study/protocol number.

2. Fetal Outcome

If there are multiple outcomes (e.g., twins, triplets) provide details for each outcome. Make copies of page 3 or indicate the information for each outcome.

2.1 **Birth Defect Noted:** Was a structural birth defect noted? Check "yes", "no", or "unknown". If yes, then list defects on the next page. *Please try to determine if a defect was present. If this information is unknown, this case cannot be included in the analysis.*

2.2 **Outcome:** Check one box for outcome (live birth, spontaneous or induced abortion, or stillbirth). For a fetal loss, provide details on page 4, section 4 of the form.

2.3 **Date of Outcome:** Provide the date live birth or fetal loss occurred.

2.4 **Gender:** Provide the gender of the infant.

2.5 **Length:** Provide the length of the infant at birth (indicate "N/A" if not available).

2.6 **Gestational Age:** Provide the gestational age at outcome.

2.7 **Birth Weight:** Provide the birth weight in grams (indicate "N/A" if not available).

2.8 **Head Circumference:** Provide the infant's head circumference at birth (indicate "N/A" if not available).

3. Birth Defects

1) List the structural birth defect(s) and 2) indicate if the defect, in your opinion, was attributed to the antiviral therapy ("yes", "no", or "unknown") and 3) if other factors might have contributed to this outcome.

4. Fetal Loss (Stillbirth, Spontaneous or Induced Abortion):

List factors, other than the birth defects, that may have had an impact on the fetal loss.

ANTIVIRAL THERAPY DURING PREGNANCY FORM

- **Course:** Enter the number of the course of treatment for each medication (i.e. if the patient received 2 courses of the same medication, list them separately and number each sequentially).
- **Med Code:** Indicate the code number from the list above. If it is a drug that 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:** Indicate the date therapy began for each course.
- **Gestation Week Calculated:** At times, we must contact providers when dates and gestation weeks provided are not consistent with the dates for LMP or EDD written on the Registration Form. To ensure that we are calculating from the same date and to save having to contact you, we have added a box for indicating how the gestation weeks were calculated.
- **Gestation Week or Date Therapy was Discontinued or if Continuing Following Delivery:** Provide date or gestation week or if therapy continues through and following delivery, check "ongoing" box. Be sure to check this field for therapies reported at Registration.

You will receive a copy of this form with the information as submitted at Registration. Please update and append any further therapy information on this form.

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

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

FOR REGISTRY USE ONLY
Baby ID: _____

☐ Abortion, Spontaneous
☐ Abortion, Induced
☐ Stillbirth

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)

2.6 Gestational Age: _____ weeks

2.4 Gender: ☐ Male ☐ Female

2.7 Birth Weight: _____ ☐ grams ☐ lbs/oz.

2.5 Length: _____ ☐ cm. ☐ in.

2.8 Head Circumference: _____ ☐ cm. ☐ in.

NOTES:

- **If DEFECT or FETAL LOSS, <u>go to page 4</u>**
- **<u>Complete</u> 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