THE ANTIRETROVIRAL PREGNANCY REGISTRY
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ATTENTION:

Reports with data through 31 July 2023 and 31 January 2024 were issued with data discrepancies and should not be referenced. While these discrepancies did not impact overall study results, each subsequent report is cumulative and replaces all prior reports which should be discarded.

THE ANTIRETROVIRAL PREGNANCY REGISTRY INTERIM REPORT

1 JANUARY 1989 THROUGH 31 JULY 2024

(Issued: February 2025)

(Expiration: 6 months after issue)

For:

ABACAVIR (ZIAGEN®, ABC)
ABACAVIR+LAMIVUDINE (EPZICOM®, EPZ)
ABACAVIR+LAMIVUDINE+ZIDOVUDINE (TRIZIVIR®, TZV)
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COBICISTAT (TYBOST®, COBI)
DARUNAVIR (PREZISTA®, DRV)
DARUNAVIR+COBICISTAT (PREZCOBIX™, REZOLSTA™, PCX)
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TIPRANAVIR (APTIVUS®, TPV)
ZALCITABINE (HIVID®, ddC) ***(HIVID NO LONGER MANUFACTURED AS OF 2006)***
ZIDOVUDINE (RETROVIR®, ZDV)

Collaborative Project Sponsored by:
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POLICY FOR PRESENTATION OF DATA

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

1. The data contained in this report will become out-of-date within 6 months of the report's issue date. Please contact the Antiretroviral Pregnancy Registry (+1-800-258-4263) to ensure you have obtained the most recently published report. You can also retrieve a copy of the most recently published report by visiting the website at www.APRegistry.com.
2. The data in Table 4 (pregnancy exposure in the first trimester and outcome by treatment regimen) are the most appropriate for presentation of therapy results. Presentation of results stratified by earliest trimester of exposure is imperative. Retrospectively collected data are useful for detecting patterns of defects but are subject to biases as described in the report; **thus, these data must not be compared to background rates in the general population**.
3. The Advisory Committee Consensus statement (page 12) 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 Interim Report for 1 January 1989 through 31 July 2024. Morrisville, NC: Registry Coordinating Center; 2024. Available from URL: www.APRegistry.com.

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Note to Patients:

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

TABLE OF CONTENTS

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 July 2024.

Abacavir, abacavir/dolutegravir/lamivudine, abacavir/lamivudine, abacavir/lamivudine/zidovudine, adefovir dipivoxil, amprenavir, atazanavir, atazanavir/cobicistat, bictegravir/emtricitabine/tenofovir alafenamide, cabotegravir, cobicistat, darunavir, darunavir/cobicistat, darunavir/cobicistat/emtricitabine/tenofovir alafenamide, delavirdine mesylate, didanosine, dolutegravir, dolutegravir/lamivudine, dolutegravir/ lamivudine/tenofovir disoproxil fumarate, dolutegravir/rilpivirine, doravirine, doravirine/lamivudine/tenofovir disoproxil fumarate, efavirenz, efavirenz/lamivudine/tenofovir disoproxil fumarate, efavirenz/tenofovir disoproxil fumarate/emtricitabine, elvitegravir, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, emtricitabine/ tenofovir alafenamide, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, fostemsavir, indinavir, lamivudine, lamivudine/ raltegravir, lamivudine/tenofovir disoproxil fumarate, lamivudine/zidovudine, lenacapavir, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpivirine, rilpivirine/emtricitabine/tenofovir disoproxil fumarate, rilpivirine/emtricitabine/tenofovir alafenamide, ritonavir, saquinavir, saquinavir mesylate, stavudine, telbivudine, tenofovir alafenamide, tenofovir disoproxil fumarate, tenofovir disoproxil fumarate/emtricitabine, tipranavir, zalcitabine, and zidovudine are the 60 brand antiretroviral (ARV) therapies being followed in this Registry. Also included are the 169 generic formulations of the above brand therapies.

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 people. These data represent the experience of what is, as yet, a relatively small number of pregnancies.

An independent Advisory Committee reviews data and establishes a consensus regarding results of the data at that time, makes recommendations on data collected and on issues arising during the conduct of the Registry, encourages referral of exposures, and disseminates information. The Advisory Committee, including a community member, along with representatives from the 27 currently participating Sponsor companies constitutes the Registry Steering Committee. The Steering Committee meets to discuss issues, review data, update the report, and discuss the general conduct of the Registry. Members of the Advisory Committee and Sponsor representatives to the Steering Committee are listed below. Committee members are listed alphabetically within their respective group.

Antiretroviral Pregnancy Registry Advisory Committee

Cynthia Holcroft Argani, MD Division of Maternal-Fetal Medicine Johns Hopkins University Medical Center	Lynne Mofenson, MD Senior HIV Technical Advisor Elizabeth Glaser Pediatric AIDS Foundation	Special Advisor: Genetics Fernando Scaglia, MD, FACMG Professor of Genetics Baylor College of Medicine
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Tara DeYampert, MD Program Officer, Extramural Division NICHD, National Institutes of Health	Rosemary Ramroop Program Coordinator/HIV Counselor Johns Hopkins University	
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The Antiretroviral Pregnancy Registry encourages reporting of all prenatal exposures to the antiretroviral therapies followed in the Registry (see page 6). Enrollment forms and instructions can be found in Appendix G. Please direct all enrollments and inquiries to the Antiretroviral Pregnancy Registry Coordinating Center at the following:

Telephone:
+1-800-258-4263 (toll free US, Canada)

Fax:
+1-800-800-1052 (toll free US, Canada)
+1-910-256-0637 (International)

Email: SM_APR@APRegistry.com

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

ATTENTION ALL HEALTH CARE PROVIDERS WORLDWIDE

Your prospective data are critical to the success of this important Registry. Any Health Care Provider with access to ARV exposure and pregnancy outcome information can report to APR (i.e., physicians, pharmacists, nurse practitioners, medical assistants).

Please visit our website at www.APRegistry.com for data forms or contact our Registry Coordinating Center at SM_APR@APRegistry.com for additional information on how to easily register and begin reporting data to the APR.

The Antiretroviral Pregnancy Registry (APR) recognizes the significant participation of the following 100% Health Care Providers (HCPs) (listed alphabetically). We greatly appreciate the contributions of all HCPs who report to the APR and we encourage all registered reporters to submit all of their cases to the Registry. Contact the Registry at SM_APR@APRegistry.com or visit www.APRegistry.com to learn more about becoming a 100% Health Care Provider.

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Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 – 31 July 2024[Δ]

EXECUTIVE SUMMARY

Prospective tracking of prenatal antiretroviral exposures during pregnancy, particularly newer agents and new combinations of therapies, remains critically important in evaluating the safety of these agents among people of reproductive-age and the exposed fetuses.

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 people are exposed (1). Registration is voluntary and confidential with information obtained from the health care provider. A Registry-assigned identifier allows for follow-up capability. Information on subjects is provided to the Registry prospectively (prior to the outcome of pregnancy being known) through their health care provider, with follow-up obtained from the health care provider after the outcome is determined. (For more details, see Appendix F: Methods beginning on page 145) Providers are strongly urged to enroll 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.

Annually, the Registry enrolls approximately 1,000 pregnant people exposed to antiretroviral drugs for the treatment of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infection and prevention of HIV infection, e.g., pre- or post-exposure prophylaxis. The estimated number of individuals living with HIV who give birth to live infants annually in the United States has decreased from 3,525 in 2019 to 3,315 (95%CI 3,202-3,428) in 2020 (2, 3). Given the continued development of newer therapies used for treatment and prevention for which there is an ongoing need for evidence of their safety in pregnancy, sustained reporting is vital to the registry's ability to fulfill its mission of early detection of a birth defect signal, if present. Health care providers are strongly encouraged to continue reporting eligible people to the Registry.

[Δ] Drugs included: abacavir (ZIAGEN®, ABC), abacavir/lamivudine (EPZICOM®, KIVEXA®, EPZ), abacavir/lamivudine/zidovudine (TRIZIVIR®, TZV), abacavir/dolutegravir/lamivudine (TRIUMEQ®, TRI), adefovir dipivoxil (HEPSERA®, ADV), amprenavir (AGENERASE®, APV), atazanavir (REYATAZ®, ATV), atazanavir/cobicistat (EVOTAZ®, EVO), bictegravir/emtricitabine/tenofovir alafenamide (BIKTARVY®, B/F/TAF), cabotegravir (VOCABRIA®, CABENUVA®, APRETUDE®, CAB), cobicistat (TYBOST®, COBI), darunavir (PREZISTA®, DRV), darunavir/cobicistat (PREZCOBIX™, REZOLSTA™, PCX), darunavir/cobicistat/emtricitabine/tenofovir alafenamide (SYMTUZA®, DCF TAF), delavirdine mesylate (RESCRIPTOR®, DLV), didanosine (VIDEX®, VIDEX® EC, ddI), dolutegravir (TIVICAY®, DTG), dolutegravir/lamivudine (DOVATO®, DTG/RPV), dolutegravir/lamivudine/tenofovir disoproxil fumarate (ACRIPTEGA/TELADOMYL/TENDOLA, TLD), dolutegravir/rilpivirine (JULUCA™, DTG/RPV), doravirine (PIFELTRO™, PIF), doravirine+lamivudine+tenofovir disoproxil fumarate (DELSTRIGO™, DEL), emtricitabine/tenofovir alafenamide (DESCOVY®, DVY), efavirenz (SUSTIVA®, STOCRIN®, EFV), efavirenz/emtricitabine/tenofovir disoproxil (ATRIPLA® ATR), efavirenz/lamivudine/tenofovir disoproxil fumarate (SYMFI™/SYMFI LO™, EFV/3TC/TDF), elvitegravir (VITEKTA®, EVG), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (GENVOYA®, GEN), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (STRIBILD®, STB), emtricitabine (EMTRIVA®, FTC), enfuvirtide (FUZEON®, T-20), entecavir (BARACLUDE®, ETV), etravirine (INTELENCE®, ETR), fosamprenavir calcium (LEXIVA®, FOS), fostemsavir (RUKOBIA®, FTR), indinavir (CRIXIVAN®, IDV), lamivudine (EPIVIR®, 3TC), lamivudine/raltegravir (DUTREBIS™, DUT), lamivudine/tenofovir disoproxil fumarate (CIMDUO™, 3TC/TDF), lamivudine/zidovudine (COMBIVIR®, CBV), lenacapavir (SUNLENCA®, LEN), lopinavir/ritonavir (KALETRA®, ALUVIA®, LPV/r), maraviroc (SELZENTRY®, CELSENTRI®, MVC), nelfinavir (VIRACEPT®, NFV), nevirapine (VIRAMUNE®, VIRAMUNE XR®, NVP), raltegravir (ISENTRESS®, RAL), rilpivirine (EDURANT®, REKAMBYS®, CABENUVA®, RPV), rilpivirine/emtricitabine/tenofovir alafenamide (ODEFSEY®,ODE), rilpivirine/emtricitabine/tenofovir disoproxil (COMPLERA®, CPA; EVIPLERA®, EPA), ritonavir (NORVIR®, RTV), saquinavir (FORTOVASE®, SQV-SGC), saquinavir mesylate (INVIRASE®, SQV-HGC), stavudine (ZERIT®, d4T), telbivudine (SEBIVO®, TYZEKA®, LdT), tenofovir alafenamide (VEMLIDY®, TAF), tenofovir disoproxil fumarate (VIREAD®, TDF), tenofovir disoproxil fumarate/emtricitabine (TRUVADA®, TVD), tipranavir (APTIVUS®, TPV), zalcitabine (HIVID®, ddC), and zidovudine (RETROVIR®, ZDV).

Data Summary

During the last report period, 471 new prospective enrollments were received bringing the total number of enrolled people to 27,338.

Primary Registry Analysis (Prospective Reports): In review of the data through 31 July 2024, among the 24,074 prospective Registry reports with outcomes, the prevalence of birth defects per 100 live births among people with a first trimester exposure to any of the antiretroviral therapies included in the Registry is 2.9 (95% confidence interval [CI]: 2.7 - 3.3 i.e., 370 outcomes with defects among 12,586 live births) (Table 7). The prevalence of defects among people with initial exposures in the first trimester is not significantly different from the prevalence of defects among people with an initial exposure during the second and/or third trimester (2.8 per 100 live births) (prevalence ratio: 1.04, 95% CI: 0.89, 1.21).

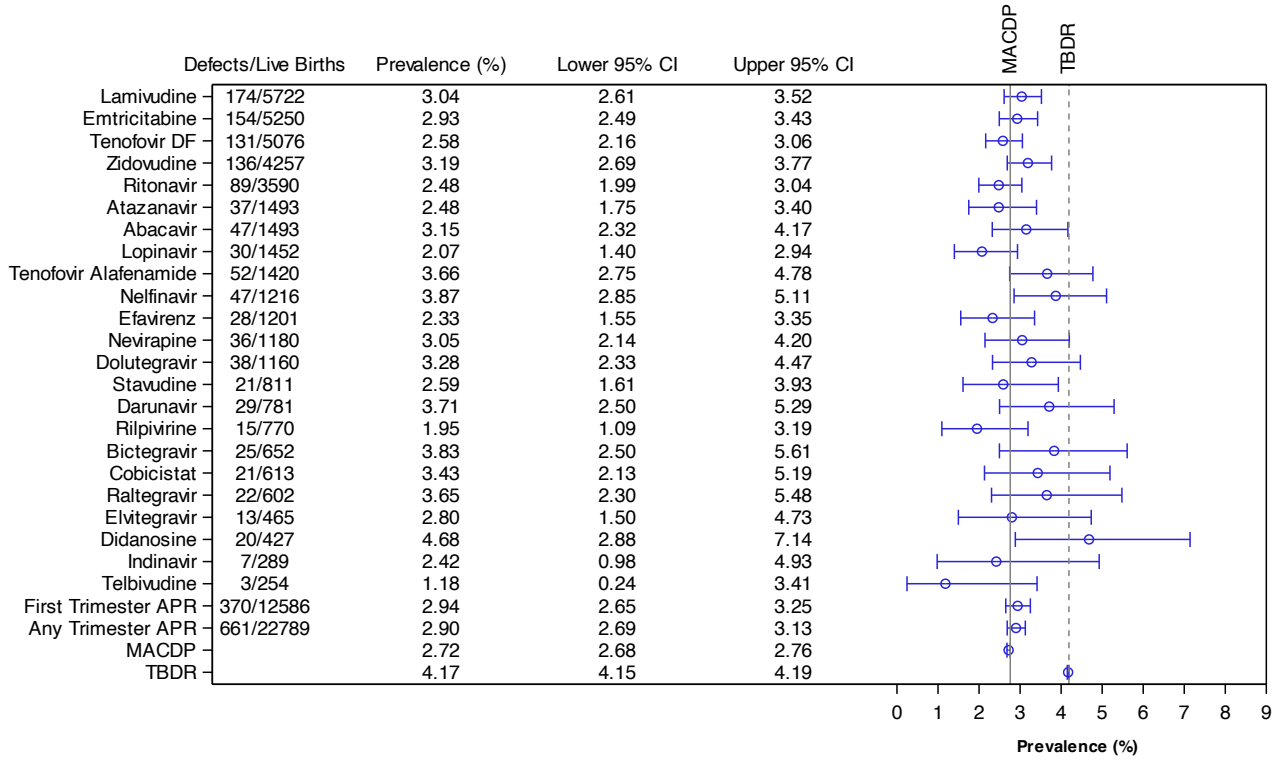
Of the 24,074 prospective Registry reports with outcomes, a total of 21,464 prospective reports are individuals living with HIV and 730 are individuals without HIV, including 464 prospective reports of Pre-Exposure Prophylaxis (PrEP)-exposed pregnancies (Table 2). Also included in the 24,074 prospective Registry reports with outcomes are 1,125 prospective reports of people diagnosed with HBV, with or without concurrent HIV infection, including a total of 887 prospective reports of HBV mono-infected pregnancies with outcomes (Table 2).

Measured against 22,789 live births with exposure at any time during pregnancy, there were 661 outcomes with birth defects identified, a prevalence of 2.9 birth defects per 100 live births (95% CI: 2.7 - 3.1). This proportion is not significantly different than those reported in the Registry's two population based comparators, the CDC's birth defects surveillance system (MACDP) (4, 5, 6, 7) (2.72 per 100 live births) and the Texas Birth Defects Registry (TBDR) (8) (4.17 per 100 live births). No increases in risk of specific defects with exposure in the first trimester have been detected to date when compared with observed MACDP or TBDR rates. Likewise, when comparing rates between first and second or third trimester exposure, no increased risks of defects have been detected. In analyzing individual drugs with sufficient data to warrant a separate analysis, with the exception of didanosine and nelfinavir, no longer in common use, no increases of concern in risk have been detected. For didanosine and nelfinavir, there was a modest but statistically significant increase in prevalence of defects among first trimester exposures when compared with the MACDP though not with the TBDR. The clinical relevance of these statistical findings is unclear. The prevalence is not expected to change given limited use.

All details of defects are listed in Appendix C. The Registry will continue to monitor these drugs for any signal or pattern of birth defects.

For cobicistat, darunavir, didanosine, elvitegravir, indinavir, raltegravir, rilpivirine, stavudine, telbivudine, and bictegravir, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date. For abacavir, atazanavir, dolutegravir, efavirenz, emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, tenofovir disoproxil fumarate, zidovudine, and tenofovir alafenamide 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 (Appendix F). No such increases have been detected to date. (See table below for number of defects and prevalence per 100 live births for first trimester exposures to all drugs with sufficient data to warrant separate analysis. See Appendix A for additional data.) There are insufficient data to make similar comparisons for other drugs or specific subgroups of defects. Detailed monitoring of first trimester exposures to efavirenz for anomalies including central nervous system defects did not reveal a pattern as summarized on page 24.

Figure 1: Summary of Birth Defects among First Trimester Exposures, Prospective Registry Cases Closed with Outcome through 31 July 2024



MACDP = Metropolitan Atlanta Congenital Defects Program (reference 5); TBDR = Texas Birth Defects Registry (reference 7).
Note: The vertical solid line is the upper 95% confidence interval endpoint for MACDP, 2.76%. The vertical dashed line is the upper 95% confidence interval endpoint for TBDR, 4.19%. Confidence intervals are calculated using the Clopper-Pearson exact binomial method.

EUROCAT is a European network of population-based registries for the epidemiological surveillance of congenital anomalies. Due to methodological and population differences, direct comparison of EUROCAT with APR prevalence is not appropriate. However, EUROCAT prevalence is provided here for contextualization purposes only. EUROCAT was established in 1979 and surveys close to 1.5 million births per year across 21 European countries. The prevalence of birth defects in EUROCAT from 1989 through 2022 is 2.59 per 100 live births and stillbirths (9).

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 Pregnancy: In the analysis of reports from clinical studies in pregnancy, 28 infants with defects were identified among 673 live births with first trimester exposures to an antiretroviral therapy. The prevalence of birth defects per 100 live births among people with first trimester exposures to an antiretroviral (primarily nucleoside reverse transcriptase inhibitors) is 4.2 (95% CI: 2.8 - 6.0) (Table 12). The number of defects identified with an initial exposure in the second or third trimester is 71 among 2,791 live births, and the prevalence of birth defects per 100 live births is 2.5 (95% CI: 2.0 - 3.2). The rate of detection of birth defects is

higher among infants born to people enrolled in clinical studies conducted in pregnant people. This group differs from both the MACDP and TBDR population-based surveillance systems and the Primary Registry Analysis. Differences include inclusion/exclusion criteria, severity of disease at the time of maternal enrollment in clinical studies and potentially longer, more rigorous infant follow-up and evaluation (e.g., echocardiography). In addition, in past reports, people with first trimester exposures appeared to have more advanced disease. This may change as antiretroviral treatment is now recommended for all individuals living with HIV regardless of clinical and immunologic or virologic status. The higher rates of defects observed in clinical studies compared to the Primary Registry Analysis are principally minor, spontaneously resolving cardiovascular defects that were detected on echocardiogram. To date, we have received 70 prospective cases of ventricular septal defect (VSD), distributed across trimesters and drug exposures. Thus, the overall rate remains low and there is no apparent excess of cases among zidovudine or any drug exposure group or relevant trimester of exposure.

Reports from the Published Literature: There is a growing body of literature on a 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), under ascertainment 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 counseling on the potential risks and known benefits of antiretroviral treatment during periconception and pregnancy. 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*

We reviewed all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure. We find no significant increases in frequency of birth defects with first trimester exposures when organogenesis occurs compared to second and third trimester exposures. In addition, we have not identified any defect pattern. 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 for patient counseling and formulating patient care plans for pregnant individuals or those considering pregnancy. Potential limitations of registries should be recognized. The Registry is ongoing. Given the use of new therapies about which data are still accumulating, health care providers are strongly encouraged to report all eligible people to the Registry at SM_APR@APRegistry.com via the data forms available at www.APRegistry.com.

PRÉCIS*

The Antiretroviral Pregnancy Registry finds no significant increases in frequency of birth defects with exposure to antiretrovirals and no pattern to suggest a common cause. Potential limitations of registries should be recognized. Providers are strongly encouraged to report all eligible people to SM_APR@APRegistry.com or visit www.APRegistry.com.

* Those wishing to cite data from this Report are encouraged to do so. However, to ensure consistency of reporting, you are required to include the consensus statement verbatim. Shorter presentations of Registry data (i.e., abstracts) may use the abbreviated précis. Editors should be reminded of this requirement and encouraged to exempt the sentence from any word count restrictions. Suggested citation: Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 July 2024. Morrisville, NC: Registry Coordinating Center; 2024. Available from URL: www.APRegistry.com.

SUMMARY OF CHANGES: JANUARY 2024 TO JULY 2024

Primary Prospective Analysis	*January 2024*	*July 2024*
Pregnancies Reported	26,867	27,338
Pending	208	261
Lost to follow-up	2,960	3,003
With follow-up data	23,699	24,074
Earliest Exposure		
1st trimester	13,602	13,882
2nd trimester	7,499	7,563
3rd trimester	2,595	2,626
Unknown (defects only)	3	3
Outcomes	24,109	24,491
Live births	22,420	22,789
Spontaneous abortions	791	798
Stillbirths	269	272
Induced abortions	629	632
Defects/Live births	365/12314	370/12586
1st trimester	3.0% (95% CI: 2.7% - 3.3%)	2.9% (95% CI: 2.7% - 3.3%)
2nd/3rd trimester	288/10103 2.9% (95% CI: 2.5% - 3.2%)	289/10200 2.8% (95% CI: 2.5% - 3.2%)
Any trimester	655/22420 2.9% (95% CI: 2.7% - 3.2%)	661/22789 2.9% (95% CI: 2.7% - 3.1%)
1st to 2nd/3rdtrimester prevalence ratio	1.04 (95% CI: 0.89, 1.21)	1.04 (95% CI: 0.89, 1.21)
Defects/Live births - 1st trimester		
Lamivudine	173/5684 3.0% (2.6%, 3.5%)	174/5722 3.0% (2.6%, 3.5%)
Emtricitabine	151/5030 3.0% (2.5%, 3.5%)	154/5250 2.9% (2.5%, 3.4%)
Tenofovir disoproxil fumarate	129/5014 2.6% (2.2%, 3.0%)	131/5076 2.6% (2.2%, 3.1%)
Zidovudine	136/4256 3.2% (2.7%, 3.8%)	136/4257 3.2% (2.7%, 3.8%)
Ritonavir	88/3578 2.5% (2.0%, 3.0%)	89/3590 2.5% (2.0%, 3.0%)
Atazanavir	37/1485 2.5% (1.8%, 3.4%)	37/1493 2.5% (1.7%, 3.4%)
Abacavir	47/1481 3.2% (2.3%, 4.2%)	47/1493 3.1% (2.3%, 4.2%)
Lopinavir	30/1452 2.1% (1.4%, 2.9%)	30/1452 2.1% (1.4%, 2.9%)
Tenofovir alafenamide	49/1242 3.9% (2.9%, 5.2%)	52/1420 3.7% (2.7%, 4.8%)
Nelfinavir	47/1216 3.9% (2.9%, 5.1%)	47/1216 3.9% (2.9%, 5.1%)
Efavirenz	28/1198 2.3% (1.6%, 3.4%)	28/1201 2.3% (1.6%, 3.4%)
Nevirapine	36/1180 3.1% (2.1%, 4.2%)	36/1180 3.1% (2.1%, 4.2%)
Dolutegravir	35/1052 3.3% (2.3%, 4.6%)	38/1160 3.3% (2.3%, 4.5%)
Stavudine	21/811 2.6% (1.6%, 3.9%)	21/811 2.6% (1.6%, 3.9%)
Darunavir	28/766 3.7% (2.4%, 5.2%)	29/781 3.7% (2.5%, 5.3%)
Rilpivirine	15/738 2.0% (1.1%, 3.3%)	15/770 1.9% (1.1%, 3.2%)
Bictegravir	23/539 4.3% (2.7%, 6.3%)	25/652 3.8% (2.5%, 5.6%)
Cobicistat	21/596 3.5% (2.2%, 5.3%)	21/613 3.4% (2.1%, 5.2%)
Raltegravir	22/592 3.7% (2.3%, 5.6%)	22/602 3.7% (2.3%, 5.5%)
Elvitegravir	13/455 2.9% (1.5%, 4.8%)	13/465 2.8% (1.5%, 4.7%)
Didanosine	20/427 4.7% (2.9%, 7.1%)	20/427 4.7% (2.9%, 7.1%)
Indinavir	7/289 2.4% (1.0%, 4.9%)	7/289 2.4% (1.0%, 4.9%)
Telbivudine	3/254 1.2% (0.2%, 3.4%)	3/254 1.2% (0.2%, 3.4%)

SUMMARY OF CHANGES: JANUARY 2024 TO JULY 2024

Clinical Studies in Pregnancy	*January 2024*	*July 2024*
1st trimester	27/661 4.1% (95% CI: 2.7% - 5.9%)	28/673 4.2% (95% CI: 2.8% - 6.0%)
2nd/3rd trimester	71/2786 2.5% (95% CI: 2.0% - 3.2%)	71/2791 2.5% (95% CI: 2.0% - 3.2%)
1st to 2nd/3rd trimester prevalence ratio	1.60 (95% CI: 1.04, 2.48)	1.64 (95% CI: 1.06, 2.51)

INTRODUCTION

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

abacavir (ZIAGEN®, ABC),	enfuvirtide (FUZEON®, T-20)¤
abacavir/lamivudine (EPZICOM®, KIVEXA®, EPZ)	entecavir (BARACLUDE®, ETV)*
abacavir/lamivudine/zidovudine (TRIZIVIR®, TZV)	etravirine (INTELENCE®, ETR)
abacavir/dolutegravir/lamivudine (TRIUMEQ®, TRI)	fosamprenavir calcium (LEXIVA®, FOS)
adefovir dipivoxil (HEPSERA®, ADV)*	fostemsavir (RUKOBIA®, FTR)
amprenavir (AGENERASE®, APV)¤	indinavir (CRIXIVAN®, IDV)¤
atazanavir (REYATAZ®, ATV)	lamivudine (EPIVIR®, ZEFFIX®, 3TC, HEPITEC, HEPTODIN, HEPTOVIR, 3TC)
atazanavir/cobicistat (EVOTAZ®, EVO)	lamivudine/raltegravir (DUTREBIS™, DUT)¤
bictegravir/emtricitabine/tenofovir alafenamide (BIKTARVY®, BVY)	lamivudine/zidovudine (COMBIVIR®, CBV)
cabotegravir (VOCABRIA®, CABENUVA®, APRETUDE®, CAB)	lamivudine/tenofovir disoproxil fumarate (CIMDUO™, 3TC/TDF)
cobicistat (TYBOST®, COBI)	lenacapavir (SUNLENCA®, LEN)
darunavir (PREZISTA®, DRV)	lopinavir/ritonavir (KALETRA®, ALUVIA®, LPV/r)
darunavir/cobicistat (PREZCOBIX™, REZOLSTA™, PCX)	maraviroc (SELZENTRY®, CENSENTRI®, MVC)
darunavir/cobicistat/emtricitabine/tenofovir alafenamide (SYMTUZA®, DCF TAF)	nelfinavir (VIRACEPT®, NFV)
delavirdine mesylate (RESCRIPTOR®, DLV)¤	nevirapine (VIRAMUNE®, VIRAMUNE XR®, NVP)
didanosine (VIDEX®, VIDEX® EC, DDI),	raltegravir (ISENTRESS®, RAL)
dolutegravir (TIVICAY®, DTG)	rilpivirine (EDURANT®, REKAMBYS®, CABENUVA®, RPV)
dolutegravir/lamivudine (DOVATO®, D3)	rilpivirine/emtricitabine/tenofovir alafenamide (ODEFSEY®, ODE)
dolutegravir/lamivudine/tenofovir disoproxil fumarate (ACRIPTEGA/TELADOMYL/TENDOLA, TLD)	rilpivirine/emtricitabine/tenofovir disoproxil fumarate (COMPLERA®, CPA; EVIPLERA®, EPA)
dolutegravir/rilpivirine (JULUCA™, DTG/RPV)	ritonavir (NORVIR®, RTV)
doravirine (PIFELTRO™, PIF)	saquinavir (FORTOVASE®, SQV-SGC)¤
doravirine/lamivudine/tenofovir disoproxil fumarate (DELSTRIGO™, DEL)	saquinavir mesylate (INVIRASE®, SQV-HGC)¤
efavirenz (SUSTIVA®, STOCRIN®, EFV)	stavudine (ZERIT®, d4T)
efavirenz/emtricitabine/tenofovir disoproxil fumarate (ATRIPLA, ATR®)	telbivudine (SEBIVO®, TYZEKA®, LdT)*
efavirenz/lamivudine/tenofovir disoproxil fumarate (SYMFI™ / SYMFI-LO™, EFV/3TC/TDF)	tenofovir alafenamide (VEMLIDY®, TAF)*
elvitegravir (VITEKTA®, EVG)¤	tenofovir disoproxil fumarate (VIREAD®, TDF)
elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (GENVOYA®, GEN)	tenofovir disoproxil fumarate/emtricitabine (TRUVADA®, TVD)
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (STRIBILD®, STB)	tipranavir, (APTIVUS®, TPV)
emtricitabine (EMTRIVA®, FTC)	zalcitabine (HIVID®, ddC)
emtricitabine/tenofovir alafenamide (DESCOVY®, DVY), enfuvirtide (FUZEON®, T-20)	zidovudine (RETROVIR®, ZDV)

*These drugs are not indicated for HIV but are in the same drug 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.

¤These drugs are either no longer manufactured or the manufacturer no longer participates in the Registry

Prospective tracking of fetal drug exposure during pregnancy, particularly newer agents and new combinations of therapies remains critically important in evaluating the safety of these agents among reproductive-age people and the exposed fetus. This study is an observational, exposure-registration and follow-up study. The study has had institutional review board (IRB) review and approval. (See IRB Review, page 148.) 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 July 2024.

The Antiretroviral Pregnancy Registry is managed by Syneos Health under the sponsorship of AbbVie, Alvogen Inc, Amneal Pharmaceuticals LLC, Apotex Inc, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Dr. Reddy's Laboratories Inc, Gilead Sciences Inc, Hetero Labs Ltd, Hikma Pharmaceuticals USA Inc., i3 Pharmaceuticals, Janssen Scientific Affairs, LLC, Lannett Company, Inc., Laurus Labs, Lupin Pharmaceuticals, Macleods Pharmaceuticals Ltd., Merck & Co. Inc, Mylan Inc., a Viatris Company, Pharmascience, Qilu Pharmaceuticals Company Ltd., SigmaPharm Laboratories, Strides Pharma Science Limited, Teva Pharmaceuticals USA, Inc, ViiV Healthcare, Yung Shin Pharm., and Zydus Pharmaceuticals. The scientific conduct and analysis of the Registry are overseen by an independent Advisory Committee consisting of members from the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the private sector. Members include specialists in maternal and fetal medicine, teratology, infectious disease, epidemiology, and biostatistics. The Advisory Committee reviews the Registry data, develops the Consensus Statement, provides recommendations on modifications or enhancements to the Registry, and assists in the dissemination of information and formulation of strategies to encourage enrollment in the Registry. The Advisory Committee and the Sponsor Company representatives constitute the Steering Committee, which jointly manages the general conduct of the Registry.

This Registry is intended to provide an early signal of teratogenicity associated with prenatal use of the drugs monitored through the Registry. The FDA's revised Pregnancy and Lactation Labeling Rule (PLLR), 21 CFR 201.57 Subpart B, published 04 December 2014, eliminated pregnancy risk letter categories (10). See Appendix D for information on each drug. One limitation of an exposure-registration study is that rates of drug-associated adverse events cannot be extrapolated to reflect true rates in the potential target population. Because reports of exposures are voluntary, they are subject to numerous potential selection biases. Information on possible teratogenic risk, which may be associated with perinatal HIV infection or with risk behaviors associated with maternal HIV infection, is currently insufficient. An analysis of relative risk comparing the antiretroviral drugs being monitored in the Registry to risks in the absence of drug exposure requires carefully designed epidemiologic studies, including a comparison population of pregnant people with a history of 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 Registry drugs*. 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 people 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 separately. These study reports are not comparable directly to the Primary Registry Analysis as the inclusion/exclusion criteria, severity of disease, and length and intensity of follow-up may differ significantly.

Annually, the Registry enrolls approximately 1,000 pregnant people exposed to antiretroviral drugs for the treatment of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infection and prevention of HIV infection, e.g., pre- or post-exposure prophylaxis. The estimated number of individuals living with HIV who give birth to live infants annually in the United States has decreased from 3,525 in 2019 to 3,315 (95%CI 3,202-3,428) in 2020 (2, 3). Given the continued development of newer therapies used for treatment and prevention for which there is an ongoing need for evidence of their safety in pregnancy, sustained reporting is vital to the registry's ability to fulfill its mission of early detection of a birth defect signal, if present. Health care providers are strongly encouraged to continue reporting eligible people to the Registry.

Included in the Primary Registry Analysis, beginning with the January 2008 Interim Report, are data from 2,106 exposed pregnancies (and 2,143 pregnancy outcomes) from the Women and Infants Transmission Study (WITS) (11) and, beginning with the July 2010 Interim Report, are data on 995 exposed pregnancies with outcomes from the NISDI Perinatal Study (2). Also included in the Primary Registry Analysis are 72 cases from a prospective study in Botswana. The rationale for these inclusions is described on pages 31 and 32, respectively.

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

DATA SUMMARY

During the last report period, 471 new prospective enrollments were received bringing the total number of enrolled people to 27,338.

PRIMARY REGISTRY ANALYSIS – PROSPECTIVE REPORTS

Through 31 July 2024 there were 27,338 pregnancies prospectively reported to the Registry (Table 1) from 75 countries. There were 261 cases pending the outcome of pregnancy and 3,003 lost to follow-up. Thus, there were 24,074 evaluable prospective reports included in the Primary Registry Analysis.

Prospective evaluable reports included in the Primary Registry Analysis are predominantly from the United States and its territories (72.6%). Reports from countries outside the US comprising ≥0.1% of enrollments include: the United Kingdom of Great Britain and Norther Ireland (5.1%), Brazil (3.7%), Uganda (3.2%), South Africa (2.7%), China (2.5%), Argentina (2.1%), France (0.9%), Germany (0.9%), Kenya (0.8%), Australia (0.5%), Israel (0.5%), Zimbabwe (0.5%), Botswana (0.4%), Canada (0.4%), Ivory Coast (0.4%), Russian Federation (0.3%), Thailand (0.3%), Belgium (0.2%), Malawi (0.2%), Spain (0.2%), Cameroon (0.1%), Denmark (0.1%), Haiti (0.1%), India (0.1%), Ireland (0.1%), Italy (0.1%), Japan (0.1%), Nigeria (0.1%), Portugal (0.1%), Sweden (0.1%), and (0.1%). Countries that have contributed <0.1% of enrollments include Austria, Bulgaria, Burkina Faso, Chile, Colombia, Costa Rica, Croatia, Curaçao, Dominican Republic, Ethiopia, Finland, French Guiana, Ghana, Greece, Guatemala, Honduras, Hungary, Iceland, Indonesia, Kazakhstan, Korea, Lithuania, Malaysia, Mali, Mexico, Mozambique, The Netherlands, New Zealand, Norway, Panama, Peru, Philippines, Poland, Romania, Saudi Arabia, Senegal, Singapore, Switzerland, Taiwan, Tanzania, Turkey, United Arab Emirates, Uruguay, and Zambia.

Table 1: Population for Analysis - Prospective Registry Cases Enrolled Through 31 July 2024

	Overall
Pregnancies Enrolled	27338
Pending Cases [1]	261 (1.0%)
Cases Lost to Follow-up [2]	3003 (11.0%)
Reports Used in Analysis	24074 (88.1%)

[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 displays information on maternal characteristics including median age and clinical status indicators for cases included in the Primary Registry Analysis and those lost to follow-up.

Table 2: Maternal Demographics at Registration - Prospective Registry Cases Closed Through 31 July 2024

	Primary Analysis	Lost to Follow-up
Pregnancies Enrolled	24074	3003
Age (years)		
N	23745	2618
Median (Interquartile Range)	29.0 (9.0)	28.0 (9.0)
Min - Max	13 - 55	15 - 54
Missing	329	385
Indication for ARV at Start of Pregnancy		
HIV Infected [1]	21464 (89.2%)	1812 (60.3%)
HIV Uninfected [2]	730 (3.0%)	233 (7.8%)
Post-Exposure Prophylaxis (PEP)	11 (0.0%)	9 (0.3%)
Pre-Exposure Prophylaxis (PrEP)	464 (1.9%)	138 (4.6%)
Hepatitis B mono-infected [3]	887 (3.7%)	240 (8.0%)
Unknown	447 (1.9%)	335 (11.2%)
Missing	539 (2.2%)	383 (12.8%)
Clinical Indicators		
CD4+ T-cell Categories at Start of Pregnancy		
≥ 500 cells/µL	8238 (34.2%)	754 (25.1%)
200-499 cells/µL	8904 (37.0%)	706 (23.5%)
<200 cells/µL	3099 (12.9%)	225 (7.5%)
Unknown	1495 (6.2%)	385 (12.8%)
N/A	875 (3.6%)	546 (18.2%)
Missing	1463 (6.1%)	387 (12.9%)
Worst Disease Severity by History		
HIV		
A. Asymptomatic, acute (primary) HIV or PGL	16498 (68.5%)	1292 (43.0%)
B. Symptomatic, not (A) or (C) conditions	1405 (5.8%)	115 (3.8%)
C. Other AIDS-indicator conditions	2325 (9.7%)	177 (5.9%)
D. CD4 < 200 cells/µL	805 (3.3%)	77 (2.6%)
Not applicable	1128 (4.7%)	228 (7.6%)
Unknown	916 (3.8%)	494 (16.5%)
Missing	742 (3.1%)	534 (17.8%)
Hepatitis B		
Compensated liver disease (Pugh score < 7)	1071 (4.4%)	90 (3.0%)
Compensated liver disease (Pugh score ≥ 7)	13 (0.1%)	5 (0.2%)
Unknown	13824 (57.4%)	1460 (48.6%)
Not applicable	656 (2.7%)	428 (14.3%)
Missing	8510 (35.3%)	1020 (34.0%)

[1] Includes 238 patients co-infected with HIV and Hepatitis B. Includes 310 patients co-infected with HIV and Hepatitis C.
[2] Where antiretroviral drugs have been used for prophylaxis.
[3] Excludes patients infected with HIV.
Note: The Registry started systematically collecting data on Hepatitis B in January 2003.
Note: The Registry began collecting data to distinguish between pre- and post-exposure prophylaxis in December 2013.

Antiretroviral Exposure

Of the 24,074 evaluable prospective reports, 13,882 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 B 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 24,074 pregnancies reported, there were 24,491 outcomes of pregnancy including 410 multiple births: 22,789 live births, 798 spontaneous abortions, 272 stillbirths, and 632 induced abortions (Table 4). Of the 22,789 live births, 12,586 had a maternal exposure to antiretroviral therapy during the first trimester.

Pregnancy Outcomes

Of the 24,491 pregnancy outcomes, there were 14,125 with a 1st trimester exposure to an antiretroviral drug with 370 reports of birth defects (344 defects in live births, 11 in stillbirths, and 15 in induced abortions occurring ≥ 20 weeks gestation). See Table 4. There were 10,363 birth outcomes in the combined second and/or third trimester exposure group, with 289 reported birth defects.

The Registry defines a defect as any major structural or chromosomal defect or two or more conditional defects occurring in an infant or fetus of at least 20 weeks gestational age. This definition differs from the public health surveillance protocols by considering reports of 2 or more conditional defects alone as a defect case, so as to cast as broad a net as possible for outcomes that may be associated with antiretroviral medication use. (See *Classification of Outcomes, page 151.*) Therefore, Table 4 excludes reports of only one conditional defect or defects identified in a fetal loss occurring earlier than 20 weeks gestation. 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 (12). See Appendix F for further description of the system. Appendix C lists all defect cases reported to the Registry with an exposure in any trimester and classified by the Registry as a birth defect. These assessments were made by the consultant medical geneticist with agreement by the Advisory Committee.

Table 3: Summary of Antiretroviral Treatment Classes [1] by Trimester of Earliest Exposure [2] - Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies in Primary Analysis	13882	7563	2626	24074
PI	123	22	2	148
NRTI	1831	1721	718	4270
nnRTI	49	4	2	55
NtRTI	335	21	93	449
InSTI	30	4	0	34
PI/NRTI	2578	3317	949	6844
PI/nnRTI	18	1	0	19
PI/NtRTI	14	1	0	15
PI/InSTI	75	4	0	79
NRTI/nnRTI	1277	791	318	2388
NRTI/NtRTI	765	145	83	993
NRTI/InSTI	382	53	15	450
nnRTI/InSTI	31	1	0	32
NtRTI/InSTI	5	0	0	5
PI/NRTI/nnRTI	264	89	34	387
PI/NRTI/NtRTI	1964	638	143	2745
PI/NRTI/EI	9	0	0	9
PI/NRTI/InSTI	59	2	9	70
PI/NRTI/PKE	10	1	0	11
PI/nnRTI/NtRTI	8	0	0	8
PI/nnRTI/InSTI	21	3	0	24
PI/NtRTI/InSTI	8	0	0	8
PI/EI/InSTI	6	0	0	6
PI/InSTI/PKE	6	0	0	6
NRTI/nnRTI/NtRTI	1345	191	34	1570
NRTI/nnRTI/InSTI	5	5	1	11
NRTI/NtRTI/EI	5	0	0	5
NRTI/NtRTI/InSTI	1446	414	153	2013
PI/NRTI/nnRTI/NtRTI	254	18	10	282
PI/NRTI/NtRTI/EI	12	1	0	13
PI/NRTI/NtRTI/InSTI	154	36	35	225
PI/NRTI/NtRTI/PKE	85	5	0	90
PI/NRTI/InSTI/PKE	5	0	0	5
NRTI/nnRTI/NtRTI/InSTI	100	15	9	124
NRTI/NtRTI/InSTI/PKE	432	46	13	491
PI/NRTI/nnRTI/NtRTI/InSTI	11	3	2	16
PI/NRTI/NtRTI/EI/InSTI	6	0	0	6
PI/NRTI/NtRTI/InSTI/PKE	91	4	1	96
NRTI/nnRTI/NtRTI/InSTI/PKE	13	1	0	14
PI/NRTI/nnRTI/NtRTI/InSTI/PKE	7	1	0	8
Other Combination	42	5	2	49

[1] PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.
NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, telbivudine, zalcitabine, and zidovudine.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, etravirine, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, tenofovir alafenamide, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes bictegravir, cabotegravir, dolutegravir, elvitegravir, and raltegravir.
PKE=pharmacokinetic enhancer, which includes cobicistat.
[2] Exposures represent earliest trimester of exposure to an antiretroviral drug. Pregnant people may have been on other medications during the pregnancy.
Note: Treatment regimens for which no exposures were reported are excluded from the table.
Note: Treatment regimens with fewer than 5 exposures have been collapsed into the Other category.
Note: Due to unknown trimester of exposure data for 3 case(s), the specific counts may not sum to the overall total.

Table 4: Pregnancy Outcomes [1] by Trimester of Earliest Exposure - Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

	With Birth Defects[2] : Without Birth Defects[3]				
	Live Births	Spontaneous Losses	Still-births	Induced Abortions	Overall
Number of Outcomes [4]	622 : 22167	0 : 798	19 : 253	20 : 612	24491
Earliest Exposure [5]					
First Trimester	344 : 12242	0 : 769	11 : 148	15 : 596	14125
Second/Third Trimester	276 : 9924	0 : 29	8 : 105	5 : 16	10363

[1] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion.
[2] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[3] Includes cases where the occurrence of a birth defect was not reported.
[4] Includes 410 multiple births.
[5] Data is not included for birth defect cases with an unknown trimester of exposure.

Comparator Analysis

The primary analysis of the APR's prospective cohort includes two comparisons. The overall rates of defects are compared with rates from two external comparator populations, the Metropolitan Atlanta Congenital Defects Program (MACDP) and the Texas Birth Defects Registry (TBDR). For individual drugs, an internal comparison is made between the rates of defects among first trimester exposed pregnancies and the rates among pregnancies with the same exposures beginning in the second or third trimester. Detailed descriptions of these comparisons and the comparison registries are included in the Methods section of this report (Appendix F: Methods). Briefly, the MACDP and the TBDR are active population-based surveillance systems. The MACDP covers all deliveries among residents of five counties of the metropolitan Atlanta area with approximately 50,000 annual births in a population of about 2.9 million (4, 5, 6). The TBDR monitors all deliveries to people who are residents of the state of Texas at the time of delivery including approximately 400,000 live births annually (8). The Registry is aware of the need for further comparison populations, particularly from outside the United States; several remain under consideration.

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

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

For first trimester tenofovir alafenamide (TAF) exposed pregnancies, the prevalence of birth defects is now 3.66% (95% CI: 2.75 - 4.78) and no longer statistically significantly elevated compared with MACDP (2.72%; 95% CI: 2.68 - 2.76). Although previously elevated at 3.95% (95% CI: 2.93 – 5.18) TAF was never statistically significantly different from TBDR (4.17%; 95% CI: 4.15 - 4.19). A detailed review of cases did not identify a pattern of birth defects for TAF. With the continued accrual of additional exposed pregnancies, the prevalence and confidence intervals will be refined.

Bictegravir (BIC) reached the threshold of 200 first trimester exposed cases during the 31 July 2022 report period with a prevalence of 4.26% (95% CI: 2.06 – 7.69). The prevalence of birth defects is now 3.83% (95% CI: 2.50 - 5.61), and although it remains elevated, it has never been statistically significantly different from either MACDP (2.72%; 95% CI: 2.68 - 2.76) or TBDR (4.17%; 95% CI: 4.15 - 4.19).

For cobicistat, darunavir, didanosine, elvitegravir, indinavir, raltegravir, rilpivirine, stavudine, telbivudine, and bictegravir, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date. For abacavir, atazanavir, dolutegravir, efavirenz, emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, tenofovir disoproxil fumarate, zidovudine, and tenofovir alafenamide, 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.

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 July 2024
Individuals may appear in more than one category, as exposures are not mutually exclusive

	Earliest Trimester of Exposure			
	First Trimester		Second/Third Trimester	
	Defects/ live births	Prevalence (95% CI) [2]	Defects/ live births	Prevalence (95% CI) [2]
Proportion of defects reported with an exposure to any ART [3]	370/12586		289/10200	
Proportion of defects reported with an exposure to: [3,4]				
Any PI containing regimen	157/5345		182/6093	
Any Amprenavir regimen	1/30		0/11	
Any Atazanavir regimen	37/1493	2.5% (1.7%, 3.4%)	19/797	2.4% (1.4%, 3.7%)
Any Darunavir regimen	29/781	3.7% (2.5%, 5.3%)	10/344	2.9% (1.4%, 5.3%)
Any Fosamprenavir Calcium regimen	2/111		2/36	
Any Indinavir regimen	7/289	2.4% (1.0%, 4.9%)	3/163	1.8% (0.4%, 5.3%)
Any Lopinavir regimen	30/1452	2.1% (1.4%, 2.9%)	77/2522	3.1% (2.4%, 3.8%)
Any Nelfinavir regimen	47/1216	3.9% (2.9%, 5.1%)	86/2730	3.2% (2.5%, 3.9%)
Any Ritonavir regimen	89/3590	2.5% (2.0%, 3.0%)	107/3566	3.0% (2.5%, 3.6%)
Any Saquinavir regimen	7/183		9/221	
Any Tipranavir regimen	0/6		0/3	
Any NRTI containing regimen	355/11972		291/10195	
Any Abacavir regimen	47/1493	3.1% (2.3%, 4.2%)	41/1372	3.0% (2.2%, 4.0%)
Any Didanosine regimen	20/427	4.7% (2.9%, 7.1%)	20/464	4.3% (2.7%, 6.6%)
Any Emtricitabine regimen	154/5250	2.9% (2.5%, 3.4%)	53/1962	2.7% (2.0%, 3.5%)
Any Entecavir regimen [5]	2/83		0/2	
Any Lamivudine regimen	174/5722	3.0% (2.6%, 3.5%)	219/7560	2.9% (2.5%, 3.3%)
Any Stavudine regimen	21/811	2.6% (1.6%, 3.9%)	6/196	3.1% (1.1%, 6.5%)
Any Telbivudine regimen [5]	3/254	1.2% (0.2%, 3.4%)	0/13	
Any Zalcitabine regimen	2/41		0/12	
Any Zidovudine regimen	136/4257	3.2% (2.7%, 3.8%)	277/9935	2.8% (2.5%, 3.1%)
Any nnRTI containing regimen	80/3083		54/1923	
Any Delavirdine regimen	0/11		0/3	
Any Doravirine regimen	1/16		0/6	
Any Efavirenz regimen	28/1201	2.3% (1.6%, 3.4%)	3/201	1.5% (0.3%, 4.3%)
Any Etravirine regimen	1/73		0/38	
Any Nevirapine regimen	36/1180	3.1% (2.1%, 4.2%)	50/1534	3.3% (2.4%, 4.3%)
Any Rilpivirine regimen	15/770	1.9% (1.1%, 3.2%)	2/220	0.9% (0.1%, 3.2%)
Any NtRTI containing regimen	179/6393		62/2459	
Any Adefovir dipivoxil regimen [5]	0/82		0/4	
Any Tenofovir Alafenamide regimen	52/1420	3.7% (2.7%, 4.8%)	15/347	4.3% (2.4%, 7.0%)
Any Tenofovir Disoproxil Fumarate regimen	131/5076	2.6% (2.2%, 3.1%)	56/2262	2.5% (1.9%, 3.2%)
Any EI containing regimen	1/57		0/21	
Any Enfuvirtide regimen	0/24		0/16	
Any Fostemsavir regimen	0/2		0/0	
Any Maraviroc regimen	1/32		0/5	
Any InSTI containing regimen	89/2698		47/1123	
Any Bictegravir regimen	25/652	3.8% (2.5%, 5.6%)	4/174	2.3% (0.6%, 5.8%)
Any Cabotegravir regimen	1/33		0/2	
Any Dolutegravir regimen	38/1160	3.3% (2.3%, 4.5%)	31/642	4.8% (3.3%, 6.8%)
Any Elvitegravir regimen	13/465	2.8% (1.5%, 4.7%)	2/71	2.8% (0.3%, 9.8%)
Any Raltegravir regimen	22/602	3.7% (2.3%, 5.5%)	19/465	4.1% (2.5%, 6.3%)
Any PKE containing regimen	21/613		3/94	
Any Cobicistat regimen	21/613	3.4% (2.1%, 5.2%)	3/94	3.2% (0.7%, 9.0%)
Any CAI containing regimen	0/1		0/0	
Any Lenacapavir regimen	0/1		0/0	

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[2] Prevalence and 95% confidence intervals are reported for drugs with a denominator of >= 200 first trimester exposed live births.
[3] Proportion of defects calculated by dividing the number of defects meeting the CDC Criteria by the number of live births reported.
[4] There were 99 outcomes with an exposure to a medication occurring in an unknown trimester. These cases are excluded where trimester is unknown, however they may be represented in a known trimester to another medication.
[5] For treatment of HBV.
Note: For each exposure category (drug classification) counts represent the number of outcomes with at least one exposure in that classification, though other classes of ARTs could have been included in the regimen. Additionally, any individual ART may have been used in combination with other ARTs, therefore, the counts represent the number of exposures to the individual ART contained in the regimen. Hence, counts are not mutually exclusive across classifications or individual ART.
Note: Data is not included for birth defect cases with an unknown trimester of exposure.
Note: Includes a small number of cases with Hepatitis B and Hepatitis C co-infection.

Table 6 lists the frequencies of defects reported by organ system for prospectively reported first trimester antiretroviral exposures in combination or single treatment regimen. The organ system classifications have been redefined to better categorize the defects to be consistent with the MACDP and the TBDR classifications and to increase the potential to identify a possible pattern or signal (13). Further refinements are ongoing.

Hypospadias Defects

The rates of hypospadias in first trimester exposed infants were statistically increased over those with only later exposures, the primary screening analysis of the Registry. This possible signal prompted more detailed and controlled analyses, in accordance with the Registry protocol. These analyses compared infants from people with similar first trimester exposure to other antiretrovirals without zidovudine/lamivudine; no increase was observed. Also, there is no elevation of hypospadias rates among those with the exposure under analysis in comparison with MACDP or the TBDR. A manuscript detailing these analyses and findings has been published (14).

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.

Central Nervous System Defects

The Advisory Committee has closely monitored first trimester exposures to efavirenz for anomalies including central nervous system defects due to concerns from animal studies. However, to date, defects have been reported in 28 (2.3%, 95% CI, 1.6%, 3.4%) among the 1,201 infants with first trimester exposure to efavirenz including only a single case of neural tube defect (0.08%) consistent with expected background prevalence. While there were initial concerns related to neural tube defects with preconception DTG exposure in data from a birth surveillance study in Botswana, increased numbers of exposures in both Botswana and Eswatini birth surveillance studies demonstrated no significant differences in neural tube defects for preconception DTG exposure when compared to preconception non-DTG exposures and women without HIV (15, 16).

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 July 2024

	Earliest Antiretroviral Therapy (ART) Exposure in First Trimester								
	Any PI(s) [3]	Any NRTI(s) [3]	Any NNRTI(s) [3]	Any NtRTI(s) [3]	Any EI(s) [3]	Any InSTI(s) [3]	Any PKE (s) [3]	Overall First Trimester Exposure	Earliest ART Exposure in Second and/or Third Trimester
Pregnancies Identified	5816	13127	3422	7078	64	2913	660	13882	10189
Number of Pregnancies with Multiple Gestations	108	231	56	124	0	52	13	239	171
Number of Outcomes [2]	5924	13362	3481	7203	64	2966	673	14125	10363
Number of Live Births	5345	11972	3083	6393	57	2698	613	12586	10200
Number of Outcomes with Defects [1,2]	157	355	80	179	1	89	21	370	289
CNS	15	33	7	19	0	6	2	34	31
Eye, ear, face and neck	16	32	7	13	0	6	1	35	39
Cleft lip and/or palate	6	11	1	5	0	2	0	11	16
Conotruncal heart defects	5	12	2	7	0	5	0	13	10
Obstructive heart defects - right sided	5	13	5	8	0	5	2	14	15
Obstructive heart defects - left sided	5	9	2	5	0	5	2	11	7
Heart - other defects	30	76	16	38	0	27	6	78	68
Other circulatory system	10	33	9	21	0	13	3	33	19
Respiratory system	0	3	1	2	0	1	0	3	1
Upper gastrointestinal system	1	4	1	2	0	0	0	5	4
Lower gastrointestinal system	7	7	0	2	0	1	0	10	8
Female genitalia	3	6	0	4	0	1	0	6	1
Male genitalia	16	36	4	15	0	8	1	39	15
Renal and urinary system	20	54	10	36	0	21	7	54	26
Limb reduction/addition defects	26	42	10	26	0	6	5	44	46
Other musculoskeletal defects	25	77	26	36	1	10	3	79	69
Skin and skin derivatives	5	12	7	7	0	2	0	13	14
Chromosome anomaly	19	35	10	24	0	9	2	37	27
Other organs and organ systems	11	16	4	8	0	3	1	18	8
Specified syndromes/sequences/associations	14	22	2	9	0	4	1	23	12

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

In summary, Table 7 shows that the prevalence of birth defects per 100 live births among people with a first trimester exposure to any of the antiretroviral therapies included in the Registry is 370 outcomes with defects among 12,586 live births or 2.9% (95% CI: 2.7 - 3.3). Measured against 22,789 live births with exposure at any time during pregnancy, there were 661 outcomes with birth defects, a prevalence of 2.9 birth defects per 100 live births (95% CI: 2.7 - 3.1). This proportion is not substantially different than the MACDP (4, 5, 6, 7) where total prevalence of birth defects identified among births from 1989 through 2003 was 2.72 per 100 live births (95% CI: 2.68 - 2.76), and the prevalence of birth defects per 100 live births diagnosed during the first seven days of life ("early diagnosis") was 2.09 (95% CI: 2.07 - 2.12). Because population-based surveillance does not involve sampling, MACDP does not publish CIs. The CIs reported around MACDP rates in this report were calculated by the Registry. The second population comparator, TBDR, reports an overall prevalence of birth defects of 4.17% (95% CI: 4.15 - 4.19) for deliveries during 2000 through 2009 (8). Although the Registry prevalence is statistically significantly lower than the Texas Birth Defects Registry, the inclusion of major malformations in outcomes of any gestational age increases the baseline prevalence in the Texas population. Additionally, the prevalence of defects among offspring of people with first trimester exposure to antiretroviral medications (2.9 per 100 live births) is not substantially different from the prevalence of defects among people with the first exposure during the second and/or third trimester (2.8 per 100 live births) (prevalence ratio: 1.04, 95% CI: 0.89, 1.21).

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

Table 7: Confidence Intervals for Birth Defects [1] - All Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

	Overall
Number of Live Births	22789
Number of Outcomes with at Least One Defect [1, 2]	661 (2.9%)
95% Confidence Intervals for Prevalence of Birth Defects for Exposures in:	
First Trimester	370/12586 (2.9%) 2.7% - 3.3%
Second/Third Trimester	289/10200 (2.8%) 2.5% - 3.2%
Any Trimester	661/22789 (2.9%) 2.7% - 3.1%
Risk of Defects for First Trimester Exposures Relative to Second/Third Trimester Exposures	1.04 (0.89, 1.21)

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

Summary of Pre-Exposure Prophylaxis Pregnancies

In 2013, the Registry began distinguishing reports of individuals without HIV infection as either pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Indication for use is collected at time of registration and

was not historically confirmed at pregnancy outcome; therefore, cases with unexpected drug exposures due to seroconversion during pregnancy may be included. In 2024, the Registry began confirming indication at pregnancy outcome. In 2012, PrEP was recognized by the FDA as a supplemental indication for emtricitabine/tenofovir disoproxil fumarate. Since then, emtricitabine/tenofovir alafenamide (2019) and cabotegravir (2021) have been approved for the prevention of HIV infection and are included in the Registry.

Through 31 July 2024, a total of 21,464 prospective ARV-exposed pregnancies with HIV and 730 without HIV. Of the 730 HIV-uninfected prospective reports, there are a total of 464 confirmed reports of PrEP-exposed pregnancies with outcome (Table 2), all of which are included in the overall primary prospective analysis. For exposure-specific details, see Table A. A total of 7 birth defect cases have been reported among 411 live births, including 239 live births with initial exposure during the first trimester of pregnancy.

Table A: Number of Outcomes with Birth Defects [1] By Trimester of Earliest Exposure to Each Drug - Prospective PrEP Cases with Follow-Up Data Closed Through 31 July 2024
Individuals may appear in more than one category, as exposures are not mutually exclusive

	Earliest Trimester of Exposure			
	First Trimester		Second/Third Trimester	
	Defects/ live births	Prevalence (95% CI) [2]	Defects/ live births	Prevalence (95% CI) [2]
Proportion of defects reported with an exposure to any ART [3]	7/239		0/172	
Proportion of defects reported with an exposure to: [3,4]				
Any NRTI containing regimen	7/232		0/171	
Any Emtricitabine regimen	7/232	3.0% (1.2%, 6.1%)	0/171	
Any Lamivudine regimen	0/1		0/0	
Any nnRTI containing regimen	0/1		0/0	
Any Efavirenz regimen	0/1		0/0	
Any NtRTI containing regimen	6/231		0/172	
Any Tenofovir Alafenamide regimen	0/1		0/0	
Any Tenofovir Disoproxil Fumarate regimen	6/231	2.6% (1.0%, 5.6%)	0/172	
Any EI containing regimen	1/2		0/0	
Any Maraviroc regimen	1/2		0/0	
Any InSTI containing regimen	0/6		0/0	
Any Cabotegravir regimen	0/6		0/0	

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[2] Prevalence and 95% confidence intervals are reported for drugs with a denominator of >= 200 first trimester exposed live births.
[3] Proportion of defects calculated by dividing the number of defects meeting the CDC Criteria by the number of live births reported.
[4] There were 0 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.
Note: For each exposure category (drug classification) counts represent the number of outcomes with at least one exposure in that classification, though other classes of ARTs could have been included in the regimen. Additionally, any individual ART may have been used in combination with other ARTs, therefore, the counts represent the number of exposures to the individual ART contained in the regimen. Hence, counts are not mutually exclusive across classifications or individual ART.
Note: Data is not included for birth defect cases with an unknown trimester of exposure.
Note: 55 cases are excluded due to non-live birth outcomes.
Note: The Registry began collecting data to distinguish between pre- and post-exposure prophylaxis in December 2013.

Summary of Hepatitis B Virus Mono-infected ARV Exposed Pregnancies

The antiviral activity of lamivudine (1998) against the hepatitis B virus (HBV) was recognized by the FDA as a supplemental indication for that drug. With the FDA approval of adefovir dipivoxil (2002) with the sole indication for

treatment of HBV, the APR agreed to provide a repository for reports of pregnancy exposures for these drugs and to include the results as part of the APR's semi-annual interim report. Based on this, and the likely future rise in the use of ARVs to treat HIV/HBV co-infected individuals as well as mono-infected HBV people, the APR began to systematically collect HBV infection status in 2003. Two additional HBV drugs, entecavir (2005) and telbivudine (2006) were added to the Registry. Additionally, tenofovir disoproxil fumarate (2008), tenofovir alafenamide (2016), tenofovir disoproxil maleate (2017), tenofovir disoproxil phosphate (2017), and tenofovir disoproxil succinate (2017) were approved for the treatment of HBV infection.

Since the addition of the hepatitis B indication, the APR has received 1,125 prospective reports of diagnosed HBV people with or without concurrent HIV infection, all of which are included in the overall primary prospective analysis. This sub-analysis is limited to the HBV mono-infected population. Through 31 July 2024, a total of 887 prospective reports of HBV mono-infected pregnancies with outcome have been reported (Table 2). Of the 887 prospective reports, there were 832 live births, 3 stillbirths, 33 spontaneous abortions and 28 induced abortions. For exposure-specific details, see Table B. Twelve birth defect cases have been reported among 832 live births, including 683 live births with initial exposure during the first trimester of pregnancy. There is no pattern among the types of births defects reported.

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

Table B: Number of Outcomes with Birth Defects [1] By Trimester of Earliest Exposure to Each Drug - Prospective Registry Hepatitis B Mono-Infected Cases with Follow-Up Data Closed Through 31 July 2024
Individuals may appear in more than one category, as exposures are not mutually exclusive

	Earliest Trimester of Exposure			
	First Trimester		Second/Third Trimester	
	Defects/ live births	Prevalence (95% CI) [2]	Defects/ live births	Prevalence (95% CI) [2]
Proportion of defects reported with an exposure to any ART [3]	11/683		1/149	
Proportion of defects reported with an exposure to: [3,4]				
Any PI containing regimen	0/3		0/4	
Any Darunavir regimen	0/2		0/1	
Any Lopinavir regimen	0/1		0/2	
Any Nelfinavir regimen	0/1		0/1	
Any Ritonavir regimen	0/1		0/3	
Any NRTI containing regimen	9/520		0/44	
Any Abacavir regimen	0/1		0/0	
Any Emtricitabine regimen	0/5		0/17	
Any Entecavir regimen [5]	2/66		0/1	
Any Lamivudine regimen	4/213	1.9% (0.5%, 4.7%)	0/26	
Any Telbivudine regimen [5]	3/253	1.2% (0.2%, 3.4%)	0/6	
Any Zidovudine regimen	0/1		0/2	
Any nnRTI containing regimen	0/1		0/0	
Any Efavirenz regimen	0/1		0/0	
Any NtRTI containing regimen	4/227		2/146	
Any Adefovir dipivoxil regimen [5]	0/74		0/4	
Any Tenofovir Alafenamide regimen	0/5		0/0	
Any Tenofovir Disoproxil Fumarate regimen	4/152		2/146	

	Earliest Trimester of Exposure			
	First Trimester		Second/Third Trimester	
	Defects/ live births	Prevalence (95% CI) [2]	Defects/ live births	Prevalence (95% CI) [2]

[1] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[2] Prevalence and 95% confidence intervals are reported for drugs with a denominator of >= 200
first trimester exposed live births.
[3] Proportion of defects calculated by dividing the number of defects meeting the CDC Criteria
by the number of live births reported.
[4] There were 1 outcomes with an exposure to a medication occurring in an unknown trimester. These cases are excluded where trimester is unknown, however they may be represented in a known trimester to another medication.
[5] For treatment of HBV.
Note: For each exposure category (drug classification) counts represent the number of outcomes with at least one exposure in that classification, though other classes of ARTs could have been included in the regimen. Additionally, any individual ART may have been used in combination with other ARTs, therefore, the counts represent the number of exposures to the individual ART contained in the regimen. Hence, counts are not mutually exclusive across classifications or individual ART.
Note: Data is not included for birth defect cases with an unknown trimester of exposure.
Note: Includes a small number of cases with Hepatitis B and Hepatitis C co-infection.

Overview of Clinical Studies Data Included in the Primary Registry Analysis

Complete data from three observational studies (ACTG 367, WITS [Women and Infants Transmission Study], and the NISDI Perinatal Study [Maternal Antiretroviral Use During Pregnancy and Infant Congenital Anomalies]) and exposed pregnancies from two clinical trials (The Development of AntiRetroviral Therapy in Africa study [DART] and The Tshepo Study) are included in the Primary Registry Analysis. The rationale for including the reports from the observational studies 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.

AIDS Clinical Trial Group (ACTG) 367

Data from 466 exposed pregnancies from the AIDS Clinical Trial Group (ACTG) 367, conducted in the US, were included. The data was not published.

Women and Infants Transmission Study (WITS)

In a published analysis from the Women and Infants Transmission Study, an elevated rate of hypospadias after first trimester zidovudine exposure was detected (11). The WITS included HIV-positive pregnant patients enrolled during pregnancy or within seven days after delivery, and this analysis included patients 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, 2,527 live births (LB) with known ARV exposure occurred to 2,353 patients. 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 patients 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 patients 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 patients 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 Registry Analysis. Further, WITS did not collect detailed information on concomitant medications

such as opportunistic infection prophylaxis, which would be expected to be more common among patients with more severe illness and first trimester antiretroviral exposure. Thus, the association noted between first trimester zidovudine exposure and hypospadias must be explored further as alternate explanations are possible. A detailed analysis was undertaken following the report of a single additional case of first trimester exposure to zidovudine/lamivudine in the 31 January 2012 period (see page 26). The Registry continues to monitor this defect closely.

The NICHD International Site Development Initiative Perinatal Study (NISDI)

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

The Development of AntiRetroviral Therapy in Africa study (DART)

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

The Adult Antiretroviral Treatment and Drug Resistance Study (The Tshepo Study)

Bussmann and colleagues (17) 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 Registry Analysis section of this report.

RETROSPECTIVE REPORTS

Though the Registry is a prospective registry, data from retrospective reports (pregnancies with a known outcome at the time of reporting) are also reviewed to assist in the detection of any unusual patterns in birth defects. Retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population experience. Therefore, the calculation of prevalence from these reports is inappropriate. See Appendix C for a list of birth defects reported retrospectively to the Registry. As with the prospective reports, these assessments were made in an initial review by the consultant medical geneticist with agreement by the Advisory Committee.

REPORTS FROM CLINICAL STUDIES IN PREGNANCY

The Registry receives reports of subjects enrolled in clinical studies conducted in pregnant people. 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 cases included in the Primary Registry Analysis. For instance, the inclusion/exclusion criteria for some of these studies may exclude people with abnormal prenatal tests, so subjects may have a lower risk for defects than the Registry group. Regarding severity of disease at enrollment, people in clinical studies with first trimester exposure appear to have more advanced disease (18). Additionally, infants born to people 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 people enrolled in the PACTG 185 study and a South African study. Data from those studies as well as from several clinical studies including ACTG 082, PACTG 326, ACTG 5084, and NIH 00861, as well as data from a German multi-site clinical study with intensive follow-up of infants for 18 months are included in Tables 8-12. The Registry pools all clinical trials data for the purposes of reporting data in this report. However, when possible, the Registry evaluates individual study results separately.

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

Table 8: Maternal Demographics at Registration - Reports from Clinical Studies in Pregnancy with Follow-up Data Closed Through 31 July 2024

	Clinical Studies in Pregnancy
Pregnancies Reported	3467
Age (years)	
N	3448
Median (Interquartile Range)	27.0 (8.0)
Min - Max	13 - 47
Missing	19
Indication for ARV at Start of Pregnancy	
HIV Infected [1]	1669 (48.1%)
HIV Uninfected [2]	1 (0.0%)
Post-Exposure Prophylaxis (PEP)	0 (0.0%)
Pre-Exposure Prophylaxis (PrEP)	0 (0.0%)
Hepatitis B mono-infected	1019 (29.4%)
Unknown	345 (10.0%)
Missing	433 (12.5%)
Clinical Indicators	
CD4+ T-cell Categories at Start of Pregnancy	
≥ 500 cells/µL	794 (22.9%)
200-499 cells/µL	1263 (36.4%)
<200 cells/µL	339 (9.8%)
Unknown	869 (25.1%)
N/A	27 (0.8%)
Missing	175 (5.0%)
Worst Disease Severity by History	
HIV	
A. Asymptomatic, acute (primary) HIV or PGL	1400 (40.4%)
B. Symptomatic, not (A) or (C) conditions	67 (1.9%)
C. Other AIDS-indicator conditions	74 (2.1%)
D. CD4 < 200 cells/µL	108 (3.1%)
Not applicable	560 (16.2%)
Unknown	361 (10.4%)
Missing	896 (25.8%)
Hepatitis B	
Compensated liver disease (Pugh score < 7)	876 (25.3%)
Compensated liver disease (Pugh score ≥ 7)	1 (0.0%)
Unknown	1395 (40.2%)
Not applicable	11 (0.3%)
Missing	1184 (34.2%)

[1] Includes 4 patients co-infected with HIV and Hepatitis B. Includes 11 patients co-infected with HIV and Hepatitis C.
[2] Where antiretroviral drugs have been used for prophylaxis.
Note: The Registry started systematically collecting data on Hepatitis B in January 2003.
Note: The Registry began to collect data to distinguish between pre- and post-exposure prophylaxis in December 2013.

Table 9 summarizes the exposure classifications and earliest trimester of exposure. As in the Primary Registry 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 July 2024

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Reported	682	1364	1421	3467
PI	3	3	2	8
NRTI	157	645	904	1706
NtRTI	2	163	59	224
PI/NRTI	75	179	17	271
PI/nnRTI	0	7	1	8
NRTI/nnRTI	39	116	85	240
NRTI/NtRTI	2	1	3	6
NRTI/InSTI	5	45	61	111
PI/NRTI/nnRTI	7	3	2	12
PI/NRTI/NtRTI	121	31	3	155
NRTI/nnRTI/NtRTI	117	96	132	345
NRTI/NtRTI/InSTI	80	49	126	255
PI/NRTI/nnRTI/NtRTI	14	6	1	21
PI/NRTI/NtRTI/InSTI	7	1	1	9
PI/NRTI/NtRTI/PKE	8	5	0	13
NRTI/nnRTI/NtRTI/InSTI	8	3	17	28
NRTI/NtRTI/InSTI/PKE	26	9	1	36
Other Combination	11	2	6	19

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

Table 10 presents a pooled summary of pregnancy exposures and outcome data from all reported studies. Among the 3,500 prospectively reported outcomes in this group, there were 673 live births with a first trimester exposure, with 28 defects reported. The number of defects identified with an initial exposure in the second or third trimester was 71 among 2791. 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.

The prevalence of birth defects per 100 live births among people with first trimester exposures to an antiretroviral is 4.2 (95% CI: 2.8 - 6.0) and 2.5 (95% CI: 2.0 - 3.2) among people with second and/or third trimester exposure (Table 12). The prevalence of defects among offspring of people with first trimester exposure to antiretroviral medications (4.2 per 100 live births) was significantly higher than the prevalence of defects among people with the first exposure during the second and/or third trimester (2.5 per 100 live births) (prevalence ratio: 1.64, 95% CI: 1.06, 2.51). 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 four 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 Registry Analysis. Thus, this finding is viewed as not establishing a signal. The Registry will continue its regular review of VSD reports from all sources. To date, we have received 70 prospective cases of VSD, distributed across trimesters and drug exposures. Thus, the overall rate remains low and there is no apparent excess of cases among zidovudine or any drug exposure group or relevant trimester of exposure.

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

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 July 2024

	With Birth Defects[3] : Without Birth Defects[4]				
	Live Births	Spontaneous Losses	Still-births	Induced Abortions	Overall
Number of Outcomes [5]	99 : 3365	0 : 10	0 : 18	0 : 8	3500
Earliest Exposure [6]					
First Trimester	28 : 645	0 : 9	0 : 5	0 : 8	695
Second/Third Trimester	71 : 2720	0 : 1	0 : 13	0 : 0	2805
First Trimester					
PI	0 : 3	0 : 0	0 : 0	0 : 0	3
NRTI	7 : 154	0 : 0	0 : 0	0 : 0	161
NtRTI	0 : 1	0 : 0	0 : 1	0 : 0	2
InSTI	1 : 1	0 : 0	0 : 0	0 : 0	2
PI/NRTI	3 : 69	0 : 2	0 : 0	0 : 2	76
NRTI/nnRTI	2 : 40	0 : 1	0 : 0	0 : 0	43
NRTI/NtRTI	0 : 2	0 : 0	0 : 0	0 : 0	2
NRTI/InSTI	1 : 4	0 : 0	0 : 0	0 : 0	5
PI/NRTI/nnRTI	1 : 6	0 : 0	0 : 0	0 : 0	7
PI/NRTI/NtRTI	3 : 117	0 : 2	0 : 0	0 : 1	123
PI/NRTI/InSTI	0 : 3	0 : 0	0 : 0	0 : 0	3
PI/nnRTI/InSTI	1 : 0	0 : 0	0 : 0	0 : 0	1
NRTI/nnRTI/NtRTI	2 : 112	0 : 0	0 : 0	0 : 4	118
NRTI/NtRTI/InSTI	4 : 70	0 : 3	0 : 4	0 : 0	81
PI/NRTI/nnRTI/NtRTI	0 : 13	0 : 1	0 : 0	0 : 0	14
PI/NRTI/NtRTI/InSTI	0 : 7	0 : 0	0 : 0	0 : 0	7
PI/NRTI/NtRTI/PKE	0 : 8	0 : 0	0 : 0	0 : 0	8
NRTI/nnRTI/NtRTI/InSTI	0 : 8	0 : 0	0 : 0	0 : 0	8
NRTI/NtRTI/InSTI/PKE	3 : 22	0 : 0	0 : 0	0 : 1	26
PI/NRTI/nnRTI/NtRTI/EI	0 : 1	0 : 0	0 : 0	0 : 0	1
PI/NRTI/nnRTI/NtRTI/InSTI	0 : 2	0 : 0	0 : 0	0 : 0	2
PI/NRTI/NtRTI/InSTI/PKE	0 : 1	0 : 0	0 : 0	0 : 0	1
NRTI/NtRTI/EI/InSTI/PKE	0 : 1	0 : 0	0 : 0	0 : 0	1

[1] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion.
[2] CAI=capsid inhibitor, which includes lenacapavir; PI=protease inhibitor, which includes amprenavir, atazanavir, darunavir, fosamprenavir calcium, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir,saquinavir, and tipranavir.
NRTI=nucleoside analog reverse transcriptase inhibitor, which includes abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine, telbivudine, zalcitabine, and zidovudine.
NNRTI=non-nucleoside analog reverse transcriptase inhibitor, which includes delavirdine mesylate, efavirenz, etravirine, nevirapine, and rilpivirine.
NtRTI=nucleotide analog reverse transcriptase inhibitor, which includes adefovir dipivoxil, tenofovir alafenamide, and tenofovir disoproxil fumarate.
EI=entry inhibitor, which includes enfuvirtide and maraviroc.
InSTI=integrase strand transfer inhibitor, which includes bictegravir, cabotegravir, dolutegravir, elvitegravir, and raltegravir.
PKE=pharmacokinetic enhancer, which includes cobicistat.
[3] Defects meeting the CDC Criteria only. Excludes reported defects in abortions <20 weeks.
[4] Includes cases where the occurrence of a birth defect was not reported.
[5] Includes 33 multiple births.
[6] Data is not included for birth defect cases with an unknown trimester of exposure.
Note: Treatment regimens for which no exposures were reported are excluded from the table.

Table 11: Summary of Clinical Study Reports of Birth Defects [1] By Organ System and Treatment Regimen – First Trimester Exposures. All Reports with Follow-up Data Closed Through 31 July 2024

	Earliest Antiretroviral Therapy (ART) Exposure in First Trimester								
	Any PI(s) [3]	Any NRTI(s) [3]	Any NNRTI(s) [3]	Any NtRTI(s) [3]	Any EI(s) [3]	Any InSTI(s) [3]	Any PKE (s) [3]	Overall First Tri-mester Exposure	Earliest ART Exposure in Second and/or Third Trimester
Pregnancies Enrolled	243	674	189	390	2	136	36	682	2785
Number of Pregnancies with Multiple Gestations	3	13	5	4	0	1	0	13	20
Number of Outcomes [2]	246	687	194	394	2	137	36	695	2805
Number of Live Births	238	666	188	377	2	129	35	673	2791
Number of Outcomes with Defects [1,2]	8	26	6	12	0	10	3	28	71
Eye, ear, face and neck	0	0	0	0	0	0	0	0	6
Cleft lip and/or palate	1	1	0	1	0	0	0	1	2
Obstructive heart defects - right sided	0	0	0	0	0	0	0	0	1
Heart - other defects	3	14	2	4	0	3	2	14	8
Other circulatory system	1	2	1	0	0	0	0	2	2
Respiratory system	1	2	0	1	0	1	0	2	1
Lower gastrointestinal system	0	0	0	0	0	0	0	0	1
Female genitalia	0	0	0	0	0	0	0	0	1
Male genitalia	2	4	2	2	0	1	1	4	5
Renal and urinary system	2	5	2	4	0	4	1	6	1
Limb reduction/addition defects	1	1	0	1	0	0	0	1	11
Other musculoskeletal defects	0	7	1	4	0	4	1	8	45
Skin and skin derivatives	0	4	0	2	0	3	0	5	26
Chromosome anomaly	1	1	0	1	0	0	0	1	2
Other organs and organ systems	0	0	0	0	0	0	0	0	2
Specified syndromes/sequences/associations	1	2	0	1	0	1	0	2	1

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

Table 12: Confidence Intervals for Birth Defects [1] - Reports from Clinical Studies in Pregnancy with Follow-up Data Closed Through 31 July 2024

	Overall
Number of Live Births	3464
Number of Outcomes with at Least One Defect [1, 2]	99 (2.9%)
95% Confidence Intervals for Prevalence of Birth Defects for Exposures in:	
First Trimester	28/673 (4.2%) 2.8% - 6.0%
Second/Third Trimester	71/2791 (2.5%) 2.0% - 3.2%
Any Trimester	99/3464 (2.9%) 2.3% - 3.5%
Risk of Defects for First Trimester Exposures Relative to Second/Third Trimester Exposures	1.64 (1.06, 2.51)

[1] Defects meeting the CDC Criteria only. Excludes reported defects in pregnancy losses < 20 weeks.
[2] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion.
Note: Includes a small number of cases with Hepatitis B and Hepatitis C co-infection.

RESULTS FROM INDEPENDENT CLINICAL STUDIES

Tsepamo Study and Neural Tube Defects

In the most recent (August 2022) report from a birth outcome surveillance study in Botswana (Tsepamo Study), there were 12 cases of neural tube defects (NTD) reported out of 11,110 deliveries (0.11%) (15) to patients who were exposed to dolutegravir-containing regimens at the time of conception, which is no longer statistically different than exposure in any of the comparison groups.

This constitutes a further decline in the Tsepamo reporting of NTD prevalence in deliveries of patients exposed to dolutegravir-containing regimens at the time of conception: March 2021 data reported 0.15% (9 among 5,860) (19), March 2019 data reported 0.30% (5 among 1,683 deliveries) (20) and the initial Tsepamo data in May 2018 reported 0.94% (4 among 426 deliveries) (21). In comparison, in the August 2022 report, the NTD prevalence rate was 0.11% (26 among 24,368 deliveries) in patients receiving non-dolutegravir-containing regimens at the time of conception.

PACTG 316

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 people in this study were on an antiretroviral therapy at enrollment into the study. This first exposure is of primary interest to the Registry since the Registry categorizes exposures by earliest trimester of exposure as most structural defects or major malformations would have occurred prior to labor and delivery.

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

During the January 2009 reporting period, the Registry received data tables describing pregnancy outcomes and birth defects among patients enrolled in the PACTG 316 study. With the addition of the PACTG 316 study data, all prior individual case reports from PACTG 316 (N=122) were removed from Registry Tables 8-12 and are presented here as unduplicated case summaries in Tables 13 and 14 including 1283 exposed pregnancies and 1311 outcomes with 60 defect cases. Tables 13 and 14 were updated in the July 31, 2011 interim report following publication of final PACTG 316 study results (22). The results presented in the interim report differ slightly from those in the published manuscript as the definition of first trimester (14 vs. 12 weeks gestation) and the denominator for the prevalence rate calculation (number of live births vs. number of outcomes) were adjusted to maintain consistency with APR methodology. In addition, to avoid duplicate reporting, 110 live births (none with reported defects) have been excluded from the data reported here.

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

A slightly increased frequency of the most common heart defects, primarily atrial septal defects and ventricular septal defects, was noted after first trimester exposure compared to later exposure to antiretroviral agents and is being evaluated further. This finding was noted also in the PACTG 185 study and may be related to severity bias, in that demographic and treatment data suggest that sicker patients would be more likely to have started therapy before pregnancy. A detailed analysis of APR cases of ventricular septal defects among prospective cases found no association between first trimester antiretroviral exposure and risk of these defects (23). These regular analyses are conducted as data accumulate. To date we have sufficient power overall and for two individual drugs most commonly used in PACTG 316.

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

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

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

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

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

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

European Collaborative Study

The European Collaborative Study initiated in 1986 is a prospective cohort study of HIV-infected pregnant patients seen at 26 centers in nine European countries (24, 25, 26). Infants are followed for at least 18 months. In a 2005 publication (2005) (26), the 3740 mother-infant pairs, including 1973 infants exposed to antiretroviral therapy in utero of whom 602 were exposed to highly active antiretroviral therapy (HAART). The prevalence of birth defects among infants exposed to antiretroviral therapy in utero (31/1973, 1.6%) was similar to those not exposed (24/1767, 1.4%). The prevalence among those exposed in the first trimester of pregnancy (14/789, 1.8%) was similar to those exposed later in pregnancy (17/1184, 1.4%) and to those exposed to HAART in the first trimester (11/546, 2.0%). A multivariable analysis controlling for potential risk factors confirmed that there were no differences in the prevalence of birth defects between the therapy groups. The birth defects reported in the 14 infants exposed to antiretroviral therapy in the first trimester included ventricular septal defects (3), other heart defects (2), other circulatory defects (1), renal defects (3), gastrointestinal defects (4), male genitalia defect (1), other (unspecified) defect (1). The numbers do not add to 14 because one infant had both a heart defect and male genitalia defect. There were no birth defects reported in infants exposed to efavirenz in the first trimester of pregnancy (26). In March 2007, the European Collaborative Study coordinating center produced Tables 15 and 16 specifically for the Registry to provide updated data following the format of tables 11 and 12. In a joint study with the National Study of HIV in Pregnancy Childhood, they reported on 7573 singleton births to HIV-infection patients diagnosed between 2000 and 2009 taking HAART with or without zidovudine. There was no difference in the overall rate of congenital anomalies in the zidovudine-sparing compared to zidovudine-containing regimens (2.7%, adjusted odds ratio [AOR] 0.98, 95% CI: 0.66-1.45) or when limited to first trimester exposures (AOR 0.79, 95% CI: 0.48-1.30) (27).

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

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

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

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

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

Integrated Screening Outcomes Surveillance Service in the United Kingdom and Ireland

The Integrated Screening Outcomes Surveillance Service, formerly National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland, is a population-based surveillance study of HIV positive patients and their children (28, 29). In their most recent publication (29), they reported data on over 8200 infants born between 1990 and 2007. Overall, 232 of 8242 infants reportedly had congenital anomalies (2.8%, 95% CI: 2.5 - 3.2), and there were no significant differences between those not exposed to ART in utero (14/498, 2.8%) and those exposed in the first trimester (53/1708, 3.1%) or later in pregnancy (147/5427, 2.7%). There were no significant differences in congenital anomalies between infants exposed to various classes of ART. A multivariable analysis controlling for potential risk factors confirmed that there were no differences in the prevalence of birth defects between therapy groups. There were no significant differences in infants exposed in the first trimester to efavirenz (5/205, 2.4%) or to didanosine (6/174, 3.4%) compared with infants with first trimester exposure to other ART. For infants exposed in the first trimester to any ART, the most commonly reported types of congenital anomalies were musculoskeletal, heart and circulatory, and urinary and digestive systems.

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

Table 17: Surveillance Data Collected Through the Integrated Screening Outcomes Surveillance Service (United Kingdom): Summary of Birth Defects by Organ System and Treatment Regimen. Pregnancies with Delivery/Outcome 1990-2023, Reported by the End of December 2023

	Earliest Antiretroviral Therapy (ART) in First Trimester							
	Any NRTI(s)	Any NtRTI(s)	Any NNRTI(s)	Any PI(s)	Any EI(s)	Any InSTI(s)	Overall First Trimester Exposure [3]	Earliest ART Exposure in Second or Third Trimester
Pregnancies Reported [4]	11337	6530	5190	5197	53	1441	11692	10761
Number of Pregnancies with Multiple Gestations	272	162	105	145	0	38	281	186
Number of Outcomes	11616	6696	5299	5344	53	1479	11980	10949
Number of Live Births	11380	6582	5186	5229	50	1455	11728	10816
Number of Outcomes with Defects [1,2]	403	226	178	185	1	58	415	313
CNS	45	29	19	19	0	6	44	29
Eye, ear, face and neck	19	14	10	8	0	2	19	9
Cleft lip and/or palate	9	5	5	3	0	1	9	9
Conotruncal heart defects	4	2	2	1	0	1	4	2
Obstructive heart defects, right-sided	9	3	4	3	0	2	9	5
Obstructive heart defects, left-sided	7	2	2	3	0	3	7	4
Heart - other defects	65	39	25	28	0	13	69	29
Other circulatory system	8	4	4	3	0	2	8	8
Respiratory system	10	6	6	4	0	2	10	11
Upper gastrointestinal system	5	2	3	1	0	1	5	4
Lower gastrointestinal system	30	14	12	16	0	3	32	14
Female genitalia	1	0	0	1	0	0	1	0
Male genitalia	25	14	14	11	0	3	26	24
Renal and urinary system	29	14	15	13	0	6	31	21
Limb reduction/addition	53	30	28	18	0	8	54	62
Other musculoskeletal defects	45	26	19	23	0	6	46	41
Skin and skin derivatives	16	5	5	7	1	4	16	14
Chromosome anomaly	23	14	9	12	0	2	24	6
Other organ systems - specified	7	4	3	5	0	1	9	6
Specified syndromes	44	30	18	23	0	3	45	34
Unspecified abnormality	11	9	5	7	0	0	11	8
	465	266	208	209	1	69	479	340

[1] Defects meeting WHO International Classification of Diseases (ICD-10) criteria only
[2] An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion at ≥20 weeks gestation
[3] 125 pregnancies had first trimester exposure to unspecified antiretroviral drugs, 5 with abnormalities reported
Note: Pregnancies/outcomes with missing information on exposure to ART or defects are excluded.
[4] Data from Republic of Ireland included to 2018 and data from Northern Ireland, Scotland and Wales included to 2019 only
Note: Case numbers have decreased in some categories from prior reports due to data cleaning efforts.

Table 18: Surveillance Data Collected Through the Integrated Screening Outcomes Surveillance Service (United Kingdom): Confidence Intervals for Birth Defects. Pregnancies with Delivery/Outcome 1990-2023, Reported by the End of December 2023

	Overall
Number of live births	22544
Number of outcomes with at least one defect*	728 (3.2%)
95% confidence intervals for % birth defects for exposures in:	
First Trimester	415/11692 (3.5%) 3.2, 3.9
Second/Third Trimester	313/10761 (2.9%) 2.6, 3.2
Any Trimester	728/22544 (3.2%) 3.0, 3.5
Risk of defects for first trimester exposures relative to second/third trimester exposures	1.23 (1.05, 1.43)

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

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AE – Adverse Event – As defined by the FDA, an adverse event is any undesirable experience associated with the use of a medical product in a patient.

ARV – Antiretroviral

Birth Defect – A “birth defect” in this Registry follows the CDC guidelines and is defined as 1) 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.

Capsid Inhibitor (CAI) – Capsid inhibitors are a class of drugs that interfere with the assembly of the HIV capsid, a protein shell that protects HIV's genetic material and enzymes needed for replication. Capsid inhibitors can disrupt HIV capsid during multiple stages of the viral life cycle. (Represented in this Registry by lenacapavir)

CDC – Centers for Disease Control and Prevention

CFR – Code of Federal Regulations

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 people exposed to one or more of the Registry drugs during the course of a clinical study conducted in pregnant people are included in the Registry.

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

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

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

EDD – Estimated date of delivery

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

Attachment Inhibitor – The first step in the process of viral entry involves the interaction between HIV’s external “viral envelope” and the area of the CD4 cells that allow HIV to bind and attach to the cell. Attachment inhibitors try to disrupt the process that leads to the next step in viral entry – coreceptor binding. (Represented in this Registry by fostemsavir)

Coreceptor Inhibitor – Following the attachment step, a change in the “viral envelope” occurs that allows the virus to interact with parts of CD4 cells known as coreceptors (e.g., CCR5, CXCR4).

Coreceptor inhibitors act as antagonists and block binding to coreceptors on the cell surface. (Represented in this Registry by maraviroc)

Fusion Inhibitor – Once attachment and coreceptor binding have occurred, the HIV envelope then drives the “fusion” of the viral membrane with the CD4 cell membrane. Successful fusion of these membranes delivers into the cell the viral machinery required for a virus to replicate. Fusion inhibitors bind to envelope proteins and block the structural changes necessary for the virus to fuse with the host CD4 cell. When the virus cannot penetrate the host cell membrane and infect the cell, HIV replication within that host cell is prevented. (Represented in this Registry by enfuvirtide)

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

FDA – Food and Drug Administration

Gestational Age – pregnancy dating calculated by actual or theoretical first day of the last menstrual period (LMP), typically 14 days before conception

HIPAA – Health Insurance Portability and Accountability Act

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

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

IRB – Institutional Review Board

LMP – Last menstrual period

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

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

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

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

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

Periconception Exposure – Any drug exposure 2 weeks prior to conception through 28 days post-conception.

PHI – protected health information

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

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

Premature Birth – When assessing reported birth defects, an infant at outcome <36 weeks gestational age or if gestational age not available, weighing <2500 grams as defined by CDC's criteria in the MACDP manual. Any analysis of prematurity as a pregnancy outcome will use the American College of Obstetrics and Gynecology (ACOG) standard definition of <37 weeks gestation age to define a premature birth.

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

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

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

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

Temporality Assessment – The determination of the probable association or non-association of the timing of the maternal antiretroviral/antiviral exposure in pregnancy relative to the probable timing of organogenesis of a defect. Assessment will be made at the defect level for each birth defect based on the earliest timing of exposure to any drug and at the defect level for each birth defect based on the earliest timing of exposure to each drug.

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

Trimester of Exposure – Trimester of exposure to an antiretroviral/antiviral medication is considered as the first trimester in which exposure to that medication occurred. Gestational weeks are calculated beginning from the first day of the LMP. The APR defines trimesters based on gestational weeks as follows: first trimester as beginning at week 1 (0 weeks, 1 day), second trimester as beginning at week 14 (13 weeks, 1 day) and the third trimester as beginning at week 28 (27 weeks, 1 day).

WIRB – Western Institutional Review Board

APPENDICES

Appendix A: Prevalence of Birth Defects

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

Report Date	3TC	ZDV	NVP	ABC	EFV	RTV	LPV	TDF	FTC	ATV	DRV	RAL	RPV	COBI	DTG	EVG	TAF	BIC
Jan 02	2.6% (1.6, 4.1) 18/687	2.5% (1.5, 4.0) 17/684																
Jul 02	2.9% (1.8, 4.3) 23/807	2.7% (1.7, 4.1) 21/782	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	2.0% (0.7, 4.7) 5/248															
Jul 03	2.7% (1.8, 3.9) 29/1075	2.7% (1.8, 3.9) 27/1003	2.1% (0.8, 4.5) 6/289															
Jan 04	2.9% (2.0, 4.0) 34/1185	3.1% (2.2, 4.3) 34/1088	2.1% (0.9, 4.3) 7/332	4.0% (1.9, 7.5) 9/223														
Jul 04	2.8% (2.0, 3.9) 37/1318	3.0% (2.1, 4.2) 36/1185	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	2.1% (1.0, 4.0) 9/419	3.1% (1.4, 5.9) 9/286	2.4% (0.8, 5.6) 5/206													
Jul 05	2.8% (2.0, 3.7) 43/1554	3.0% (2.2, 4.0) 41/1371	2.0% (0.9, 3.8) 9/449	3.4% (1.7, 6.0) 11/322	2.2% (0.7, 5.1) 5/228	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	1.9% (0.9,3.5) 9/479	3.2% (1.6, 5.6) 11/345	2.5% (0.9 5.3) 6/244	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	1.9% (0.9, 3.6) 10/515	2.9% (1.5, 5.2) 11/378	2.4% (0.9, 5.1) 6/255	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	2.4% (1.3, 4.1) 13/543	3.2% (1.7, 5.4) 13/404	2.5% (1.0, 5.1) 7/281	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	2.4% (1.3, 4.0) 14/584	3.2% (1.8, 5.3) 14/436	2.4% (1.0, 4.8) 7/295	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	2.4% (1.5, 3.8) 18/737	3.3% (1.9, 5.3) 17/512	2.7% (1.3, 5.0) 10/364	2.5% (1.5, 4.1) 16/628	1.8% (0.7, 3.9) 6/328	2.2% (1.1, 4.0) 11/491										
Jul 08	2.9% (2.4, 3.6) 91/3089	3.1% (2.5, 3.7) 94/3068	2.3% (1.4, 3.6) 18/785	3.1% (1.9, 4.9) 18/578	3.2% (1.7, 5.4) 13/407	2.3% (1.4, 3.6) 18/783	1.9% (0.8, 3.7) 8/420	2.3% (1.3, 3.9) 14/606	3.2% (1.4, 6.2) 8/252	2.0% (0.7, 4.7) 5/246								

Report Date	3TC	ZDV	NVP	ABC	EFV	RTV	LPV	TDF	FTC	ATV	DRV	RAL	RPV	COBI	DTG	EVG	TAF	BIC
Jan 09	2.9% (2.3, 3.5) 93/3226	3.1% (2.5, 3.7) 95/3108	2.2% (1.3, 3.5) 18/817	3.0% (1.8, 4.6) 18/608	2.9% (1.6, 4.9) 14/477	2.3% (1.4, 3.5) 20/883	1.7% (0.7, 3.3) 8/470	2.4% (1.4, 3.8) 16/678	2.9% (1.3, 5.4) 9/313	2.4% (1.0, 4.9) 7/292								
Jul 09	2.9% (2.3, 3.5) 96/3314	3.1% (2.5, 3.7) 97/3167	2.1% (1.3, 3.4) 18/842	3.0% (1.8, 4.7) 19/628	2.8% (1.5, 4.7) 14/501	2.2% (1.4, 3.3) 22/1000	1.7% (0.8, 3.2) 9/526	2.4% (1.4, 3.7) 18/756	2.9% (1.4, 5.1) 11/384	2.6% (1.2, 4.9) 9/343								
Jan 10	2.8% (2.3, 3.5) 99/3481	3.0% (2.5, 3.7) 100/3289	2.2% (1.3, 3.3) 19/882	2.8% (1.7, 4.4) 19/670	2.6% (1.4, 4.3) 14/546	2.1% (1.4, 3.2) 24/1122	1.7% (0.8, 3.1) 10/590	2.2% (1.3, 3.4) 19/879	2.6% (1.4, 4.6) 12/456	2.3% (1.0, 4.3) 9/393								
Jul 10	3.0% (2.5, 3.6) 113/3754	3.2% (2.6, 3.8) 113/3534	2.6% (1.7, 3.8) 25/970	2.9% (1.8, 4.5) 21/717	2.8% (1.6, 4.5) 17/604	2.4% (1.6, 3.4) 30/1271	2.1% (1.1, 3.5) 14/676	2.5% (1.6, 3.7) 25/981	3.0% (1.7, 4.8) 16/542	2.5% (1.2, 4.4) 11/448								
Jan 11	3.1% (2.5, 3.7) 118/3864	3.3% (2.7, 3.9) 118/3620	2.5% (1.6, 3.7) 25/987	3.0% (1.9, 4.5) 22/744	2.7% (1.6, 4.3) 17/623	2.4% (1.6,3.3) 33/1401	2.2% (1.2, 3.5) 16/738	2.4% (1.6, 3.5) 26/1092	2.7% (1.5, 4.2) 17/641	2.4% (1.2, 4.1) 12/502								
Jul 11	3.1% (2.6, 3.7) 122/3966	3.2% (2.7, 3.9) 120/3699	2.6% (1.7, 3.8) 26/1002	3.2% (2.1, 4.7) 25/781	2.6% (1.5, 4.2) 17/644	2.2% (1.6, 3.1) 35/1567	2.2% (1.3, 3.5) 18/816	2.2% (1.5, 3.2) 27/1219	2.4% (1.4, 3.7) 18/764	2.1% (1.1, 3.6) 12/576								
Jan 12	3.1% (2.6, 3.7) 127/4088	3.3% (2.7, 3.9) 124/3789	2.7% (1.8, 4.0) 28/1020	3.0% (2.0, 4.5) 25/823	2.7% (1.6, 4.2) 18/679	2.2% (1.6, 3.0) 39/1741	2.4% (1.5, 3.6) 21/883	2.3% (1.5, 3.2) 31/1370	2.3% (1.4, 3.5) 21/899	1.9% (1.0, 3.3) 13/669								
Jul 12	3.2% (2.7, 3.8) 133/4185	3.3% (2.7, 3.9) 127/3864	3.0% (2.0, 4.2) 31/1036	3.1% (2.0, 4.5) 26/848	2.6% (1.5, 4.0) 18/702	2.3% (1.7, 3.1) 45/1923	2.4% (1.5, 3.5) 23/969	2.4% (1.7, 3.3) 39/1612	2.5% (1.7, 3.7) 27/1068	2.1% (1.2, 3.5) 16/.746								
Jan 13	3.2% (2.6, 3.7) 135/4273	3.3% (2.7, 3.9) 128/3932	3.0% (2.0, 4.2) 31/1049	3.1% (2.0, 4.4) 27/880	2.4% (1.4, 3.9) 18/735	2.2% (1.6, 3.0) 47/2096	2.3% (1.5, 3.4) 24/1049	2.3% (1.7, 3.1) 42/1800	2.4% (1.6, 3.5) 30/1230	2.1% (1.2, 3.3) 17/813								
Jul 13	3.1% (2.6, 3.7) 136/4360	3.2% (2.7, 3.8) 129/4000	2.9% (2.0, 4.1) 31/1061	3.0% (2.0, 4.3) 27/905	2.3% (1.4, 3.7) 18/766	2.3% (1.7, 3.0) 52/2260	2.3% (1.5, 3.4) 26/1125	2.3% (1.7, 3.1) 46/1982	2.4% (1.7, 3.4) 34/1400	2.2% (1.3, 3.4) 19/878	2.4% (0.8, 5.4) 5/212							
Jan 14	3.1% (2.6, 3.7) 137/4418	3.2% (2.7, 3.8) 129/4034	2.9% (2.0, 4.1) 31/1068	3.0% (2.0, 4.4) 28/925	2.3% (1.3, 3.5) 18/797	2.2% (1.7, 2.9) 53/2391	2.2% (1.4, 3.2) 26/1174	2.2% (1.6, 2.9) 47/2141	2.3% (1.6, 3.1) 35/1543	2.2% (1.3, 3.3) 20/922	2.3% (0.9, 5.0) 6/258							
Jul 14	3.1% (2.6, 3.7) 140/4485	3.2% (2.7, 3.8) 132/4069	2.9% (1.9, 4.0) 31/1083	2.9% (1.9, 4.2) 28/957	2.3% (1.4, 3.6) 19/825	2.4% (1.8, 3.0) 60/2542	2.4% (1.6, 3.4) 29/1218	2.3% (1.7, 3.0) 53/2330	2.4% (1.7, 3.2) 41/1721	2.2% (1.4, 3.3) 22/993	2.7% (1.2, 5.3) 8/293							
Jan 15	3.1% (2.6, 3.7) 142/4527	3.3% (2.7, 3.9) 133/4092	2.9% (2.0, 4.1) 32/1096	3.0% (2.0, 4.2) 29/976	2.3% (1.4, 3.6) 20/852	2.4% (1.8, 3.0) 62/2628	2.3% (1.6, 3.3) 29/1242	2.4% (1.8, 3.0) 58/2452	2.5% (1.8, 3.3) 46/1834	2.2% (1.4, 3.3) 23/1037	2.9% (1.3, 5.4) 9/314							
Jul 15	3.1% (2.6, 3.7) 143/4566	3.2% (2.7, 3.8) 133/4113	2.9% (2.0, 4.1) 32/1105	2.9% (2.0, 4.2) 29/993	2.4% (1.5, 3.6) 21/883	2.3% (1.8, 3.0) 63/2720	2.3% (1.5, 3.3) 29/1261	2.3% (1.8, 3.0) 60/2608	2.4% (1.7, 3.1) 47/1984	2.2% (1.4, 3.2) 24/1093	2.7% (1.2, 5.1) 9/333							
Jan 16	3.1% (2.6, 3.7) 143/4589	3.2% (2.7, 3.8) 133/4128	2.9% (2.0, 4.0) 32/1113	3.0% (2.0, 4.2) 30/1007	2.4% (1.5, 3.7) 22/902	2.3% (1.7, 2.9) 64/2815	2.2% (1.5, 3.2) 29/1290	2.2% (1.7, 2.8) 61/2779	2.2% (1.6, 3.0) 48/2145	2.1% (1.3, 3.1) 24/1142	2.8% (1.4, 5.2) 10/352	3.0% (1.1, 6.4) 6/201						
Jul 16	3.1% (2.6, 3.6) 144/4671	3.2% (2.7, 3.8) 133/4144	2.8% (1.9, 4.0) 32/1124	2.9% (2.0, 4.1) 30/1031	2.4% (1.5, 3.5) 22/934	2.2% (1.7, 2.8) 65/2983	2.1% (1.4, 3.0) 29/1384	2.2% (1.7, 2.8) 67/3007	2.2% (1.7, 3.0) 54/2326	2.1% (1.4, 3.1) 25/1187	2.6% (1.2, 4.7) 10/385	2.8% (1.1, 5.8) 7/247	0.5% (0.0, 2.7) 1/202					
Jan 17	3.0% (2.6, 3.6) 145/4763	3.2% (2.7, 3.8) 133/4161	2.8% (1.9, 4.0) 32/1134	2.8% (1.9, 4.0) 30/1063	2.2% (1.4, 3.4) 22/978	2.2% (1.7, 2.8) 67/3056	2.1% (1.4, 3.0) 30/1400	2.3% (1.8, 2.9) 75/3229	2.4% (1.8, 3.1) 60/2523	2.1% (1.4, 3.1) 26/1227	2.5% (1.2, 4.5) 10/407	2.7% (1.1, 5.4) 7/263	1.2% (0.3, 3.5) 3/247					

Report Date	3TC	ZDV	NVP	ABC	EFV	RTV	LPV	TDF	FTC	ATV	DRV	RAL	RPV	COBI	DTG	EVG	TAF	BIC
Jul 17	3.1% (2.6, 3.6) 149/4880	3.2% (2.7, 3.8) 134/4160	2.8% (1.9, 4.0) 32/1135	2.8% (1.9, 3.9) 30/1088	2.2% (1.4, 3.3) 22/990	2.2% (1.7, 2.8) 67/3071	2.1% (1.4, 3.0) 30/1400	2.3% (1.8, 2.8) 76/3342	2.3% (1.8, 2.9) 60/2614	2.2% (1.4, 3.2) 27/1235	2.1% (1.0, 4.0) 9/425	2.9% (1.2, 5.6) 8/278	1.1% (0.2, 3.3) 3/263					
Jan 18	3.0% (2.6, 3.5) 151/5008	3.2% (2.7, 3.8) 134/4178	2.8% (1.9, 3.9) 32/1142	2.8% (1.9, 4.0) 32/1131	2.3% (1.5, 3.5) 24/1023	2.2% (1.7, 2.8) 70/3155	2.1% (1.4, 3.0) 30/1418	2.3% (1.8, 2.9) 82/3535	2.4% (1.9, 3.1) 68/2785	2.2% (1.5, 3.1) 28/1279	2.4% (1.2, 4.3) 11/456	3.1% (1.4, 5.8) 9/291	1.0% (0.2, 2.9) 3/297	2.5% (0.8, 5.6) 5/204				
Jul 18	3.0% (2.6, 3.5) 154/5069	3.2% (2.7, 3.8) 134/4186	2.8% (1.9, 3.9) 32/1148	3.0% (2.1, 4.1) 35/1183	2.3% (1.5, 3.4) 24/1040	2.2% (1.8, 2.8) 72/3209	2.1% (1.4, 3.0) 30/1421	2.3% (1.8, 2.8) 85/3715	2.3% (1.8, 2.9) 70/2996	2.2% (1.5, 3.2) 29/1309	2.6% (1.4, 4.4) 13/496	2.9% (1.3, 5.4) 9/312	0.9% (0.2, 2.5) 3/352	2.3% (0.9, 5.0) 6/258	3.5% (1.5, 6.8) 8/229	2.3% (0.8, 5.4) 5/213		
Jan 19	3.0% (2.6, 3.5) 156/5132	3.2% (2.7, 3.8) 134/4196	2.8% (1.9, 3.9) 32/1153	2.9% (2.1, 4.0) 36/1228	2.4% (1.5, 3.5) 25/1061	2.2% (1.8, 2.8) 73/3245	2.1% (1.4, 3.0) 30/1424	2.4% (1.9, 2.9) 91/3851	2.4% (1.9, 3.0) 77/3158	2.2% (1.5, 3.1) 29/1328	3.1% (1.8, 4.9) 16/524	2.8% (1.3, 5.2) 9/327	1.3% (0.4, 3.0) 5/392	3.0% (1.4, 5.6) 9/302	3.6% (1.8, 6.3) 11/307	2.5% (0.9, 5.4) 6/240		
Jul 19	3.1% (2.6, 3.6) 161/5209	3.2% (2.7, 3.8) 134/4204	2.8% (1.9, 3.9) 32/1159	3.1% (2.2, 4.2) 39/1276	2.5% (1.6, 3.6) 27/1087	2.3% (1.8, 2.9) 76/3308	2.1% (1.4, 3.0) 30/1427	2.4% (2.0, 2.9) 97/4005	2.6% (2.1, 3.2) 86/3345	2.2% (1.5, 3.1) 30/1361	3.4% (2.0, 5.2) 19/563	3.4% (1.8, 5.8) 12/355	1.4% (0.5, 3.0) 6/429	3.7% (2.0, 6.3) 13/347	3.2% (1.7, 5.5) 12/375	3.6% (1.8, 6.6) 10/274	5.2% (2.7, 8.8) 12/233	
Jan 20	3.1% (2.7, 3.6) 167/5353	3.2% (2.7, 3.8) 136/4218	3.0% (2.1, 4.1) 35/1169	3.2% (2.3, 4.3) 42/1320	2.4% (1.6, 3.4) 27/1142	2.3% (1.8, 2.9) 78/3378	2.1% (1.4, 3.0) 30/1431	2.4% (1.9, 2.9) 101/4256	2.6% (2.1, 3.2) 94/3601	2.2% (1.5, 3.1) 31/1401	3.6% (2.3, 5.5) 22/604	3.1% (1.6, 5.2) 13/422	1.4% (0.6, 2.9) 7/495	3.9% (2.2, 6.3) 16/410	3.2% (1.7, 5.5) 16/455	3.4% (1.7, 6.0) 11/323	4.9% (2.9, 7.7) 17/349	
Jul 20	3.1% (2.7, 3.6) 168/5398	3.2% (2.7, 3.8) 136/4222	3.0% (2.1, 4.1) 35/1169	3.1% (2.3, 4.2) 42/1342	2.4% (1.6, 3.5) 28/1160	2.3% (1.8, 2.9) 79/3417	2.1% (1.4, 3.0) 30/1435	2.4% (2.0, 2.9) 105/4388	2.6% (2.1, 3.2) 99/3788	2.2% (1.5, 3.2) 32/1424	3.5% (2.2, 5.3) 22/625	3.1% (1.7, 5.1) 14/458	1.3% (0.5, 2.7) 7/533	3.5% (2.0, 5.7) 16/452	3.3% (1.9, 5.3) 17/512	3.1% (1.5, 5.4) 11/359	4.4% (2.7, 6.8) 19/434	
Jan 21	3.1% (2.7, 3.6) 169/5433	3.2% (2.7, 3.8) 136/4225	3.0% (2.1, 4.1) 35/1171	3.1% (2.3, 4.2) 43/1368	2.4% (1.6, 3.5) 28/1166	2.3% (1.9, 2.9) 81/3453	2.1% (1.4, 3.0) 30/1439	2.4% (2.0, 2.9) 108/4483	2.6% (2.2, 3.2) 104/3952	2.3% (1.6, 3.2) 33/1447	3.7% (2.4, 5.5) 24/643	3.1% (1.7, 5.0) 15/486	1.4% (0.6, 2.8) 8/557	3.6% (2.1, 5.7) 17/473	3.3% (2.0, 5.1) 19/576	3.0% (1.5, 5.2) 11/371	4.2% (2.6, 6.3) 22/526	
Jul 21	3.1% (2.7, 3.6) 170/5472	3.2% (2.7, 3.8) 136/4229	3.0% (2.1, 4.1) 35/1173	3.2% (2.3, 4.2) 44/1391	2.4% (1.6, 3.4) 28/1177	2.4% (1.9, 3.0) 84/3482	2.1% (1.4, 3.0) 30/1441	2.5% (2.0, 3.0) 113/4576	2.7% (2.2, 3.2) 110/4094	2.5% (1.7, 3.4) 36/1457	3.6% (2.3, 5.3) 24/665	3.5% (2.1, 5.5) 18/514	1.5% (0.7, 2.9) 9/583	3.7% (2.2, 5.7) 18/490	3.3% (2.1, 5.0) 21/634	2.8% (1.4, 5.0) 11/386	3.8% (2.4, 5.6) 23/606	
Jan 22	3.1% (2.6, 3.6) 170/5510	3.2% (2.7, 3.8) 136/4234	3.0% (2.1, 4.1) 35/1175	3.1% (2.3, 4.2) 44/1413	2.4% (1.6, 3.4) 28/1182	2.4% (1.9, 3.0) 84/3505	2.1% (1.4, 3.0) 30/1442	2.5% (2.0, 3.0) 115/4657	2.7% (2.2, 3.2) 113/4226	2.5% (1.7, 3.4) 36/1464	3.5% (2.3, 5.2) 24/686	3.4% (2.0, 5.2) 18/537	1.6% (0.8, 3.0) 10/612	3.5% (2.1, 5.5) 18/509	3.2% (2.0, 4.7) 22/696	2.8% (1.4, 4.9) 11/396	3.5% (2.3, 5.2) 24/684	
Jul 22	3.1% (2.6, 3.6) 171/5571	3.2% (2.7, 3.8) 136/4244	3.1% (2.2, 4.2) 36/1176	3.1% (2.3, 4.2) 45/1440	2.4% (1.6, 3.4) 28/1191	2.4% (1.9, 2.9) 84/3526	2.1% (1.4, 2.9) 30/1447	2.5% (2.1, 3.0) 121/4758	2.8% (2.4, 3.4) 124/4372	2.4% (1.7, 3.4) 36/1475	3.4% (2.2, 5.0) 24/710	3.4% (2.1, 5.3) 19/554	1.9% (1.0, 3.2) 12/643	3.4% (2.0, 5.3) 18/532	3.1% (2.0, 4.5) 24/783	2.7% (1.3, 4.7) 11/411	3.9% (2.6, 5.5) 30/774	4.3% (2.1, 7.7) 10/235
Jan 23	3.1% (2.6, 3.6) 173/5613	3.2% (2.7, 3.8) 136/4252	3.1% (2.1, 4.2) 36/1178	3.2% (2.4, 4.3) 47/1455	2.3% (1.6, 3.4) 28/1193	2.5% (2.0, 3.0) 88/3554	2.1% (1.4, 2.9) 30/1451	2.6% (2.2, 3.1) 125/4840	2.9% (2.5, 3.5) 134/4567	2.5% (1.8, 3.4) 37/1478	3.7% (2.4, 5.3) 27/737	3.9% (2.4, 5.8) 22/570	2.1% (1.1, 3.5) 14/668	3.6% (2.2, 5.5) 20/560	3.3% (2.2, 4.7) 29/874	3.0% (1.6, 5.1) 13/432	3.9% (2.8, 5.4) 36/915	4.3% (2.4, 7.1) 14/324
Jul 23	3.1% (2.6, 3.6) 173/5643	3.2% (2.7, 3.8) 136/4254	3.1% (2.1, 4.2) 36/1179	3.2% (2.4, 4.2) 47/1468	2.3% (1.6, 3.4) 28/1196	2.5% (2.0, 3.0) 88/3564	2.1% (1.4, 2.9) 30/1452	2.6% (2.1, 3.0) 126/4936	2.9% (2.5, 3.4) 141/4813	2.5% (1.8, 3.4) 37/1482	3.6% (2.4, 5.2) 27/753	3.8% (2.4, 5.7) 22/581	2.0% (1.1, 3.3) 14/711	3.4% (2.1, 5.2) 20/587	3.3% (2.3, 4.7) 32/957	2.9% (1.5, 4.9) 13/450	3.9% (2.8, 5.2) 42/1086	4.3% (2.5, 6.6) 18/423
Jan 24	3.0% (2.6, 3.5) 173/5684	3.2% (2.7, 3.8) 136/4256	3.1% (2.1, 4.2) 36/1180	3.2% (2.3, 4.2) 47/1481	2.3% (1.6, 3.4) 28/1196	2.5% (2.0, 3.0) 88/3578	2.1% (1.4, 2.9) 30/1452	2.6% (2.2, 3.0) 129/5014	3.0% (2.5, 3.5) 151/5030	2.5% (1.8, 3.4) 37/1485	3.7% (2.4, 5.2) 28/766	3.7% (2.3, 5.6) 22/592	2.0% (1.1, 3.3) 15/737	3.5% (2.2, 5.3) 21/596	3.3% (2.3, 4.6) 35/1052	2.9% (1.5, 4.8) 13/455	3.9% (2.9, 5.2) 49/1242	4.3% (2.7, 6.3) 23/539
Jul 24	3.0% (2.6, 3.5) 174/5722	3.2% (2.7, 3.8) 136/4257	3.1% (2.1, 4.2) 36/1180	3.1% (2.3, 4.2) 47/1493	2.3% (1.6, 3.4) 28/1201	2.5% (2.0, 3.0) 89/3590	2.1% (1.4, 2.9) 30/1452	2.6% (2.2, 3.1) 131/5076	2.9% (2.5, 3.4) 154/5250	2.5% (1.7, 3.4) 37/1493	3.7% (2.5, 5.3) 29/781	3.7% (2.3, 5.5) 22/602	1.9% (1.1, 3.2) 15/770	3.4% (2.1, 5.2) 21/613	3.3% (2.3, 4.5) 38/1160	2.8% (1.5, 4.7) 13/465	3.7% (2.7, 4.8) 52/1420	3.8% (2.5, 5.6) 25/652

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

3TC = lamivudine
ZDV = zidovudine
NVP = nevirapine
ABC = abacavir
EFV = efavirenz
RTV = ritonavir
LPV = lopinavir
TDF = tenofovir disoproxil fumarate
FTC = emtricitabine
ATV = atazanavir
DRV = darunavir
RAL = raltegravir
RPV = rilpivirine
COBI = cobicistat
DTG = dolutegravir
EVG = elvitegravir
TAF = tenofovir alafenamide
BIC = bictegravir

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

Report Date	NFV	d4T	DDI	IDV	LdT
Jan 02	3.1% (1.4, 6.1) 8/256	2.0% (0.7, 4.6) 5/250			
Jul 02	3.0% (1.4, 5.6) 9/301	1.8% (0.6, 4.1) 5/283			
Jan 03	2.9% (1.4, 5.3) 10/343	2.2% (0.9, 4.4) 7/323			
Jul 03	2.9% (1.4, 5.1) 11/381	2.3% (1.0, 4.5) 8/345			
Jan 04	3.6% (2.0, 5.9) 15/416	2.9% (1.4, 5.1) 11/381			
Jul 04	4.0% (2.4, 6.2) 18/455	2.6% (1.3, 4.7) 11/418			
Jan 05	3.8% (2.3, 5.9) 19/496	2.6% (1.3, 4.5) 11/431	6.3% (3.4, 10.6) 13/205		
Jul 05	3.7% (2.3, 5.7) 20/534	2.7% (1.4, 4.7) 12/446	6.4% (3.5, 10.5) 14/220		
Jan 06	3.7% (2.3, 5.6) 21/572	2.7% (1.4, 4.6) 12/451	6.0% (3.3, 9.8) 14/234		
Jul 06	3.7% (2.3, 5.5) 22/601	2.6% (1.4, 4.5) 12/459	5.6% (3.1, 9.3) 14/248		
Jan 07	3.8% (2.4, 5.6) 24/638	2.8% (1.5, 4.7) 13/468	5.8% (3.3, 9.4) 15/259		
Jul 07	3.6% (2.3, 5.3) 24/670	2.7% (1.4, 4.6) 13/480	5.3% (2.9, 8.7)* 14/266		
Jan 08	3.4% (2.3, 4.7) 33/972	2.9% (1.8, 4.5) 19/651	4.5% (2.6, 7.3) 16/353	2.2% (0.8, 4.7) 6/272	
Jul 08	3.5% (2.5, 4.8) 37/1066	2.7% (1.7, 4.2) 19/696	4.4% (2.5, 7.1) 16/362	2.2% (0.8, 4.7) 6/275	
Jan 09	3.4% (2.4, 4.7) 37/1074	2.5% (1.5, 3.9) 19/754	4.4% (2.5, 7.0) 16/365	2.2% (0.8, 4.7) 6/276	
Jul 09	3.4% (2.4, 4.7) 37/1075	2.5% (1.5, 3.8) 19/771	4.6% (2.7, 7.3) 17/370	2.2% (0.8, 4.7) 6/276	

Report Date	NFV	d4T	DDI	IDV	LdT
Jan 10	3.4% (2.4, 4.7) 37/1080	2.4% (1.4, 3.7) 19/795	4.5% (2.6, 7.1) 17/380	2.2% (0.8, 4.7) 6/276	
Jul 10	3.8% (2.8, 5.1) 45/1182	2.4% (1.4, 3.7) 19/797	4.7% (2.8, 7.3) 19/404	2.1% (0.8, 4.6) 6/284	
Jan 11	3.9% (2.8, 5.1) 46/1193	2.4% (1.4, 3.7) 19/797	4.7% (2.8, 7.2) 19/406	2.1% (0.8, 4.5) 6/285	
Jul 11	3.8% (2.8, 5.1) 46/1196	2.4% (1.4, 3.7) 19/799	4.6% (2.8, 7.2) 19/409	2.1% (0.8, 4.5) 6/285	
Jan 12	3.9% (2.9, 5.2) 47/1204	2.5% (1.5, 3.8) 20/801	4.6% (2.8, 7.2) 19/409	2.1% (0.8, 4.5) 6/286	
Jul 12	3.9% (2.9, 5.2) 47/1207	2.6% (1.6, 4.0) 21/802	4.8% (3.0, 7.4) 20/413	2.4% (1.0, 5.0) 7/287	
Jan 13	3.9% (2.9, 5.1) 47/1210	2.6% (1.6, 4.0) 21/803	4.8% (3.0, 7.4) 20/413	2.4% (1.0, 5.0) 7/288	
Jul 13	3.9% (2.9, 5.1) 47/1211	2.6% (1.6, 4.0) 21/805	4.8% (3.0, 7.3) 20/416	2.4% (1.0, 4.9) 7/289	
Jan 14	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 4.0) 21/809	4.8% (2.9, 7.3) 20/418	2.4% (1.0, 4.9) 7/289	
Jul 14	3.9% (2.8, 5.1) 47/1214	2.6% (1.6, 3.9) 21/810	4.7% (2.9, 7.2) 20/423	2.4% (1.0, 4.9) 7/289	
Jan 15	3.9% (2.8, 5.1) 47/1214	2.6% (1.6, 3.9) 21/810	4.7% (2.9, 7.2) 20/423	2.4% (1.0, 4.9) 7/289	
Jul 15	3.9% (2.8, 5.1) 47/1215	2.6% (1.6, 3.9) 21/810	4.7% (2.9, 7.2) 20/423	2.4% (1.0, 4.9) 7/289	
Jan 16	3.9% (2.9, 5.1) 47/1213	2.6% (1.6, 3.9) 21/810	4.7% (2.9, 7.2) 20/422	2.4% (1.0, 4.9) 7/289	
Jul 16	3.9% (2.9, 5.1) 47/1211	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.2) 20/426	2.4% (1.0, 4.9) 7/289	
Jan 17	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.2) 20/427	2.4% (1.0, 4.9) 7/289	
Jul 17	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	
Jan 18	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.3, 3.5) 3/245

Report Date	NFV	d4T	DDI	IDV	LdT
Jul 18	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jan 19	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jul 19	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jan 20	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jul 20	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jan 21	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jul 21	3.9% (2.9, 5.1) 47/1212	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jan 22	3.9% (2.9, 5.1) 47/1213	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jul 22	3.9% (2.9, 5.1) 47/1214	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jan 23	3.9% (2.9, 5.1) 47/1216	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jul 23	3.9% (2.9, 5.1) 47/1216	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jan 24	3.9% (2.9, 5.1) 47/1216	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254
Jul 24	3.9% (2.9, 5.1) 47/1216	2.6% (1.6, 3.9) 21/811	4.7% (2.9, 7.1) 20/427	2.4% (1.0, 4.9) 7/289	1.2% (0.2, 3.4) 3/254

NFV = nelfinavir
d4T = stavudine
DDI = didanosine
IDV = indinavir
LdT = telbivudine

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 July 2024

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Enrolled	13882	7563	2626	24074
3TC	6250	5714	1852	13863
ABC	1620	998	358	2985
ADV	100	1	3	104
APV	33	4	8	45
ATV	1605	613	183	2405
BIC	682	120	54	856
CAB	41	1	1	43
COBI	660	70	24	756
d4T	912	112	87	1120
ddC	62	8	5	76
ddI	488	298	168	964
DLV	13	1	2	16
DRV	839	228	112	1188
DTG	1252	457	181	1892
EFV	1384	131	64	1588
ETR	83	29	10	123
ETV	104	2	0	106
EVG	506	53	18	577
FOS	124	23	13	161
FTC	5714	1428	534	7683
FTR	2	0	0	2
IDV	335	116	47	505
LdT	269	9	4	282
LEN	2	0	0	2
LPV	1629	1860	668	4164
MVC	34	5	0	39
NFV	1270	1987	734	4003
NVP	1290	974	572	2854
PIF	16	3	3	22
RAL	654	257	206	1120
RPV	832	179	44	1056
RTV	3911	2634	938	7500
SQV	205	137	86	429
T20	29	7	10	46
TAF	1511	249	98	1859
TDF	5660	1563	698	7931
TPV	6	1	2	9
ZDV	4656	6296	3614	14600

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies Enrolled	13882	7563	2626	24074
3TC & NFV & ZDV	696	1529	465	2690
3TC & LPV & RTV & ZDV	525	1260	352	2137
ZDV	539	658	407	1604
3TC & NVP & ZDV	549	652	247	1450
ATV & FTC & RTV & TDF	793	302	40	1135
ABC & 3TC & ZDV	259	575	168	1002
3TC & ZDV	306	383	108	797
BIC & FTC & TAF	548	74	31	653
FTC & TDF	435	118	75	628
FTC & RPV & TDF	465	111	11	587
EFV & FTC & TDF	359	36	7	402
FTC & LPV & RTV & TDF	260	106	24	390
TDF	271	21	93	385
DRV & FTC & RTV & TDF	301	72	4	377
DTG & FTC & TDF	222	110	35	367
ABC & DTG & 3TC	293	31	8	332
FTC & RAL & TDF	232	70	20	322
DTG & FTC & TAF	187	75	18	280
3TC	217	12	16	245
LdT	232	5	4	241
COBI & EVG & FTC & TAF	193	21	7	221
IDV & 3TC & ZDV	139	58	17	214
3TC & TDF & ZDV	194	10	6	210
COBI & EVG & FTC & TDF	180	23	3	206
FTC & RPV & TAF	167	9	0	176
EFV & 3TC & ZDV	103	55	12	170
ABC & ATV & 3TC & RTV	116	27	1	144
EFV & 3TC & TDF	129	6	2	137
3TC & NVP & d4T	102	11	3	116
ATV & 3TC & RTV & ZDV	63	48	5	116
EFV & 3TC & d4T	111	0	0	111
3TC & NFV & d4T	95	8	0	103
ABC & 3TC & LPV & RTV & ZDV	45	47	10	102
FTC & NVP & TDF	89	5	1	95
ddI	21	59	11	91
3TC & RAL & TDF	24	44	17	85
DTG & 3TC & TDF	65	17	2	84
3TC & NFV & NVP & ZDV	27	40	16	83
ABC & 3TC & NVP	75	4	0	79
3TC & LPV & RTV & TDF	71	5	0	76
3TC & RTV & SQV & ZDV	19	42	12	73
ABC & 3TC & LPV & RTV	55	13	4	72
ETV	69	1	0	70
ADV	57	0	0	57
ABC & 3TC & NVP & ZDV	24	16	12	52
ABC & ATV & 3TC	45	6	1	52
EFV & 3TC & NVP & ZDV	52	0	0	52
EFV & FTC & 3TC & LPV & RTV & TDF & ZDV	47	2	1	50
EFV & FTC & LPV & RTV & TDF	48	1	1	50
DRV & 3TC & RTV & ZDV	20	28	1	49

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

	First Trimester	Second Trimester	Third Trimester	Overall
3TC & LPV & RTV & TDF & ZDV	25	17	6	48
3TC & SQV & ZDV	31	11	5	47
ABC & 3TC & NFV & ZDV	20	22	5	47
3TC & LPV & NFV & RTV & ZDV	12	23	8	43
ATV & 3TC & ZDV	33	8	2	43
ABC & EFV & 3TC	40	2	0	42
ATV & 3TC & LPV & RTV & ZDV	21	18	2	41
ATV & 3TC & RTV & TDF	30	11	0	41
3TC & d4T	36	4	0	40
DTG & 3TC	36	2	2	40
EFV & 3TC & NFV & ZDV	40	0	0	40
LPV & RAL & RTV	38	2	0	40
ABC & DRV & 3TC & RTV	32	7	0	39
DRV & FTC & RAL & RTV & TDF	26	7	6	39
FTC & FOS & RTV & TDF	33	4	2	39
LPV & RTV	31	7	1	39
BIC & DTG & FTC & TAF & TDF	35	2	1	38
EFV & 3TC & NVP & d4T	38	0	0	38
ddI & NFV & ZDV	18	15	5	38
ddI & NFV & d4T	32	4	1	37
ATV & FTC & 3TC & LPV & RTV & TDF & ZDV	26	6	2	34
NFV	27	7	0	34
ABC & 3TC & RAL	26	7	0	33
ATV & FTC & RAL & RTV & TDF	17	9	7	33
ATV & FTC & RTV & TDF & ZDV	5	2	26	33
IDV & 3TC & d4T	31	1	0	32
FTC & 3TC & LPV & RTV & TDF & ZDV	18	11	2	31
ABC & 3TC & TDF & ZDV	20	8	2	30
ddI & 3TC & NFV & ZDV	4	16	10	30
IDV	25	3	0	28
ddI & 3TC & NVP & ZDV	0	10	18	28
ddI & ZDV	17	9	2	28
COBI & DRV & FTC & TAF	26	1	0	27
EFV	27	0	0	27
ATV & EFV & FTC & RTV & TDF	24	2	0	26
ATV & FTC & TDF	16	7	1	24
COBI & DRV & FTC & TDF	22	2	0	24
3TC & NVP & TDF	21	2	0	23
BIC & DTG & FTC & TAF	21	2	0	23
ADV & 3TC	22	0	0	22
FTC & NFV & TDF	18	4	0	22
FTC & RAL & TAF	18	4	0	22
ddC & ZDV	20	2	0	22
3TC & RAL & ZDV	8	10	3	21
3TC & d4T & TDF	21	0	0	21
ABC & ATV & 3TC & RTV & TDF	19	2	0	21
DRV & DTG & RTV	19	2	0	21
NVP	16	3	2	21
NVP & ZDV	2	0	19	21
ddI & NFV	4	10	7	21
3TC & LPV & NVP & RTV & ZDV	3	11	6	20
3TC & LPV & RTV & d4T	16	1	3	20

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

	First Trimester	Second Trimester	Third Trimester	Overall
CAB & RPV	20	0	0	20
FTC & LPV & RTV & TDF & ZDV	10	0	10	20
ddI & NVP & d4T	14	6	0	20
3TC & NFV & d4T & ZDV	13	4	2	19
3TC & RTV & ZDV	13	5	1	19
BIC & FTC & RAL & TAF & TDF	17	1	1	19
DRV & DTG & FTC & RTV & TDF	10	5	4	19
DRV & FTC & RTV & TAF	14	3	1	18
3TC & TDF	16	1	0	17
ABC & FOS & 3TC & RTV	16	1	0	17
DRV & ETR & RAL & RTV	15	2	0	17
EFV & 3TC & LPV & RTV & ZDV	16	1	0	17
FTC & LPV & RTV & ZDV	3	9	5	17
FTC & RPV & TAF & TDF	17	0	0	17
ddI & 3TC & ZDV	6	9	2	17
3TC & NFV & TDF & ZDV	6	8	2	16
ABC & ATV & 3TC & RTV & ZDV	11	3	2	16
ddI & NVP & ZDV	13	2	1	16
3TC & NVP & d4T & ZDV	5	7	3	15
ATV & DRV & FTC & RTV & TDF	9	4	2	15
ATV & FTC & LPV & RTV & TDF	13	2	0	15
DTG & FTC & RPV & TAF	14	1	0	15
ETV & TDF	15	0	0	15
FOS & 3TC & RTV & ZDV	10	4	1	15
ddI & NFV & NVP	3	7	5	15
ABC & EFV & 3TC & ZDV	13	1	0	14
ATV & FTC & 3TC & RTV & TDF & ZDV	12	2	0	14
COBI & EVG & FTC & RAL & TAF & TDF	14	0	0	14
DTG & FTC & RAL & TDF	12	1	1	14
ETR & 3TC & ZDV	7	7	0	14
IDV & 3TC & RTV & ZDV	10	4	0	14
LPV & RTV & TDF & ZDV	8	4	2	14
d4T	14	0	0	14
ddI & LPV & RTV & TDF	11	3	0	14
ABC & 3TC & d4T	12	1	0	13
ABC & ATV & 3TC & ZDV	9	3	1	13
DRV & DTG & 3TC & RTV & ZDV	13	0	0	13
DTG	12	1	0	13
DTG & FTC & RPV & TDF	9	3	1	13
EFV & FTC & RAL & TDF	10	2	1	13
FTC & RAL & TDF & ZDV	1	1	11	13
IDV & 3TC & NFV & ZDV	9	3	1	13
3TC & LPV & RAL & RTV & ZDV	5	0	7	12
ABC & ddI & LPV & RTV	12	0	0	12
ADV & LdT	12	0	0	12
ATV & COBI & FTC & TDF	12	0	0	12
ATV & DTG & FTC & RTV & TDF	11	0	1	12
ATV & RTV	10	2	0	12
DTG & 3TC & RAL & TDF	12	0	0	12
FTC & ETR & TDF	9	3	0	12
FTC & LPV & RAL & RTV & TDF	4	4	4	12
ABC & 3TC & LPV & RTV & TDF	8	3	0	11

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
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Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

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Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

	First Trimester	Second Trimester	Third Trimester	Overall
COBI & DRV & EVG & FTC & RTV & TDF	4	0	0	4
COBI & DRV & EVG & FTC & TDF	3	0	1	4
COBI & DRV & FTC & RTV & TAF & TDF	4	0	0	4
DRV	3	0	0	4
DRV & DTG & FTC & RTV & TAF	4	0	0	4
DRV & FTC & ETR & RAL & RTV & TDF	4	0	0	4
DRV & FTC & MVC & RAL & RTV & TDF	4	0	0	4
DRV & RTV & TDF & ZDV	4	0	0	4
DTG & EFV & FTC & TDF	4	0	0	4
DTG & FTC & 3TC & RPV & TDF	3	1	0	4
DTG & FTC & TDF & ZDV	0	0	4	4
EFV & 3TC	4	0	0	4
EFV & 3TC & LPV & RTV & TDF	4	0	0	4
EFV & 3TC & NFV & TDF & ZDV	4	0	0	4
EFV & 3TC & TDF & ZDV	4	0	0	4
EFV & FTC & TDF & ZDV	0	0	4	4
ETR & 3TC & LPV & RTV & ZDV	2	2	0	4
FOS & 3TC & RTV & TDF	2	0	2	4
FTC	3	1	0	4
FTC & 3TC & LPV & RAL & RTV & TDF & ZDV	3	0	1	4
FTC & 3TC & LPV & RPV & RTV & TDF & ZDV	4	0	0	4
FTC & 3TC & NFV & TDF & ZDV	0	4	0	4
IDV & 3TC & NVP & ZDV	2	2	0	4
LPV & NVP & RTV & TDF	4	0	0	4
LPV & RTV & d4T & TDF	4	0	0	4
SQV	3	1	0	4
ddI & 3TC	4	0	0	4
3TC & LPV & RAL & RTV & TDF	3	0	0	3
3TC & LPV & RTV & d4T & TDF	3	0	0	3
3TC & NFV & NVP & d4T	3	0	0	3
3TC & NFV & ddC & ZDV	2	1	0	3
3TC & NVP & RTV & SQV & ZDV	1	1	1	3
3TC & RTV & SQV	3	0	0	3
ABC & 3TC & NFV & NVP & ZDV	2	0	1	3
ABC & 3TC & NVP & d4T	2	1	0	3
ABC & 3TC & RTV & SQV & ZDV	1	2	0	3
ABC & 3TC & TDF	3	0	0	3
ABC & ATV & 3TC & RAL & RTV	3	0	0	3
ABC & COBI & DRV & DTG & 3TC	3	0	0	3
ABC & DRV & DTG & FTC & 3TC & RTV & TDF	1	2	0	3
ABC & DTG & EFV & FTC & 3TC & TDF	2	1	0	3
ABC & DTG & FTC & 3TC & RPV & TDF	2	1	0	3
ABC & EFV & 3TC & NVP & d4T & ZDV	3	0	0	3
ABC & FOS & 3TC & RTV & ZDV	2	0	1	3
ABC & FTC & LPV & RTV & TDF	3	0	0	3
ABC & IDV & 3TC & ZDV	2	1	0	3
ABC & LPV & RTV & d4T	2	1	0	3
ABC & NVP & TDF	3	0	0	3
ABC & ddI & NVP & d4T	3	0	0	3
ABC & ddI & T20 & FOS & 3TC & TDF	3	0	0	3
APV & 3TC & d4T	3	0	0	3
ATV & 3TC & RAL & RTV & TDF	0	3	0	3

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

APPENDIX B
Summary of Antiretroviral Treatments by Trimester of Earliest Exposure
Prospective Registry Cases with Follow-up Data Closed Through 31 July 2024

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

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

Appendix C: List of Defects as Reported to the Registry

Appendix C lists the individual defects reported to the Registry and classified by the Registry as defects. Defect cases are listed separately by prospective and retrospective status, trimester of exposure, and treatment regimen. Appendix C has been removed from the main body of the interim report and is now available as a stand-alone document on the Antiretroviral Pregnancy Registry website at http://www.apregistry.com/InterimReport.aspx.

Appendix D: Index

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

This appendix includes a periodically updated 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 the most complete and current safety data, please consult the appropriate manufacturer's website, local product label and/or relevant published literature.

Generic products are available for many brand products. The safety information for generic drugs is, by law, identical to the parent drug for drugs approved in the US.

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

Abacavir (ZIAGEN®, ABC)

ZIAGEN (abacavir sulfate) is a nucleoside analogue human immunodeficiency virus (HIV-1) reverse transcriptase inhibitor, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Pregnancy: Available data from the APR shows no difference in the overall risk of birth defects for abacavir compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population (see Data). The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks' gestation. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, oral administration of abacavir to pregnant rats during organogenesis resulted in fetal malformations and other embryonic and fetal toxicities at exposures 35 times the human exposure (AUC) at the recommended clinical daily dose. However, no adverse developmental effects were observed following oral administration of abacavir to pregnant rabbits during organogenesis, at exposures approximately 9 times the human exposure (AUC) at the recommended clinical dose.

Human Data: Based on prospective reports to the APR of exposures to abacavir during pregnancy resulting in live births (including over 1,300 exposed in the first trimester and over 1,300 exposed in the second/third trimester), there was no difference between the overall risk of birth defects for abacavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of

defects in live births was 3.2% (95% CI: 2.3% to 4.3%) following first trimester exposure to abacavir-containing regimens and 2.9% (95% CI: 2.1% to 4.0%) following second/third trimester exposure to abacavir-containing regimens.
Abacavir has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.

Animal Data: Abacavir was administered orally to pregnant rats (at 100, 300, and 1,000 mg per kg per day) and rabbits (at 125, 350, or 700 mg per kg per day) during organogenesis (on gestation Days 6 through 17 and 6 through 20, respectively). Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) or developmental toxicity (decreased fetal body weight and crown-rump length) were observed in rats at doses up to 1,000 mg per kg per day, resulting in exposures approximately 35 times the human exposure (AUC) at the recommended daily dose. No developmental effects were observed in rats at 100 mg per kg per day, resulting in exposures (AUC) 3.5 times the human exposure at the recommended daily dose. In a fertility and early embryo-fetal development study conducted in rats (at 60, 160, or 500 mg per kg per day), embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) or toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at doses up to 500 mg per kg per day. No developmental effects were observed in rats at 60 mg per kg per day, resulting in exposures (AUC) approximately 4 times the human exposure at the recommended daily dose. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In pregnant rabbits, no developmental toxicities and no increases in fetal malformations occurred at up to the highest dose evaluated, resulting in exposures (AUC) approximately 9 times the human exposure at the recommended dose.

Lactation: The Centers for Disease Control and Prevention recommends that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Abacavir is present in human milk. There is no information on the effects of abacavir on the breastfed infant or the effects of the drug on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving ZIAGEN.

Pediatric Use: The safety and effectiveness of ZIAGEN have been established in pediatric patients aged 3 months and older. Use of ZIAGEN is supported by pharmacokinetic trials and evidence from adequate and well-controlled trials of ZIAGEN in adults and pediatric subjects

Impairment of Fertility: Abacavir did not affect male or female fertility in rats at a dose associated with exposures (AUC) approximately 3.3 times (male) or 4.1 times (female) those in humans at the clinically recommended dose.

Carcinogenicity: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose of 600 mg.

Mutagenesis: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. 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.

Patient Counseling Information

Pregnancy Registry: Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZIAGEN during pregnancy.

Lactation: Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk.

(Last reviewed May 2023)

Adefovir dipivoxil (HEPSERA®, ADV)

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

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

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

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

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

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

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

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

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

(Last reviewed April 2023)

Amprenavir (AGENERASE®, APV)

AGENERASE® no longer manufactured as of 2007. The latest product information can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21007s11,21039s10lbl.pdf

Atazanavir (REYATAZ®, ATV)

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

Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

Clinical Considerations

Dose Adjustments during Pregnancy and the Postpartum Period

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

Maternal Adverse Reactions

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

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

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

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

Data

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

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

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

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

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

Lactation

Risk Summary

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

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

(Last reviewed October 2021)

Bictegravir (BIKTARVY®, BIC/FTC/TAF)

Bictegravir (BIC) is an HIV-1 integrase strand transfer inhibitor that is one component of Biktarvy®, a three-drug combination of BIC and two HIV-1 nucleoside analog reverse transcriptase inhibitors, emtricitabine (FTC) and tenofovir alafenamide (TAF). Biktarvy® is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 14 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no known or suspected substitutions associated with resistance to bictegravir or tenofovir. The recommended dosage of Biktarvy® is one tablet containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF taken orally once daily with or without food. The recommended dosage in pediatric patients weighing at least 14 kg to less than 25 kg is one tablet containing 30 mg BIC, 120 mg FTC, and 15 mg TAF taken once daily with or without food. Recommended dosage in pregnant individuals who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no known substitutions associated with resistance to the individual components of Biktarvy® is one tablet containing 50 mg BIC, 200 mg FTC, and 25 mg TAF taken orally once daily with or without food.

No data are available on which to make a dose recommendation for pediatric patients weighing less than 14 kg.

Biktarvy® is recommended in pregnant individuals who are virologically-suppressed on a stable antiretroviral regimen with no known substitutions associated with resistance to any of the individual components of Biktarvy®. Biktarvy® was only studied in pregnant individuals who were virologically suppressed, and lower plasma exposures of Biktarvy® were observed during pregnancy compared to post-partum. Biktarvy® was evaluated in an open-label clinical trial of 33 virologically suppressed (HIV-1 RNA < 50 copies/mL) pregnant adults with HIV-1 and no known. substitutions associated with resistance to BIC, FTC, or TAF. Pregnant adults were administered Biktarvy® (containing 50 mg of BIC, 200 mg of FTC and 25 mg of TAF) once daily from the second or third trimester through postpartum. Exposures of BIC, FTC, and TAF were lower during pregnancy as compared to postpartum. All 32 adult participants who completed the study maintained viral suppression during pregnancy, at delivery, and through Week 18 postpartum. The median CD4+ cell count at baseline was 558 cells/μL, and the median change in CD4+ cell count from baseline to Week 12 postpartum was 159 cells/μL. All 29 neonate participants had negative/nondetectable HIV-1 PCR results at birth and/or at 4 to 8 weeks post-birth. The safety findings in this trial were consistent with other trials in adults.

Data from the published literature report the presence of BIC, FTC, TAF, and tenofovir in human milk. There are no data on the effects of BIC on the breastfed child. There are no data on the effects of BIC, FTC or TAF on milk production. Potential risks of breastfeeding include: (1) HIV-1 transmission to HIV-1–negative infants; (2) developing viral resistance in HIV-1–positive infants; and (3) adverse reactions in a breastfed infant similar to those seen in adults.

In pediatric patients, the safety and effectiveness of Biktarvy® have been established as a complete regimen for the treatment of HIV-1 infection in patients weighing at least 14 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no known or suspected resistance to

bictegravir or tenofovir. Use of Biktarvy® in pediatric patients weighing at least 14 kg is supported by the following: trials in adults as well as an open-label trial in three age-based cohorts of virologically-suppressed pediatric subjects (Cohort 1: 12 to less than 18 years of age and weighing at least 35 kg receiving Biktarvy® through Week 48 (N=50), Cohort 2: 6 to less than 12 years of age and weighing at least 25 kg receiving Biktarvy® through Week 24 (N=50), and Cohort 3: at least 2 years of age and weighing at least 14 to less than 25 kg through Week 24 (N=22)) No pediatric subjects 2 years of age were enrolled; of the 6 pediatric subjects who were 3 years of age at enrollment, 3 subjects weighed between 14 to less than 15 kg. The safety and efficacy of Biktarvy® in these pediatric subjects were similar to that in adults, and there was no clinically significant change in exposure for the components of Biktarvy®. Safety and effectiveness of Biktarvy® in pediatric patients weighing less than 14 kg have not been established.

Bictegravir (BIC) was not carcinogenic in a 6-month rasH2 transgenic mouse study at doses of up to 100 mg/kg/day in males and 300 mg/kg/day in females. BIC was not carcinogenic in a 2-year rat study at doses up to 300 mg/kg/day, which resulted in exposures of approximately 31 times the exposure in humans at the recommended dose of Biktarvy®. BIC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays. BIC did not affect fertility, reproductive performance or embryonic viability in male and female rats at 29 times higher exposures (AUC) than in humans at the recommended dose of Biktarvy®.

Patient counseling information of relevance to pregnancy should be provided. Biktarvy® may interact with certain drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or non-prescription medication or herbal products. Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant individuals exposed to Biktarvy®. Inform individuals with HIV-1 infection that the potential risks of breastfeeding include: (1) HIV-1 transmission to HIV-1–negative infants, (2) developing viral resistance in HIV-1–positive infants, and (3) adverse reactions in a breastfed infant similar to those seen in adults.

(Last reviewed October 2024)

Cabotegravir (VOCABRIA®, CABENUVA®, CAB)

Cabotegravir oral (VOCABRIA®, CAB)

VOCABRIA is a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with EDURANT (rilpivirine) for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as:

- oral lead-in to assess the tolerability of cabotegravir prior to administration of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions
- oral therapy for patients who will miss planned injection dosing with CABENUVA.

Pregnancy: There are insufficient human data on the use of VOCABRIA during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. Discuss the benefit-risk of using VOCABRIA with individuals of childbearing potential or during pregnancy.

In animal reproduction studies with oral cabotegravir, a delay in the onset of parturition and increased stillbirths and neonatal deaths were observed in a rat pre- and postnatal development study at >28 times the exposure at the recommended human dose (RHD). No evidence of adverse developmental outcomes was observed with oral cabotegravir in rats or rabbits (>28 times or similar to the exposure at the RHD, respectively) given during organogenesis.

Animal Data: Cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1,000 mg/kg/day from 15 days before cohabitation, during cohabitation, and from Gestation Days 0 to 17. There were no effects on fetal viability when fetuses were delivered by caesarean, although a minor decrease in fetal body weight was observed at 1,000 mg/kg/day (>28 times the 13 exposure in humans at the RHD). No drug-related fetal

toxicities were observed at 5 mg/kg/day (approximately 13 times the exposure in humans at the RHD), and no drug-related fetal malformations were observed at any dose.

Cabotegravir was administered orally to pregnant rabbits at 0, 30, 500, or 2,000 mg/kg/day from Gestation Days 7 to 19. No drug-related fetal toxicities were observed at 2,000 mg/kg/day (approximately 0.7 times the exposure in humans at the RHD). In a rat pre- and postnatal development study, cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1,000 mg/kg/day from Gestation Day 6 to Lactation Day 21. A delay in the onset of parturition and increases in the number of stillbirths and neonatal deaths by Lactation Day 4 were observed at 1,000 mg/kg/day (>28 times the exposure in humans at the RHD); there were no alterations to growth and development of surviving offspring. In a cross-fostering study, similar incidences of stillbirths and early postnatal deaths were observed when rat pups born to cabotegravir-treated mothers were nursed from birth by control mothers. There was no effect on neonatal survival of control pups nursed from birth by cabotegravir-treated mothers. A lower dose of 5 mg/kg/day (13 times the exposure at the RHD) was not associated with delayed parturition or neonatal mortality in rats. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in fetal tissue.

Lactation: There are no data on the presence of cabotegravir in human milk, the effects on the breastfed infant, or the effects on milk production. Cabotegravir is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1–positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults.

In mothers without HIV-1, breastfeeding should only be considered if the expected benefit justifies the potential risk to the infant, including the potential risk for adverse reaction in the breastfed child, along with the risk of HIV-1 acquisition due to nonadherence and subsequent vertical transmission to the child. Breastfeeding is not recommended if acute HIV-1 infection is suspected to avoid the risk of postnatal transmission of HIV-1 infection.

Animal Data: Animal lactation studies with cabotegravir have not been conducted. However, cabotegravir was detected in the plasma of nursing pups on Lactation Day 10 in the rat pre- and postnatal development study.

Pediatric Use: The safety and effectiveness of VOCABRIA have been established in adolescents aged 12 to younger than 18 years and weighing at least 35 kg, which is supported by the following:

- Trials in adults

- MOCHA (NCT03497676) trial in adolescents, in which virologically suppressed adolescents (aged 12 to younger than 18 years and weighing at least 35 kg) with HIV-1 received either cabotegravir or rilpivirine in addition to their background antiretroviral regimen (cohort 1), or cabotegravir plus rilpivirine as a complete regimen (cohort 2).

The safety and efficacy of VOCABRIA in adolescents (aged 12 to younger than 18 years and weighing at least 35 kg) were similar to that in adults and there was no clinically significant change in drug exposure.

The safety, efficacy, and pharmacokinetics of VOCABRIA have not been established in pediatric patients younger than 12 years of age or weighing <35 kg.

HIV-1 Pre-exposure Prophylaxis: The safety and effectiveness of VOCABRIA for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg is supported by data from 2 adequate and well-controlled trials of VOCABRIA for HIV-1 PrEP in adults with additional safety and pharmacokinetic data from studies in HIV-1–infected adults who were administered CABENUVA and in HIV-1–infected pediatric subjects who were administered separate components of CABENUVA in addition to their current antiretroviral therapy.

Carcinogenesis: Two-year carcinogenicity studies in mice and rats were conducted with cabotegravir. In mice, no drug-related increases in tumor incidence were observed at cabotegravir exposures (AUC) up to approximately 8 times (males) and 7 times (females) higher than those in humans at the RHD. In rats, no drug-related increases in tumor incidence were observed at cabotegravir exposures up to approximately 26 times higher than those in humans at the RHD.

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

Impairment of Fertility: In rats, no effects on fertility were observed at cabotegravir exposures (AUC) greater than 20 times (male) and 28 times (female) the exposure in humans at the RHD.

Patient Counseling Information:

Pregnancy Registry: Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to VOCABRIA during pregnancy.

Lactation: Inform individuals with HIV-1 infection that the potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV1-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults.

In mothers without HIV-1, the benefits and risks of VOCABRIA while breastfeeding should be evaluated, including the risk of HIV-1 acquisition due to medication nonadherence and subsequent mother to child transmission. Instruct mothers not to breastfeed if acute HIV-1 infection is suspected because of the risk of passing the HIV-1 virus to the baby.

Cabotegravir injection (CABENUVA®, APRETUDE®, CAB)

CABENUVA, a 2-drug co-packaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

APRETUDE is an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in at-risk adults and adolescents weight at least 35kd for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test prior to initiating APRETUDE (with or without an oral lead-in with oral cabotegravir) for HIV-1 PrEP.

Pregnancy: There are insufficient human data on the use of CABENUVA or APRETUDE during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. While there are insufficient human data to assess the risk of neural tube defects (NTDs) with exposure to CABENUVA or APRETUDE during pregnancy, NTDs were associated with dolutegravir, another integrase inhibitor. Discuss the benefit-risk of using CABENUVA or APRETUDE with individuals of childbearing potential or during pregnancy.

Cabotegravir use in pregnant women has not been evaluated. APRETUDE should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

In animal reproduction studies with oral cabotegravir, a delay in the onset of parturition and increased stillbirths and neonatal deaths were observed in a rat pre- and postnatal development study at greater than 28 times the exposure at the recommended human dose (RHD). No evidence of adverse developmental outcomes was observed with oral cabotegravir in rats or rabbits (greater than 28 times or similar to the exposure at the RHD, respectively) given during organogenesis.

Human Data: Data from an observational study in Botswana showed that dolutegravir, another integrase inhibitor, was associated with increased risk of NTDs when administered at the time of conception and in early pregnancy. Data from clinical trials are insufficient to address this risk with cabotegravir.

Animal Data: Cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1,000 mg/kg/day from 15 days before cohabitation, during cohabitation, and from Gestation Days 0 to 17. There were no effects on fetal viability when fetuses were delivered by caesarean, although a minor decrease in fetal body weight was observed at 1,000 mg/kg/day (greater than 28 times the exposure in humans at the RHD). No drug-related

fetal toxicities were observed at 5 mg/kg/day (approximately 13 times the exposure in humans at the RHD), and no drug-related fetal malformations were observed at any dose.

Cabotegravir was administered orally to pregnant rabbits at 0, 30, 500, or 2,000 mg/kg/day from Gestation Days 7 to 19. No drug-related fetal toxicities were observed at 2,000 mg/kg/day (approximately 0.7 times the exposure in humans at the RHD).

In a rat pre- and postnatal development study, cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1,000 mg/kg/day from Gestation Day 6 to Lactation Day 21. A delay in the onset of parturition and increases in the number of stillbirths and neonatal deaths by Lactation Day 4 were observed at 1,000 mg/kg/day (greater than 28 times the exposure in humans at the RHD); there were no alterations to growth and development of surviving offspring. In a cross-fostering study, similar incidences of stillbirths and early postnatal deaths were observed when rat pups born to cabotegravir-treated mothers were nursed from birth by control mothers. There was no effect on neonatal survival of control pups nursed from birth by cabotegravir-treated mothers. A lower dose of 5 mg/kg/day (13 times the exposure at the RHD) was not associated with delayed parturition or neonatal mortality in rats. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in fetal tissue.

Lactation: The Centers for Disease Control and Prevention recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. It is not known if cabotegravir is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, cabotegravir was present in milk. If cabotegravir is present in human milk, residual exposures may remain for 12 months or longer after the last injections have been administered.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving CABENUVA .

Because of detectable cabotegravir concentrations in systemic circulation for up to 12 months or longer after discontinuing injections of APRETUDE, it is recommended that women breastfeed only if the expected benefit justifies the potential risk to the infant.

Animal Data: Animal lactation studies with cabotegravir have not been conducted. However, cabotegravir was detected in the plasma of nursing pups on Lactation Day 10 in the rat pre- and postnatal development study.

Pediatric Use: The safety and efficacy of CABENUVA have not been established in pediatric patients. The safety and effectiveness of APRETUDE for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg is supported by data from 2 adequate and well-controlled trials of APRETUDE for HIV-1 PrEP in adults with additional safety and pharmacokinetic data from studies in HIV-1 infected adults who were administered CABENUVA, and in HIV-1 infected pediatric subjects who were administered separate components of CABENUVA in addition to their current antiretroviral therapy. APRETUDE for HIV-1 PrEP was evaluated in 2 open-label multicenter clinical trials, HPTN 083-01 and HPTN 084-01, in adolescent individuals 12 to less than 18 years of age weighing at least 35 kg who are at risk for HIV-1 acquisition. Sixty-four adolescents were enrolled. Of these, 62 adolescent participants received one or more injections after receiving VOCABRIA. In adolescents receiving VOCABRIA and APRETUDE for HIV-1 PrEP, the safety data were comparable to the safety data reported in adults receiving APRETUDE for HIV-1 PrEP.

While using APRETUDE, HIV-1 testing should be conducted prior to initiating APRETUDE (with or without an oral lead-in with oral cabotegravir) and prior to each injection of APRETUDE. Adolescents may benefit from more frequent visits and counseling to support adherence to the dosing and testing.

The safety, efficacy, and pharmacokinetics of APRETUDE in pediatric participants younger than 12 years of age or weighing <35 kg have not been established.

Carcinogenesis: Two-year carcinogenicity studies in mice and rats were conducted with cabotegravir. In mice, no drug-related increases in tumor incidence were observed at cabotegravir exposures (AUC) up to approximately 8 times (males) and 7 times (females) higher than those in humans at the RHD. In rats, no drug-related increases in tumor incidence were observed at cabotegravir exposures up to approximately 26 times higher than those in humans at the RHD.

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

Impairment of Fertility: In rats, no effects on fertility were observed at cabotegravir exposures (AUC) greater than 20 times (male) and 28 times (female) the exposure in humans at the RHD.

Patient Counseling Information:

Pregnancy Registry: Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VOCABRIA during pregnancy.

Inform individuals that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to APRETUDE during pregnancy. Individuals who are of reproductive potential should be informed of the long duration of exposure of APRETUDE and that there is very limited clinical experience in human pregnancy.

Lactation: Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk.

Inform individuals that due to the potential for adverse reactions and residual concentrations in the systemic circulation for up to 12 months or longer after discontinuing injections of APRETUDE, it is recommended that women breastfeed only if the expected benefit justifies the potential risk to the infant.

(Last reviewed November 2024)

Cobicistat (TYBOST®, COBI)

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

Cobicistat coadministered with atazanavir or darunavir is not recommended for use during pregnancy because of substantially lower exposures of cobicistat (when coadministered with atazanavir) and darunavir and cobicistat (when coadministered with darunavir) during the second and third trimesters. It should not be initiated in pregnant individuals, and an alternative regimen is recommended for individuals who become pregnant during therapy with Cobicistat coadministered with atazanavir or darunavir.

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

The safety and effectiveness of TYBOST coadministered with atazanavir or darunavir and two nucleoside reverse transcriptase inhibitors for the treatment of HIV-1 infection have been established in virologically suppressed pediatric patients weighing at least 35 kg for TYBOST coadministered with atazanavir or weighing at least 40 kg for TYBOST coadministered with darunavir. Use of TYBOST for this indication is supported by evidence from adequate and well-controlled studies in adults, and by pharmacokinetic, safety, and virologic data from an open-label trial in virologically suppressed, HIV-1 infected pediatric subjects aged 12 years and older. The safety in these subjects through 48 weeks was similar to that in antiretroviral treatment-naïve adults. Safety and effectiveness of TYBOST in combination with atazanavir in pediatric patients weighing less than 35 kg have not been established. Safety and effectiveness of TYBOST in combination with darunavir in pediatric patients weighing less than 40 kg have not been established.

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

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

In animal reproduction studies in rats and rabbits, no evidence of fetal harm was observed with oral administration of cobicistat during organogenesis at doses that produced exposures up to 1.4 and 3.3 times, respectively, the maximal recommended human dose (MRHD) of 150 mg. Because TYBOST is coadministered with atazanavir or darunavir and other antiretroviral drugs, also refer to the prescribing information of each drug for information about pregnancy.

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

(Last reviewed September 2024)

Darunavir (PREZISTA®, PREZCOBIX®, SYMTUZA®, DRV)

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

Darunavir is also one of the components of the fixed dose combination PREZCOBIX (DRV/COBI) and the single tablet regimen SYMTUZA (DRV/COBI/FTC /TAF). Darunavir boosted with cobicistat (PREZCOBIX, SYMTUZA) is not recommended for use during pregnancy because of substantially lower exposures of darunavir and cobicistat during pregnancy. PREZCOBIX and SYMTUZA should not be initiated in pregnant individuals. An alternative regimen is recommended for individuals who become pregnant during therapy with PREZCOBIX or SYMTUZA.

Pregnancy:

Pregnancy Exposure Registry

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

Risk Summary

Available limited data from the APR show no difference in rate of overall birth defects for darunavir (2.7%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks gestation.

The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Studies in animals did not show evidence of developmental toxicity. Exposures (based on AUC) in rats were 3-fold higher, whereas in mice and rabbits, exposures were lower (less than 1-fold) than human exposures at the recommended daily dose.

Clinical Considerations

The recommended dosage in pregnant patients is PREZISTA 600 mg taken with ritonavir 100 mg twice daily with food.

PREZISTA 800 mg taken with ritonavir 100 mg once daily should only be considered in certain pregnant patients who are already on a stable PREZISTA 800 mg with ritonavir 100 mg once daily regimen prior to pregnancy, are virologically suppressed (HIV-1 RNA less than 50 copies per mL), and in whom a change to twice daily PREZISTA 600 mg with ritonavir 100 mg may compromise tolerability or compliance.

Human Data

PREZISTA/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 36 pregnant women during the second and third trimesters, and postpartum. Eighteen subjects were enrolled in each BID and QD treatment arms. Twenty-nine subjects completed the trial through the postpartum period (6-12 weeks after delivery) and 7 subjects discontinued before trial completion, 5 subjects in the BID arm and 2 subjects in the QD arm.

The pharmacokinetic data demonstrate that exposure to darunavir and ritonavir as part of an antiretroviral regimen was lower during pregnancy compared with postpartum (6-12 weeks). Exposure reductions during pregnancy were greater for the once daily regimen as compared to the twice daily regimen.

Virologic response was preserved. In the BID arm, the proportion of subjects with HIV-1 RNA <50 copies/mL were 39% (7/18) at baseline, 61% (11/18) through the third trimester visit, and 61% (11/18) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥50 copies/mL for 11% (2/18) of subjects and were missing for 5 subjects (1 subject discontinued prematurely due to virologic failure). In the QD arm, the proportion of subjects with HIV-1 RNA <50 copies/mL were 61% (11/18) at baseline, 83% (15/18) through the third trimester visit, and 78% (14/18) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥50 copies/mL for none of the subjects and were missing for 3 subjects (1 subject discontinued prematurely due to virologic failure)

PREZISTA/ritonavir was well tolerated during pregnancy and postpartum. There were no new clinically relevant safety findings compared with the known safety profile of PREZISTA/ritonavir in HIV-1-infected adults.

Among the 31 infants with HIV test results available data, born to the 31 HIV-infected pregnant women who completed trial through delivery or postpartum period, all 31 infants had test results that were negative for HIV-

1 at the time of delivery and/or through 16 weeks postpartum. All 31 infants received antiretroviral prophylactic treatment containing zidovudine.

Based on prospective reports to the APR of over 980 exposures to darunavir-containing regimens during pregnancy resulting in live births (including over 660 exposed in the first trimester and over 320 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6.% (95% CI: 2.3% to 5.3.%) with first trimester exposure to darunavir-containing regimens and 2.5% (95% CI: 1.1% to 4.8%) with second/third trimester exposure to darunavir-containing regimens.

Animal Data
Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice (doses up to 1000 mg/kg from gestation day (GD) 6-15 with darunavir alone) and rats (doses up to 1000 mg/kg from GD 7-19 in the presence or absence of ritonavir) as well as in rabbits (doses up to 1000 mg/kg/day from GD 8-20 with darunavir alone). In these studies, darunavir exposures (based on AUC) were higher in rats (3-fold), whereas in mice and rabbits, exposures were lower (less than 1-fold) compared to those obtained in humans at the recommended clinical dose of darunavir boosted with ritonavir.

Nursing Mothers:
Risk Summary
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. There are no data on the presence of darunavir in human milk, the effects on the breastfed infant, or the effects on milk production. Darunavir is present in the milk of lactating rats. Because of the potential for HIV transmission (in HIV-negative infants), developing viral resistance (in HIV-positive infants), and serious adverse reactions in breastfed infants, **instruct mothers not to breastfeed if they are receiving PREZISTA®**.

Animal Data
Studies in rats (with darunavir alone or with ritonavir) have demonstrated that darunavir is secreted in the milk. In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed due to exposure of pups to drug substances via milk. The maximal maternal plasma exposures achieved with darunavir (up to 1000 mg/kg with ritonavir) were approximately 50% of those obtained in humans at the recommended clinical dose with ritonavir.

Pediatric Use: PREZISTA/ritonavir is not recommended in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age.

The safety, pharmacokinetic profile, and virologic and immunologic responses of PREZISTA/ritonavir administered twice daily were evaluated in treatment-experienced HIV-1-infected pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg. These subjects were evaluated in clinical trials TMC114-C212 (80 subjects, 6 to less than 18 years of age) and TMC114-228 (21 subjects, 3 to less than 6 years of age). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults. Please refer to Dosage and Administration (2.5) for twice-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

In clinical trial TMC114-C230, the safety, pharmacokinetic profile and virologic and immunologic responses of PREZISTA/ritonavir administered once daily were evaluated in treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age (12 subjects). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults. Once daily dosing recommendations for pediatric patients 3 to less than 12 years of age were derived using population pharmacokinetic modeling and simulation. Although a PREZISTA/ritonavir once daily dosing pediatric trial was not conducted in children less than 12 years of age, there is sufficient clinical safety data to support the predicted PREZISTA exposures for the dosing recommendations in this age group. Please see Dosage and Administration (2.5) for once-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

Juvenile Animal Data
In a juvenile toxicity study where rats were directly dosed with darunavir (up to 1000 mg/kg), deaths occurred from post-natal day 5 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 2 times the human plasma exposure levels.

Carcinogenesis, mutagenesis, impairment of fertility:

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

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

Impairment of Fertility
No effects on fertility or early embryonic development were observed with darunavir in rats.

(Last reviewed November 2024)

Delavirdine mesylate (RESCRIPTOR®, DLV)

RESCRIPTOR® no longer manufactured as of 2020. The latest product information can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/20705s03lbl.pdf

Didanosine (VIDEX®, VIDEX® EC, ddI®)

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

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

Lifetime carcinogenicity studies were conducted in mice and rats for 22 and 24 months, respectively. In the mouse study, initial doses of 120, 800, and 1200 mg/kg/day for each sex, were lowered after 8 months to 120,

210, and 210 mg/kg/day for females and 120, 300, and 600 mg/kg/day for males. The two higher doses exceeded the maximally tolerated doses in females and the high dose exceeded the maximally tolerated doses in males. The low dose in females represented 0.68-fold maximum human exposure and the intermediate dose in males represented 1.7-fold maximum human exposure based on relative AUC comparisons. In the rat study, initial doses were 100, 250, and 1000 mg/kg/day, and the high dose was lowered to 500 mg/kg/day after 18 months. The upper dose in male and female rats represented 3-fold maximum human exposure. Didanosine induced no significant increase in neoplastic lesions in mice or rats at maximally tolerated doses.

Didanosine was positive in the following genetic toxicology assays: 1) the *Escherichia Coli* tester strain WP2 uvrA bacterial mutagenicity assay; 2) the L5178Y/TK+/- mouse lymphoma mammalian cell gene mutation assay; 3) the *in vitro* chromosomal aberrations assay in cultured human peripheral lymphocytes; 4) the *in vitro* chromosomal aberrations assay in Chinese Hamster Lung cells; and 5) the BALB/c 3T3 *in vitro* transformation assay. No evidence of mutagenicity was observed in an AMES *Salmonella* bacterial mutagenicity assay or in rat and mouse *in vivo* micronucleus assay.

Pregnancy Exposure Registry

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

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

Risk Summary

Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome, which was also reported in non-pregnant individuals receiving nucleoside analogues. **The combination of didanosine and stavudine is contraindicated.**

Based on APR reports, congenital malformations were reported when administered during pregnancy. The prevalence of birth defects was 4.7% in the first trimester compared with 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) and 4.2% in the Texas Birth Defects Registry (TBDR) *(see Data)*. No pattern of defects was identified by the APR. Based on these findings, the clinical relevance is uncertain.

The rate of miscarriage is not reported in the APR. In the U.S. general population, the estimated background risks of miscarriage in clinically recognized pregnancies is 15 to 20%. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with didanosine at systemic exposures (AUC) up to 12 (rats) and 14 (rabbits) times the exposure in humans at the recommended daily human dose of VIDEX (see Data).

Clinical Considerations
Maternal Adverse Reactions
Cases of lactic acidosis syndrome, sometimes fatal have occurred in pregnant individuals using VIDEX in combination with stavudine. VIDEX is associated with an increased risk of lactic acidosis syndrome/hepatic steatosis syndrome

Data

Human Data
Based on prospective reports to the APR exposure to didanosine-containing regimens during pregnancy (including 427 exposed in the first trimester and 462 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.7 % (95% CI: 2.9% to 7.1%) with first trimester exposure to didanosine-containing regimens and 4.3% (95% CI: 2.7% to 6.6%) with the second/third trimester exposure to didanosine-containing regimens compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP and 4.2% in the TBDR.

Prospective reports from the APR of overall major birth defects in pregnancies exposed to VIDEX is compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP and TBDR as the external comparator groups. Limitations of using external comparators include differences in methodology and populations, as well as confounding due to the underlying disease.

Animal Data
Didanosine was administered orally at up to 1000 mg per kg daily to pregnant rats and at up to 600 mg per kg daily to pregnant rabbits on gestation Days 7 to 17 and 6 to 18, respectively, and also to rats 14 days before mating through weaning. No adverse effects on embryo-fetal development (rats and rabbits) were observed up to the highest dose tested. During organogenesis, systemic exposures (AUC) to didanosine were up to 12 (rats) and 14.2 (rabbits) times the estimated human exposure at the recommended daily human dose. Didanosine and/or its metabolites are transferred to the fetus through the placenta. In the rat pre/postnatal development study, reduced food intake and body weight gain was observed in the offspring of females administered didanosine at a maternally toxic exposure (approximately 12 times the exposure at the recommended human dose).

Lactation

Risk Summary
The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. It is not known whether VIDEX is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, didanosine was present in milk (see Data).

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) adverse reactions in breastfed infants similar to those seen in adults, instruct mothers not to breastfeed if they are receiving VIDEX.

Data
Didanosine and its metabolites were excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on lactation Day 14, with milk concentrations 5 times that of maternal plasma concentrations at 8 and 24 hours post-dose

(Last reviewed May 2021)

Dolutegravir (TIVICAY®, DTG)

TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 30 kg.

Pregnancy: Data from two, ongoing birth outcome surveillance studies in Botswana and Eswatini which together include over 14,000 individuals evaluated during pregnancy show similar prevalence of neural tube

defects among infants born to individuals taking dolutegravir at the time of conception compared to those born to individuals taking non-dolutegravir-containing regimens at conception or infants born to HIV-negative individuals.

There are insufficient human data on the use of TIVICAY during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of TIVICAY.

Human Data: The first interim analysis from an ongoing birth outcome surveillance study in Botswana identified an association between dolutegravir and an increased risk of neural tube defects when dolutegravir was administered at the time of conception and in early pregnancy. A subsequent analysis was conducted based on a larger cohort from the birth outcome surveillance study in Botswana and included over 9,460 individuals exposed to dolutegravir at conception, 23,664 individuals exposed to non-dolutegravir-containing regimens, and 170,723 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.11% (95% CI: 0.05-0.19%). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.11%, 95% CI: 0.07-0.16%), or to HIV-negative individuals (0.06%, 95% CI: 0.05-0.08%).

The Eswatini birth outcome surveillance study includes 9,743 individuals exposed to dolutegravir at conception, 1,838 individuals exposed to non-dolutegravir-containing regimens, and 32,259 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.08% (95% CI: 0.04-0.16%). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.22%, 95% CI: 0.06-0.56%) or to HIV-negative individuals (0.08%, 95% CI: 0.06-0.12%). The observed prevalence of neural tube defects in infants delivered to individuals taking non-dolutegravir-containing regimens had a wide confidence interval due to low sample size.

Limitations of these birth outcome surveillance studies include insufficient data to determine if baseline characteristics were balanced between the study groups or to assess other factors such as the use of folic acid during the preconception or first trimester periods.

Antiretroviral Pregnancy Registry: Based on prospective reports to the APR, of 1,377 exposures to dolutegravir during pregnancy resulting in live births (including 874 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 2.2% to 4.7%) following first-trimester exposure to dolutegravir-containing regimens and 5.0% (95% CI: 3.2% to 7.3%) following second-/third-trimester exposure to dolutegravir-containing regimens. In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%.

Dolutegravir has been shown to cross the placenta. In a clinical trial in Uganda and South Africa in women during the last trimester of pregnancy receiving dolutegravir 50 mg once daily, the ratio of median dolutegravir concentration in fetal umbilical cord to that in maternal peripheral plasma was 1.21 (range 0.51-2.11) (n = 15).

Animal Data: Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on gestation Days 6 to 17 and 6 to 18, respectively, and to rats on gestation day 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/post-natal development study, decreased body weight of the

developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

Lactation: Dolutegravir is present in human milk. It is not known whether dolutegravir affects human milk production or has effects on the breastfed infant.

Potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1–positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults.

Pediatric use: The safety, pharmacokinetics, and effectiveness of TIVICAY was evaluated in 75 HIV-1-infected, treatment-naïve or treatment-experienced, INSTI-naïve pediatric and adolescent subjects aged 4 weeks to less than 18 years weighing at least 3 kg in an ongoing, open-label, multicenter, dose-finding clinical trial, IMPAACT P1093. Additional pharmacokinetics data were evaluated in 2 pharmacokinetic substudies in ODYSSEY, an ongoing open-label, randomized, non-inferiority trial to evaluate the safety, efficacy, and pharmacokinetic parameters of TIVICAY plus two NRTIs compared with standard of care in HIV-1– infected pediatric subjects younger than 18 years.

Overall, the safety data in pediatric subjects from the IMPAACT P1093 trial were comparable to those observed in adults. The pharmacokinetic parameters of TIVICAY in pediatric subjects from IMPAACT P1093 and ODYSSEY were comparable to those of adults receiving 50 mg once daily or twice daily. The effectiveness observed in IMPAACT P1093 is comparable to that of treatment-experience adult subjects.

Safety and effectiveness of TIVICAY has not been established in pediatric patients aged less than 4 weeks or weighing less than 3 kg or in any pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (e.g., raltegravir, elvitegravir).

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

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

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

Patient Counseling Information:

Pregnancy Registry: Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to TIVICAY during pregnancy.

Lactation: Inform individuals with HIV-1 infection that the potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1– positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults.

Updated perinatal guidelines for information regarding treatment during pregnancy available at: https://clinicalinfo.hiv.gov/en/guidelines/perinatal/appendix-d-dolutegravir-counseling-guide-health-care-providers

Doravirine (PIFELTRO™, PIF)

PIFELTRO, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg:
- with no prior antiretroviral treatment history, **OR**
- to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to doravirine.

Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

No adequate human data are available to establish whether or not PIFELTRO poses a risk to pregnancy outcomes. In animal reproduction studies, no adverse developmental effects were observed when doravirine was administered at exposures ≥8 times the exposure in humans at the recommended human dose (RHD) of PIFELTRO (see Data).

The background rate of major birth defects is 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15-20%. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates individuals and infants from the limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

Data

Animal Data

Doravirine was administered orally to pregnant rabbits (up to 300 mg/kg/day on gestation days (GD) 7 to 20) and rats (up to 450 mg/kg/day on GD 6 to 20 and separately from GD 6 to lactation/postpartum day 20). No significant toxicological effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at exposures (AUC) approximately 9 times (rats) and 8 times (rabbits) the exposure in humans at the RHD. Doravirine was transferred to the fetus through the placenta in embryo-fetal studies, with fetal plasma concentrations of up to 40% (rabbits) and 52% (rats) that of maternal concentrations observed on GD 20.

Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking potential transmission of HIV-1 infection.

It is unknown whether doravirine is present in human milk, affects human milk production, or has effects on the breastfed infant. Doravirine is present in the milk of lactating rats (see Data). Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving PIFELTRO.

Data

Doravirine was excreted into the milk of lactating rats following oral administration (450 mg/kg/day) from GD 6 to lactation day 14, with milk concentrations approximately 1.5 times that of maternal plasma concentrations observed 2 hours post dose on lactation day 14.

Pediatric use
The safety and efficacy of PIFELTRO for the treatment of HIV-1 infection have been established in pediatric patients weighing at least 35 kg.

Use of PIFELTRO in this group is supported by evidence from adequate and well-controlled trials in adults and an open-label trial in virologically-suppressed or treatment-naïve pediatric subjects 12 to less than 18 years of age. The safety, efficacy, and exposure of doravirine in these pediatric subjects were similar to that in adults.

Safety and efficacy of PIFELTRO in pediatric patients weighing less than 35 kg have not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Doravirine was not carcinogenic in long-term oral carcinogenicity studies in mice and rats at exposures up to 6 and 7 times, respectively, the human exposures at the RHD. A statistically significant incidence of thyroid parafollicular cell adenoma and carcinoma seen only in female rats at the high dose was within the range observed in historical controls.

Mutagenesis

Doravirine was not genotoxic in a battery of *in vitro* or *in vivo* assays, including microbial mutagenesis, chromosomal aberration in Chinese hamster ovary cells, and in *in vivo* rat micronucleus assays.

Impairment of fertility

There were no effects on fertility, mating performance or early embryonic development when doravirine was administered to rats at systemic exposures (AUC) approximately 7 times the exposure in humans at the RHD.

Patient Counseling Information

Pregnancy Registry
Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in pregnant individuals exposed to PIFELTRO.

(Last reviewed October 2024)

Efavirenz (SUSTIVA®, STOCRIN®, EFV)

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

Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

Data

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

Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of approximately 1000 live births following exposure to efavirenz containing regimens (including over 800 live births exposed in the first trimester), there was no difference between efavirenz and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program. As of the interim APR report issued June 2019, the prevalence of birth defects following first-trimester exposure was 2.4% (95% CI: 1.5%-3.5%). One of these prospectively reported defects with first trimester exposure was a neural tube defect. A single case of myelomeningocele and a single case of anophthalmia with first-trimester exposure to efavirenz have also been prospectively reported. This case of anophthalmia also included severe oblique facial clefts and amniotic banding, which have a known association with anophthalmia.

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

(Last reviewed October 2021)

Elvitegravir (VITEKTA®, EVG)

VITEKTA® is no longer manufactured as of 2021. The latest product information can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203093s000lbl.pdf

Emtricitabine (EMTRIVA®, FTC)

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

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

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 trials in pregnant women. Because animal reproduction studies are not always predictive of human response.

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

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

The safety and efficacy of emtricitabine in patients between 3 months and 21 years of age is supported by data from three open-label, nonrandomized clinical trials 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) subjects. The pharmacokinetics of emtricitabine were studied in 20 neonates born to HIV-1 positive mothers. All neonates were HIV-1 negative at the end of the trial; the efficacy of emtricitabine in preventing or treating HIV-1 could not be determined.

Long-term carcinogenicity studies of emtricitabine in rats and mice did not show any carcinogenicity potential. No drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the

human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose). Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

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

(Last reviewed April 2023)

Enfuvirtide (FUZEON®, T-20)

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

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

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

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

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

(References: FUZEON Core Data Sheet version 6.0 September 28, 2015; FUZEON USPI Revised: December 2018)

(Last Reviewed April 2019)

Entecavir (BARACLUDE®, ETV)

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

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

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

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

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

Importantly, data from a long-term clinical study (AI463080) showed that BARACLUDE was not associated with an increased risk of malignant neoplasms as compared to other standard of care hepatitis B virus nucleos(t)ide analogues (nucs) in subjects with chronic HBV (CHB) infection.

Study AI463080 was a randomized, global, observational, open-label phase 4 study to assess long-term risks and benefits of BARACLUDE (0.5 mg/day or 1.mg/day) treatment as compared to other standard of care hepatitis B virus nucleos(t)ide analogues (nucs) in subjects with chronic HBV (CHB) infection.
A total of 12,485 patients with CHB were randomized (1:1), of whom 12,378 were treated to receive ETV (n=6,216) or other standard of care HBV nucleoside (acid) treatment (non-ETV) (n=6,162) respectively. The patients were evaluated at baseline and subsequently twice a year (every 6 months) on clinical outcome events (COEs) for up to 10 years during the study. The principal COEs assessed in the study were overall malignant neoplasms, liver-related HBV disease progression, non-HCC malignant neoplasms, HCC, non-HCC HBV disease progression, and deaths including liver-related deaths. The study data showed that ETV was not significantly associated with an increased risk of malignant neoplasms compared to use of other standard of care HBV nucs, as assessed by either the composite endpoint of overall malignant neoplasms or the individual endpoint of non-HCC malignant neoplasm. The most commonly reported malignancy were HCC followed by gastrointestinal malignancies with colorectal and gastric cancers representing the majority of the observed tumor types within the gastrointestinal system in both ETV and non-ETV groups. The data also showed that long-term ETV use was not associated with a lower occurrence of HBV disease progression or a lower rate of death overall. ETV treatment was generally well tolerated, with the reported events consistent with the cumulative safety experience. There was a greater number of treatment-related serious adverse events (SAEs) in the non-ETV vs ETV-treated subjects (0.8% vs 0.2%), primarily driven by neuropathic and musculoskeletal events occurring in subjects treated with the L-nucleosides (eg, lamivudine, telbivudine, and clevudine). The principal COE assessment are shown in Table 1 below:

Table 1: Principal Analyses of Time to Adjudicated Events - Randomized Treated Subjects

Endpoint[d]	Number of Subjects with Events			
	ETV N=6,216	Non-ETV N=6,162	Hazard Ratio [ETV:Non-ETV] (CI[b])	P-value[a]
Primary Endpoints				
Overall malignant neoplasm	331	337	0.93 (0.800, 1.084)	0.3553
Liver-related HBV disease progression	350	375	0.89 (0.769, 1.030)	0.1182
Death	238	264	0.85 (0.713, 1.012)	0.0676
Secondary Endpoints				
Non-HCC malignant neoplasm	95	81	1.10 (0.817, 1.478)	
HCC	240[c]	263	0.87 (0.727, 1.032)	
Liver-related death	46	48	0.91 (0.608, 1.365)	
Post-hoc Exploratory Endpoint				
Non-HCC HBV disease progression	137	146	0.90 (0.712, 1.135)	

Analyses were stratified by geographic region and prior HBV nucleos(t)ide experience.
[a] P-values are provided to the COEs that are primary endpoints per protocol specification.
[b] 95.03% CI for overall malignant neoplasm, death, and liver-related HBV disease progression; 95% CI for non-HCC malignant neoplasm, HCC, liver-related death, and non-HCC HBV disease progression.
[c] One subject had a pre-treatment HCC event and was excluded from the analysis.
[d] Overall malignant neoplasm is a composite event of HCC or non-HCC malignant neoplasm. Liver-related HBV disease progression is a composite event of liver-related death, HCC, or non-HCC HBV disease progression.
CI = confidence interval; N = total number of subjects.

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 at the highest recommended dose of 1 mg/day. In rodent and dog toxicology studies, seminiferous tubular degeneration was observed at exposures 35 times or greater than those achieved in humans. No testicular changes were evident in monkeys.

Developmental toxicity studies were performed in rats and rabbits. In rats, maternal toxicity, embryo-fetal toxicity including post-implantation loss, 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 at the MRHD. In rabbits, embryo-fetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed at exposures 883 times those in humans. In a peri-post-natal study, no adverse effects on offspring were seen with entecavir administered orally to rats at exposures > 94 times those in humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, entecavir should be used during pregnancy only if clearly needed and after consideration of the risks and benefits.

(Last reviewed May 2021)

Etravirine (INTELENCE®, ETR)

INTELENCE® is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1) indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients and pediatric patients 2 years of age and older.

The clinical efficacy of INTELENCE® for adult use is derived from the analyses of Week 48 data from 2 randomized, double-blind, placebo-controlled, Phase 3 trials, TMC125-C206 and TMC125-C216 (DUET-1 and DUET-2) in subjects with 1 or more NNRTI resistance-associated substitutions. The efficacy of INTELENCE® for treatment experienced pediatric patients (2 years to less than 18 years of age) is based on two Phase 2 trials, TMC125-C213 and TMC125-C234/IMPAACT P1090.

Pregnancy:

Pregnancy Exposure Registry

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

Risk Summary

Prospective pregnancy data from clinical trials and the APR are not sufficient to adequately assess the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Etravirine use during pregnancy has been evaluated in a limited number of individuals as reported by the APR, and available data show 1 birth defect in 66 first trimester exposures to etravirine-containing regimens.

The estimated background rate for major birth defects is 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, no adverse developmental effects were observed with orally administered etravirine at exposures equivalent to those at the maximum recommended human dose (MRHD) of 400 mg daily.

Human Data

Based on prospective reports to the APR of 116 live births following exposure to etravirine-containing regimens during pregnancy (including 66 exposed in the first trimester and 38 exposed in the second/third trimester), the number of birth defects in live births for etravirine was 1 out of 66 with first trimester exposure and 0 out of 38 with second/third trimester exposure. Prospective reports from the APR of overall major birth defects in pregnancies exposed to INTELENCE is compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations, as well as confounding due to the underlying disease; these limitations preclude an accurate comparison of outcomes.

INTELENCE (200 mg twice daily) in combination with other antiretroviral agents was evaluated in a clinical trial enrolling 15 pregnant subjects during the second and third trimesters of pregnancy and postpartum. Thirteen subjects completed the trial through postpartum period (6-12 weeks after delivery). The pharmacokinetic data demonstrated that exposure to total etravirine was generally higher during pregnancy compared with postpartum.

Among subjects who were virologically suppressed (HIV-1 RNA less than 50 copies/mL) at baseline (9/13), virologic suppression was maintained through the third trimester and postpartum period. Among subjects with HIV-1 RNA greater than 50 copies/mL and less than 400 copies/mL at baseline (3/13), viral loads remained less than 400 copies/mL. In one subject with HIV-1 RNA greater than 1,000 copies/mL at baseline (1/13), HIV-

1 RNA remained greater than 1,000 copies/mL during the study period. Thirteen infants were born to 13 HIV-infected pregnant individuals in this study. HIV-1 test results were not available for 2 infants. Among the eleven infants with HIV-1 test results available, who were born to 11 HIV-infected pregnant individuals who completed the study, all had test results that were negative for HIV-1 at the time of delivery. No unexpected safety findings were observed compared with the known safety profile of INTELENCE in non-pregnant adults.

Animal Data
Reproductive and developmental toxicity studies were performed in rats (at 250, 500 and 1,000 mg/kg/day) and rabbits (at 125, 250 and 375 mg/kg/day) administered etravirine on gestation days 6 through 16, and 6 through 19, respectively. In both species, no treatment-related embryo-fetal effects were observed. In addition, no treatment-related effects were observed in a pre- and postnatal development study performed in rats administered oral doses up to 500 mg/kg/day on gestation days 7 through lactation day 7. The systemic drug exposures achieved at the high dose in these animal studies were equivalent to those at the MRHD.

Nursing mothers:
Risk Summary
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

Based on limited data, etravirine has been shown to be present in human breast milk. There are no data on the effects of etravirine on the breastfed infant, or the effects of etravirine on milk production.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) adverse reactions in breastfed infants similar to those seen in adults, instruct mothers not to breastfeed if they are receiving INTELENCE.

Pediatric Use:
The safety and effectiveness of INTELENCE have been established for the treatment of HIV-infected pediatric patients from 2 years of age to less than 18 years. Use of INTELENCE in pediatric patients 2 years to less than 18 years of age is supported by evidence from adequate and well-controlled studies of INTELENCE in adults with additional data from two Phase 2 trials in treatment-experienced pediatric subjects, TMC125-C213, 6 years to less than 18 years of age (N=101) and TMC125-C234/IMPAACT P1090, 2 years to less than 6 years of age (N=20). Both studies were open-label, single arm trials of etravirine plus an optimized background regimen. In clinical trials, the safety, pharmacokinetics, and efficacy were comparable to that observed in adults except for rash (greater than or equal to Grade 2) which was observed more frequently in pediatric subjects.

Treatment with INTELENCE is not recommended in pediatric patients less than 2 years of age. Five HIV-infected subjects from 1 year to < 2 years of age were enrolled in TMC125-C234/IMPAACT P1090. Etravirine exposure was lower than reported in HIV-infected adults (AUC12h geometric mean ratio [90% CI] was 0.59 [0.34, 1.01] for pediatric subjects from 1 year to < 2 years of age compared to adults). Virologic failure at Week 24 (confirmed HIV-RNA greater than or equal to 400 copies/mL) occurred in 3 of 4 evaluable subjects who discontinued before or had reached Week 24. Genotypic and phenotypic resistance to etravirine developed in 1 of the 3 subjects who experienced virologic failure.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis and Mutagenesis
Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to approximately 104 weeks. Daily doses of 50, 200 and 400 mg/kg were administered to mice and doses of 70, 200 and 600 mg/kg were administered to rats in the initial period of approximately 41-52 weeks. The high and middle doses were subsequently adjusted due to tolerability and reduced by 50% in mice and by 50-66% in rats to allow for completion of the studies. In the mouse study, statistically significant increases in the incidences of hepatocellular carcinoma and incidences of hepatocellular adenomas or carcinomas combined were observed in treated females. In the rat study, no statistically significant increases in tumor findings were

observed in either sex. The relevance of these liver tumor findings in mice to humans is not known. Because of tolerability of the formulation in these rodent studies, maximum systemic drug exposures achieved at the doses tested were lower than those in humans at the clinical dose (400 mg/day), with animal vs. human AUC ratios being 0.6-fold (mice) and 0.2-0.7-fold (rats).

Etravirine tested negative in the *in vitro* Ames reverse mutation assay, *in vitro* chromosomal aberration assay in human lymphocyte, and *in vitro* clastogenicity mouse lymphoma assay, tested in the absence and presence of a metabolic activation system. Etravirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

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

(Last reviewed October 2024)

Fosamprenavir calcium (LEXIVA®, FOS)

LEXIVA® (fosamprenavir calcium) is a prodrug of amprenavir, an inhibitor of HIV protease, and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Pregnancy: There are insufficient prospective pregnancy data to adequately assess the risk of adverse developmental outcome as fosamprenavir use during pregnancy has been evaluated in a limited number of women. Available data has shown 2 birth defects in 109 first trimester exposures and 2 birth defects in 36 second and third trimester exposures compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (see Data). The estimated rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population evaluates women and infants from a limited geographic area and does not include birth defects in pregnancy outcomes for births that occurred at less than 20 weeks' gestation.

In animal reproduction studies, no evidence of major adverse developmental outcomes was observed following oral administration of fosamprenavir. Systemic exposure to amprenavir (the active ingredient) was less than (rabbits) or up to 2 times (rats) those in humans at the maximum recommended human dose (MRHD) with or without ritonavir. In contrast, oral administration of amprenavir was associated with abortions in pregnant rabbits at doses that produced approximately one-twentieth the human exposure at the MRHD.

In the rat pre- and post-natal development study, toxicities to the offspring, including reduced survival and reproductive performance, were observed at maternal systemic exposures (AUC) to amprenavir that were approximately 2 times the exposure in humans at the MRHD of fosamprenavir alone or approximately the same as those seen in humans following administration of the MRHD of fosamprenavir in combination with ritonavir

Human Data: Based on prospective reports to the APR of approximately 146 live births following exposure to fosamprenavir-containing regimens (including 109 live births exposed in the first trimester and 36 live births exposed in the second and third trimesters) there were 4 birth defects reported in live-born infants.

Animal Data: Fosamprenavir was administered orally to pregnant rats (300, 820, or 2,240 mg per kg per day) and rabbits (74.8, 224.3, or 672.8 mg per kg per day) on gestation Days 6 to 17 and Days 7 to 20, respectively. No major adverse effects on embryo-fetal development were observed at these dose levels, resulting in exposures ($AUC_{0\text{-}24\ h}$) approximately 2 times (rats) and 0.8 times (rabbits) human exposures at the

MRHD of fosamprenavir alone or 0.7 times (rats) and 0.3 times (rabbits) human exposures at the MRHD of fosamprenavir in combination with ritonavir. However, increased incidence of abortion was observed in rabbits administered a maternally toxic dose of fosamprenavir (672.8 mg per kg per day). In a study where amprenavir was administered orally to pregnant rabbits (25, 50, or 100 mg per kg per day) on gestation Days 8 to 20, increased abortions and an increased incidence of minor skeletal variations (deficient ossification of the femur, humerus, and trochlea) were observed at doses that produced approximately one-twentieth the exposure seen at the MRHD.

In the rat pre- and post-natal development study, fosamprenavir was administered orally (300, 820, or 2,240 mg per kg per day) on gestation Day 6 to lactation/post-partum Day 20. Fosamprenavir caused a reduction in pup survival and body weights. In surviving female offspring from the high-dose group, 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 were observed. Systemic exposure ($AUC_{0\text{-}24\ h}$) to amprenavir in rats was approximately 2 times the exposures in humans at the MRHD of fosamprenavir alone or approximately the same as those seen in humans at the MRHD of fosamprenavir in combination with ritonavir.

Lactation: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

There is no information available on the presence of amprenavir in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. When administered to lactating rats, amprenavir was present in milk (see Data). Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving LEXIVA.

Data: Amprenavir was excreted into the milk of lactating rats following a single dose of amprenavir (100 mg per kg); a maximal milk concentration was achieved 2 hours post-administration at a milk concentration approximately 1.2 times that of maternal plasma concentrations.

Contraception: Use of LEXIVA may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception.

Pediatric Use: The safety, pharmacokinetic profile, virologic, and immunologic responses of LEXIVA with and without ritonavir were evaluated in protease inhibitor-naive and -experienced HIV-1-infected pediatric subjects aged at least 4 weeks to younger than 18 years and weighing at least 3 kg in 3 open-label trials.

Treatment with LEXIVA is not recommended in protease inhibitor-experienced pediatric patients younger than 6 months. The pharmacokinetics, safety, tolerability, and efficacy of LEXIVA in pediatric patients younger than 4 weeks have not been established. Available pharmacokinetic and clinical data do not support once-daily dosing of LEXIVA alone or in combination with ritonavir for any pediatrics or twice-daily dosing without ritonavir in pediatric patients younger than 2 years.

Fertility: The effects of fosamprenavir on fertility and general reproductive performance were investigated in male (treated for 4 weeks before mating) and female rats (treated for 2 weeks before mating through postpartum Day 6) that received doses of 300, 820, or 2,240 mg per kg per day. Systemic exposures ($AUC_{0\text{-}24\ h}$) to amprenavir in these studies were 3 (males) to 4 (females) times higher than exposures in humans following administration of the MRHD of fosamprenavir alone or similar to those seen in humans following administration of fosamprenavir in combination with ritonavir. Fosamprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats.

Carcinogenicity: In long-term carcinogenicity studies, fosamprenavir was administered orally for up to 104 weeks at doses of 250, 400, or 600 mg per kg per day in mice and at doses of 300, 825, or 2,250 mg per kg per day in rats. Exposures at these doses were 0.3- to 0.7-fold (mice) and 0.7- to 1.4-fold (rats) those in

humans given 1,400 mg twice daily of fosamprenavir alone, and 0.2- to 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1,400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily. Exposures in the carcinogenicity studies were 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily. There was an increase in hepatocellular adenomas and hepatocellular carcinomas at all doses in male mice and at 600 mg per kg per day in female mice, and in hepatocellular adenomas and thyroid follicular cell adenomas at all doses in male rats, and at 825 mg per kg per day and 2,250 mg per kg per day in female rats. The relevance of the hepatocellular findings in the rodents for humans is uncertain. Repeat-dose studies with fosamprenavir in rats produced effects consistent with enzyme induction, which predisposes rats, but not humans, to thyroid neoplasms. In addition, in rats only there was an increase in interstitial cell hyperplasia at 825 mg per kg per day and 2,250 mg per kg per day, and an increase in uterine endometrial adenocarcinoma at 2,250 mg per kg per day. The incidence of endometrial findings was slightly increased over concurrent controls, but was within background range for female rats. The relevance of the uterine endometrial adenocarcinoma findings in rats for humans is uncertain.

Mutagenesis: Fosamprenavir was not mutagenic or genotoxic in a battery of in vitro and in vivo assays. These assays included bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus, and chromosome aberrations in human lymphocytes.

Patient Counseling Information:

Pregnancy Registry: Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LEXIVA during pregnancy.

Lactation: Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk.

Contraception: Use of LEXIVA may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception.

(Last reviewed May 2023)

Fostemsavir (RUKOBIA®, FTR)

RUKOBIA®, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

Pregnancy: There are insufficient human data on the use of RUKOBIA during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. In animal reproduction studies, oral administration of fostemsavir to pregnant rats and rabbits during organogenesis resulted in no adverse developmental effects at clinically relevant temsavir exposures.

Animal Data: Fostemsavir was administered orally to pregnant rats (50, 200, 600 mg/kg/day) and rabbits (25, 50, or 100 mg/kg/day) during Gestation Days 6 to 15 (rat) and 7 to 19 (rabbit). No fetal abnormalities were observed at temsavir exposures of approximately 180 (rat) and 30 (rabbit) times those in humans at the maximum recommended human dose (MRHD). In rabbits, increased embryonic death associated with maternal toxicity was observed at temsavir exposures approximately 60 times those in humans at the MRHD. In a separate rat study conducted at drug exposures approximately 200 times those in humans at the MRHD, fetal abnormalities (cleft 10 palate, open eyes, shortened snout, microstomia, misaligned mouth/jaw, and protruding tongue) and reductions in fetal body weights occurred in the presence of maternal toxicity.

In a rat pre- and postnatal development study, fostemsavir was administered orally at doses of 10, 50, or 300 mg/kg/day from Gestation Day 6 through Lactation Day 20. Reduced neonatal survival (7 to 14 days after birth) in the absence of other adverse fetal or neonatal effects was observed at maternal temsavir exposures approximately 130 times those in humans at the MRHD. No adverse fetal or neonatal effects were observed at maternal temsavir exposures approximately 35 times those in humans at the MRHD.

In a distribution study in pregnant rats, fostemsavir-related drug materials (i.e., temsavir and/or temsavir-derived metabolites) crossed the placenta and were detectable in fetal tissue.

Lactation: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

It is not known whether RUKOBIA is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, fostemsavir-related drug was present in rat milk.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving RUKOBIA.

Animal Data: In a distribution study, fostemsavir-related drug materials (i.e., temsavir and/or temsavir-derived metabolites) were excreted in rat milk following a single dose of fostemsavir administered to lactating rats 7 to 9 days postpartum. In the pre- and postnatal development study in rats, temsavir was present in milk at concentrations similar to those measured in maternal plasma, as determined 11 days postpartum. In addition, lactational exposure was associated with reduced offspring survival at maternal temsavir exposures not thought to be clinically relevant.

Pediatric use: The safety and effectiveness of RUKOBIA have not been established in pediatric patients.

Carcinogenesis: In a 2-year carcinogenicity study conducted in rats and a 26-week carcinogenicity study conducted in transgenic mice, fostemsavir produced no statistically significant increases in tumors over controls. The maximum daily exposures in rats were approximately 5 times (males) and 16 times (females) greater than those in humans at the MRHD.

Mutagenesis: Fostemsavir was not genotoxic in the bacterial reverse mutation assay (Ames test in Salmonella and E. coli), a chromosome aberration test in human lymphocytes, and rat bone marrow micronucleus test.

Impairment of Fertility: Oral administration of fostemsavir had no adverse effects on male or female fertility in rats at exposures approximately 10 times (males) and 186 times (females) of those in humans at the MRHD. At higher exposures (>80 times those in humans at the MRHD) in male rats, decreases in prostate gland/seminal vesicle weights, sperm density/motility, and increased abnormal sperm were observed.

Patient Counseling Information:

Pregnancy Registry: Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to RUKOBIA during pregnancy.

Lactation: Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk.

Updated perinatal guidelines for information regarding treatment during pregnancy available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/ 204790s016s018lbl.pdf

(Last reviewed May 2023)

Indinavir (CRIXIVAN®, IDV)

Indinavir is no longer manufactured as of 2023. The latest product information can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020685s078lbl.pdf

(Last reviewed April 2023)

Lamivudine (EPIVIR®, 3TC)

EPIVIR® (formerly known as 3TC) is a nucleoside analogue indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

Pregnancy: Available data show no difference in the overall risk of birth defects for lamivudine compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population. APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks' gestation. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown.

Animal Data: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

Human data: Based on prospective reports to the APR of over 13,000 exposures to lamivudine during pregnancy resulting in live births (including over 5,000 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.9% (95% CI: 2.5% to 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Pharmacokinetics and Transmission: Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks' gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks' gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks' gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

Animal data: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at

exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

Lactation: The Centers for Disease Control and Prevention recommends that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Lamivudine is present in human milk. There is no information on the effects of lamivudine on the breastfed infant or the effects of the drugs on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving EPIVIR.

Pediatric Use: The safety and effectiveness of EPIVIR in combination with other antiretroviral agents have been established in pediatric patients aged 3 months and older. EPIVIR scored tablet is the preferred formulation for HIV-1-infected pediatric patients who weigh at least 14 kg and for whom a solid dosage form is appropriate because pediatric subjects who received EPIVIR oral solution had lower rates of virologic suppression, lower plasma lamivudine exposure, and developed viral resistance more frequently than those receiving EPIVIR tablets in the ARROW trial.

Carcinogenicity: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg.

Mutagenesis: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver. Lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2,000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

Impairment of Fertility: In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg per kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Patient Counseling Information:

Pregnancy Registry: Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to EPIVIR during pregnancy.

Lactation: Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk.

(Last reviewed May 2023)

Lenacapavir (SUNLENCA®, LEN)

Lenacapavir, a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, which in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. SUNLENCA® is the brand name of lenacapavir and is a long-acting medication administered subcutaneously every 6 months after initiation dosage. Please refer to the local prescribing information for details.

There are insufficient human data on the use of SUNLENCA® during pregnancy to inform a drug-associated risk of birth defects and miscarriage. In animal reproduction studies, no adverse developmental effects were

observed when lenacapavir was administered to rats and rabbits at exposures (AUC) ≥16 times the exposure in humans at the recommended human dose (RHD) of SUNLENCA®.

Lenacapavir was administered intravenously to pregnant rabbits (up to 20 mg/kg/day on gestation days (GD) 7 to 19), orally to rats (up to 300 mg/kg/day on GD 6 to 17), and subcutaneously to rats (up to 300 mg/kg on GD 6). No significant toxicological effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at exposures (AUC) approximately 16 times (rats) and 39 times (rabbits) the exposure in humans at the RHD of SUNLENCA.

It is not known whether SUNLENCA® is present in human breast milk, affects human milk production, or has effects on the breastfed infant. After administration to pregnant rats, lenacapavir was detected in the plasma of nursing rat pups, without effects on these nursing pups. Lenacapavir was detected at low levels in the plasma of nursing rat pups in the pre/postnatal development study (post-natal day 10). Because of the potential for 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving SUNLENCA®.

The safety and effectiveness of SUNLENCA® have not been established in pediatric patients.

Lenacapavir was not carcinogenic in a 6-month rasH2 transgenic mouse study in males or females at doses of up to 300 mg/kg/dose once every 13 weeks. A 2-year rat carcinogenicity study is ongoing.

Lenacapavir was not mutagenic in a battery of in vitro and in vivo genotoxicity assays, including microbial mutagenesis, chromosome aberration in human peripheral blood lymphocytes, and in in vivo rat micronucleus assays.

There were no effects on fertility, mating performance or early embryonic development when lenacapavir was administered to rats at systemic exposures (AUC) 5 times the exposure to humans at the RHD of SUNLENCA®.

(Last reviewed April 2023)

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

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

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

Lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6-2.2 times (mice) and 0.5 times

(rats) the human exposure (based on AUC0-24hr measurement) at the recommended dose of 400/100 mg LPV/r twice daily. Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg LPV/r twice daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. There were no carcinogenic effects in rats. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg LPV/r twice daily regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known.

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

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

Pregnancy

Risk Summary

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

Clinical Considerations

Dose Adjustments During Pregnancy and the Postpartum Period

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

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

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

of overall birth defects and a 2 fold increase in risk of birth defects in the cardiovascular and genitourinary systems.

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

(Last reviewed October 2024)

Maraviroc (CELSENTRI®, SELZENTRY®, MVC)

SELZENTRY (maraviroc) is indicated in combination with other antiretroviral agents for the treatment of only CCR5-tropic human immunodeficiency virus type 1 (HIV-1) infection in patients 2 years of age and older weighing at least 10 kg.

Pregnancy: Limited data on the use of SELZENTRY during pregnancy from the APR and case reports are not sufficient to inform a drug-associated risk of birth defects and miscarriage. The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with maraviroc in rats at exposures (AUC) approximately 20-fold higher and in rabbits at approximately 5-fold higher than human exposures at the recommended daily dose (up to 1000 mg/kg/day in rats and 75 mg/kg/day in rabbits). During the pre-and post-natal development studies in the offspring, development of the offspring, including fertility and reproductive performance, was not affected by the maternal administration of maraviroc.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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

Animal Data: Maraviroc was administered orally to pregnant rats (up to 1,000 mg per kg per day) and rabbits (up to 75 mg per kg per day) on gestation Days 6 to 17 and 7 to 19, respectively. No adverse effects on embryo-fetal development were observed at these dose levels, resulting in exposures (AUC) approximately 20 times (rats) and 5 times (rabbits) higher than human exposures at the recommended daily dose. In the rat pre- and post-natal development study, maraviroc was administered orally at up to 1,000 mg per kg per day on gestation Day 6 to lactation/post-partum Day 20, with development of the offspring (including fertility and reproductive performance) unaffected by maternal administration of maraviroc at an exposure (AUC) approximately 14 times higher than human exposure at the recommended daily dose.

Lactation: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

There are no data on the presence of maraviroc in human milk, the effects on the breastfed infant, or the effects on milk production. When administered to lactating rats, maraviroc was present in milk [see Data]. Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving SELZENTRY.

Data: Maraviroc (and related metabolites) was excreted into the milk of lactating rats following a single oral dose of maraviroc (100 mg per kg) on lactation Day 12, with a maximal milk concentration achieved one hour post-administration at a milk concentration approximately 2.5 times that of maternal plasma concentrations.

Pediatric Use: The safety, pharmacokinetic (PK) profile, and antiviral activity of SELZENTRY were evaluated in treatment-experienced, CCR5-tropic, HIV-1-infected pediatric subjects aged 2 to less than 18 years weighing at least 10 kg in an open-label, multicenter clinical trial, A4001031 [see Adverse Reactions (6.1), Clinical Studies (14.2)]. Pharmacokinetics were evaluated in a total of 98 pediatric subjects: 85 subjects received SELZENTRY and concomitant medications that included potent CYP3A inhibitors with or without potent CYP3A inducers, 10 subjects received SELZENTRY and noninteracting medications (not containing potent CYP3A inhibitors or potent CYP3A inducers), and three subjects received SELZENTRY and medications that included potent CYP3A inducers without potent CYP3A inhibitors.

The pharmacokinetics, safety, and efficacy of maraviroc in patients younger than 2 years have not been established. Therefore, SELZENTRY is not recommended in this patient population. Additionally, there are insufficient data to make dosing recommendations for use of SELZENTRY in pediatric patients concomitantly receiving noninteracting medications and weighing less than 30 kg or in pediatric patients concomitantly receiving potent CYP3A inducers without a potent CYP3A inhibitor. Selzentry is not recommended in pre-term neonates or in pediatric patients weighing less than 2 kg.

Fertility: Maraviroc did not impair mating or fertility of male or female rats and did not affect sperm of treated male rats at approximately 20-fold higher exposures (AUC) than in humans given the recommended 300-mg twice-daily dose.

Carcinogenicity: Long-term oral carcinogenicity studies of maraviroc were carried out in rasH2 transgenic mice (6 months) and in rats for up to 96 weeks (females) and 104 weeks (males). No drug-related increases in tumor incidence were found in mice at 1,500 mg per kg per day and in male and female rats at 900 mg per kg per day. The highest exposures in rats were approximately 11 times those observed in humans at the therapeutic dose of 300 mg twice daily for the treatment of HIV-1 infection.

Mutagenesis: Maraviroc was not genotoxic in the reverse mutation bacterial test (Ames test in Salmonella and E. coli), a chromosome aberration test in human lymphocytes, and rat bone marrow micronucleus test.

Patient Counseling Information:

Pregnancy Registry: Inform patients that there is insufficient data on the safety of SELZENTRY in pregnancy. Inform patients that there is an antiretroviral pregnancy registry that monitors pregnancy outcomes in women exposed to SELZENTRY during pregnancy.

Lactation: Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk.

(Last reviewed May 2023)

Nelfinavir (VIRACEPT®, NFV)

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

Pregnancy: VIRACEPT 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 taking VIRACEPT. There were no effects on fetal development or maternal toxicity when nelfinavir was administered to pregnant rats at systemic exposures (AUC) 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.

Lactation: The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats have demonstrated that nelfinavir is excreted in milk. Based on limited published data, nelfinavir is present in low levels in human milk, and adverse effects in infants exposed to nelfinavir have been reported. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) the potential for serious adverse reactions in breastfed infants similar to those seen in adults, mothers should be instructed not to breast-feed if they are receiving VIRACEPT.

Pediatric Use: The safety, tolerability, pharmacokinetic profile and efficacy of VIRACEPT were evaluated in HIV infected pediatric patients from 2 to 13 years of age in multicenter clinical trials, Study 556 and PACTG 337. In patients less than 2 years of age, VIRACEPT was found to be safe at the doses studied, but a reliably effective dose could not be established. The pharmacokinetic profile, safety and antiviral activity of VIRACEPT in adolescent patients 13 years and older is supported by data from the adult clinical trials where some trials allowed enrolment of subjects 13 years and older. Thus, the data for adolescents and adults were analyzed collectively.

Fertility: Nelfinavir produced no effects on either male or female mating and fertility or embryo survival in rats at systemic exposures comparable to the human therapeutic exposure.

Carcinogenesis: Carcinogenicity studies in mice and rats were conducted with nelfinavir at oral doses up to 1000 mg/kg/day. No evidence of a tumorigenic effect was noted in mice at systemic exposures (C_{max}) up to 9-fold those measured in humans at the recommended therapeutic dose (750 mg TID or 1250 mg BID). In rats, thyroid follicular cell adenomas and carcinomas were increased in males at 300 mg/kg/day and higher and in females at 1000 mg/kg/day. Systemic exposures (C max) at 300 and 1000 mg/kg/day were 1-to 3-fold, respectively, those measured in humans at the recommended therapeutic dose. Repeated administration of nelfinavir to rats produced effects consistent with hepatic microsomal enzyme induction and increased thyroid hormone deposition; these effects predispose rats, but not humans, to thyroid follicular cell neoplasms.

Mutagenesis: Nelfinavir showed no evidence of mutagenic or clastogenic activity in a battery of in vitro and in vivo genetic toxicology assays. These studies included bacterial mutation assays in S. typhimurium and E. coli, a mouse lymphoma tyrosine kinase assay, a chromosomal aberration assay in human lymphocytes, and an in vivo mouse bone marrow micronucleus assay.

Patient Counseling Information:

Pregnancy Registry: Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VIRACEPT during pregnancy.

Lactation: Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk.

Contraception: Patients receiving oral contraceptives should be instructed that alternate or additional contraceptive measures should be used during therapy with VIRACEPT.

(Last reviewed November 2024)

Nevirapine (VIRAMUNE®, VIRAMUNE XR®, NVP)

Pregnancy: Risk Summary
Available data from the APR show no difference in the risk of overall major birth defects for nevirapine compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *[see Data]*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

In literature reports, immediate-release nevirapine exposure (C_{min}) can be up to 29% lower during pregnancy. However, as this reduction was not found to be clinically meaningful, dose adjustment is not necessary.

There is a risk for severe hepatic events in pregnant women exposed to VIRAMUNE. In animal reproduction studies, no evidence of adverse developmental outcomes were observed following oral administration of nevirapine during organogenesis in the rat and rabbit, at systemic exposures (AUC) to nevirapine approximately equal (rats) and 50% higher (rabbits) than the exposure in humans at the recommended 400 mg daily dose.

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

Data
Human Data
Based on prospective reports to the APR of over 2600 exposures to nevirapine during pregnancy resulting in live births (including over 1100 exposed in the first trimester), there was no difference between nevirapine and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.8% (95% CI: 1.9 %, 4.0%) following first trimester exposure to nevirapine-containing regimens and 3.2% (95% CI: 2.4%, 4.3%) for second/third trimester exposure to nevirapine-containing regimens.

There are several literature reports of chronic administration of immediate-release nevirapine during pregnancy, in which nevirapine pharmacokinetics were compared between pregnancy and postpartum. In these studies, the mean difference in nevirapine C_{min} during pregnancy as compared to postpartum ranged from no difference to approximately 29% lower.

Animal Data
Nevirapine was administered orally to pregnant rats (at 0, 12.5, 25, and 50 mg per kg per day) and rabbits (at 0, 30, 100, and 300 mg per kg per day) through organogenesis (on gestation days 7 through 16, and 6 through 18, respectively). No adverse developmental effects were observed at doses producing systemic exposures (AUC) approximately equivalent to (rats) or approximately 50% higher (rabbits) than human exposure at the recommended daily dose. In rats, decreased fetal body weights were observed at a maternally toxic dose at an exposure approximately 50% higher than the recommended daily dose.

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

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

HEPATOTOXICITY:

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

SKIN REACTIONS:

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue VIRAMUNE and seek medical evaluation immediately. Transaminase levels should be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. The 14-day lead-in period with VIRAMUNE 200 mg daily dosing has been observed to decrease the incidence of rash and must be followed.

MONITORING:

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

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

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

Lactation:

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Published data report that nevirapine is present in human milk [see Data]. There are limited data on the effects of nevirapine on the

breastfed infant. There is no information on the effects of nevirapine on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in nursing infants, mothers should not breastfeed if they are receiving VIRAMUNE.

Data
Based on five publications, immediate-release nevirapine was excreted in breast-milk at median concentrations ranging from 4080 to 6795 ng/mL, and the median maternal breast-milk to maternal plasma concentration ratio range was 59 to 88%. Reported infant nevirapine median plasma concentrations were low, ranging from 734 to 1140 ng/mL. The estimated nevirapine dose of 704 to 682 µg/kg/day for infants fed exclusively with breast-milk was lower than the daily recommended nevirapine dose for infants. Published literature indicates that rash and hyperbilirubinemia have been seen in infants exposed to nevirapine through breastmilk.

(Last reviewed April 2023)

Raltegravir (ISENTRESS®, RAL)

Indications and usage:
Adult Patients:
ISENTRESS® and ISENTRESS® HD are human immunodeficiency virus integrase strand transfer inhibitors (HIV-1 INSTI) indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients (1).

Pediatric Patients:
ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients weighing at least 2 kg (1).

ISENTRESS HD is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg (1).

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

Risk Summary
Available data from the APR show no difference in the rate of overall birth defects for raltegravir compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data).* The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk for major birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation *(see Data).*
In animal reproduction studies in rats and rabbits, no evidence of adverse developmental outcomes was observed with oral administration of raltegravir during organogenesis at doses that produced exposures up to approximately 4 times the maximal recommended human dose (MRHD) of 1200 mg *(see Data).*

Data
Human Data

Based on prospective reports from the APR of over 850 exposures to raltegravir during pregnancy resulting in live births (including over 450 exposures in the first trimester), there was no difference between the overall risk of birth defects for raltegravir compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.1% (95% CI: 1.7% to 5.1%) following first trimester exposure to raltegravir-containing regimens and 3.7% (95% CI: 2.1% to 6.0%) following second and third trimester exposure to raltegravir-containing regimens.

There are limited data on the use of ISENTRESS 1200 mg (2 x 600 mg) once daily in pregnant women.

Animal Data
In a combined embryo/fetal and pre/postnatal development study, raltegravir was administered orally to rats at doses of 100, 300, 600 mg/kg/day on gestation day 6 to 20 or from gestation day 6 to lactation day 20. No effects on pre/postnatal development were observed up to the highest dose tested. Embryofetal findings were limited to an increase in the incidence of supernumerary ribs in the 600 mg/kg/day group. Systemic exposure (AUC) at 600 mg/kg/day was approximately 3 times higher than exposure at the MRHD of 1200 mg.

In pregnant rabbits, raltegravir was administered orally at doses of 100, 500, or 1000 mg/kg/day during the gestation days 7 to 20. No embryo/fetal effects were noted up to the highest dose of 1000 mg/kg/day. Systemic exposure (AUC) at 1000 mg/kg/day was approximately 4 times higher than exposures at the MRHD of 1200 mg. In both species, raltegravir has been shown to cross the placenta, with fetal plasma concentrations observed in rats approximately 1.5 to 2.5 times greater than in maternal plasma and fetal plasma concentrations in rabbits approximately 2% that of maternal concentrations on gestation day 20.

Lactation
Risk Summary
The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. There are no data on the presence of raltegravir in human milk, the effects on the breastfed infant, or the effects on milk production. When administered to lactating rats, raltegravir was present in milk *[see Data].* Because of the potential for: 1) HIV transmission (in HIV-negative infants), 2) developing viral resistance (in HIV- positive infants), and 3) adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving ISENTRESS/ISENTRESS HD.

Data
Raltegravir was excreted into the milk of lactating rats following oral administration (600 mg/kg/day) from gestation day 6 to lactation day 14, with milk concentrations approximately 3 times that of maternal plasma concentrations observed 2 hours postdose on lactation day 14**.**

Pediatric use
ISENTRESS
HIV-1 Infected Children
The safety, tolerability, pharmacokinetic profile, and efficacy of twice daily ISENTRESS were evaluated in HIV-1 infected infants, children and adolescents 4 weeks to 18 years of age in an open-label, multicenter clinical trial, IMPAACT *P1066 [see Dosage and Administration (2.3), Clinical Pharmacology (12.3) and Clinical Studies (14.4)].* The safety profile was comparable to that observed in adults *[see Adverse Reactions (6.1)].*

HIV-1 Exposed Neonates
The safety and pharmacokinetics of ISENTRESS for oral suspension were evaluated in 42 full-term HIV-1 exposed neonates at high risk of acquiring HIV-1 infection in a Phase 1, open-label, multicenter clinical study, IMPAACT P1110. Cohort 1 neonates received 2 single doses of ISENTRESS for oral suspension: the first within 48 hours of birth and the second at 7 to 10 days of age. Cohort 2 neonates received daily dosing of ISENTRESS for oral suspension for 6 weeks: 1.5 mg/kg once daily starting within 48 hours of birth through Day 7 (week 1); 3 mg/kg twice daily on Days 8 to 28 of age (weeks 2 to 4); and 6 mg/kg twice daily on Days 29 to 42 of age (weeks 5 and 6). Sixteen neonates were enrolled in Cohort 1 (10 were exposed and 6 were unexposed to raltegravir in utero) and 26 in Cohort 2 (all unexposed to raltegravir in utero); all infants received a standard of care antiretroviral drug regimen for prevention of mother to child transmission. All enrolled

neonates were followed for safety for a duration of 24 weeks. The 42 infants were 52% male, 69% Black and 12% Caucasian. HIV-1 status was assessed by nucleic acid test at birth, week 6 and week 24; all patients were HIV-1 negative at completion of the study. The safety profile was comparable to that observed in adults *[see Adverse Reactions (6.1)].*
ISENTRESS is not recommended in pre-term neonates or in pediatric patients weighing less than 2 kg.

ISENTRESS HD
ISENTRESS HD once daily has not been studied in pediatric patients. However population PK modeling and simulation support the use of 1200 mg (2 x 600 mg) once daily in pediatric patients weighing at least 40 kg *[see Clinical Pharmacology (12.3)].*

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

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

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

(Last reviewed April 2023)

Rilpivirine (EDURANT®, REKAMBYS®, CABENUVA®, RPV)

EDURANT® (oral Rilpivirine), in combination with other antiretroviral agents, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients approved in children under 12, EDURANT and EDURANT PED, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients 2 years of age and older and weighing at least 14 kg with plasma HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

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

- More EDURANT®-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥50 copies/mL) compared to EDURANT®-treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL
- Regardless of HIV-1 RNA at the start of therapy, more EDURANT®-treated subjects with CD4+ cell count less than 200 cells/mm^3 experienced virologic failure compared to EDURANT®-treated subjects with CD4+ cell count greater than or equal to 200 cells/mm^3
- The observed virologic failure rate in EDURANT®-treated subjects conferred a higher rate of treatment resistance to a background drug and cross-resistance to the NNRTI class compared to efavirenz
    - More subjects treated with EDURANT® developed tenofovir disoproxil fumarate and lamivudine/emtricitabine-associated resistance compared to efavirenz.

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

patients 2 years of age and older and weighing at least 14 kg with plasma HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

Pregnancy:

Studies in animals with rilpivirine have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. In offspring from rats and rabbits treated with rilpivirine during pregnancy and lactation, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily. No dosage adjustment is required for pregnant patients who are already on a stable EDURANT regimen prior to pregnancy and who are virologically suppressed (HIV-1 RNA less than 50 copies per mL). Lower exposures of rilpivirine were observed during pregnancy, therefore viral load should be monitored closely.

The Antiretroviral Pregnancy Registry showed no difference in the overall risk of birth defects for rilpivirine compared with the background rate for major birth defects. In animal reproduction studies, no evidence of adverse developmental outcomes was observed following oral administration of rilpivirine.

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

Pediatric Use: EDURANT and EDURANT PED, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients 2 years of age and older and weighing at least 14 kg with plasma HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis and Mutagenesis

Rilpivirine was evaluated for carcinogenic potential in mice and rats. In rats, there were no drug related neoplasms at exposures 3 times those observed in humans at the recommended daily dose of 25 mg. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. At the lowest tested doses in the mouse carcinogenicity study, the systemic exposure (based on AUC) to rilpivirine was 21-times that observed in humans at the recommended dose (25 mg q.d.).

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

Impairment of Fertility

In rat fertility and early embryonic development studies with rilpivirine, there were no effects on fertility were observed with rilpivirine exposures (AUC) greater than 36 times (male) and 40 times (female) higher than the exposure in humans at the recommended daily dose of 25 mg.

Patient Counseling Information

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

- Pregnant or planning to become pregnant. It is not known if EDURANT® will harm your unborn baby. **Pregnancy Registry**: There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry. Tell your healthcare provider if you become pregnant during treatment with EDURANT.

- It is not known if EDURANT® can be passed to your baby in your breast milk and whether it could harm your baby. Talk with your healthcare provider about the best way to feed your baby.

(Last reviewed Nov 2024)

Ritonavir (NORVIR®, RTV)

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

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

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

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

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

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

Pregnancy
Risk Summary

Prospective pregnancy data from the Antiretroviral Pregnancy Registry (APR) are not sufficient to adequately assess the risk of birth defects or miscarriage. Available data from the APR show no difference in the rate of overall birth defects for ritonavir compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP).

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with oral administration of ritonavir to pregnant rats and rabbits. During organogenesis in the rat and rabbit, systemic exposure (AUC) was approximately 1/3 lower than human exposure at the recommended daily dose. In the rat pre- and post-natal developmental study, maternal systemic exposure to ritonavir was approximately 1/2 of the exposure in humans at the recommended daily dose, based on a body surface area conversion factor.

NORVIR oral solution is not recommended during pregnancy because there is no known safe level of ethanol exposure during pregnancy. The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Dose Adjustments During Pregnancy and the Postpartum Period
NORVIR is available in tablet, oral powder for suspension and oral solution dosage forms. NORVIR oral solution contains approx. 43% ethanol (v/v) and approx. 27% (w/v) propylene glycol and is not recommended during pregnancy because there is no known safe level of ethanol exposure during pregnancy. The tablet and oral powder dosage forms do not have these excipients.

Data

Human Data
Based on prospective reports to the APR of approximately 6100 live births following exposure to ritonavir-containing regimens (including over 2800 live births exposed in the first trimester and over 3200 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.3% (95% CI: 1.7%-2.9%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.3%-3.5%) following second and third trimester exposure to ritonavir-containing regimens. While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal Data
Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on gestation days 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at doses producing systemic exposures (AUC) equivalent to approximately 1/3 lower than human exposure at the recommended daily dose. Developmental toxicity observed in rats (early resorptions, decreased fetal body weight and ossification delays and developmental variations) occurred at a maternally toxic dose, at an exposure equivalent to approximately 1/3 lower than human exposure at the recommended daily dose. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 1/5 lower than human exposure at the recommended daily dose. Developmental toxicity was observed in rabbits (resorptions, decreased litter size and decreased fetal weights) at maternally toxic doses approximately 1.8 times higher than the recommended daily dose, based on a body surface area conversion factor. In pre-and postnatal development study in rats, ritonavir was administered at doses of 0, 15, 35, and 60 mg/kg/day from gestation day 6 through postnatal day 20. At doses of 60 mg/kg/day, no developmental toxicity was noted with ritonavir dosage equivalent to 1/2 of the recommended daily dose, based on a body surface area conversion factor.

(Last reviewed October 2024)

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

FORTOVASE® no longer manufactured as of 2006. The latest product information can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020628s032,021785s009lbl.pdf#:~:text=INVIRASE%20brand%20of%20saquinavir%20mesylate%20is%20an%20inhibitor,in%20a%20200-mg%20strength%20%28as%20saquinavir%20free%20base%29.

Stavudine (ZERIT®, d4T)

Stavudine is a nucleoside reverse transcriptase inhibitor for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV)-1 infection. Stavudine is a nucleoside analogue of thymidine is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate thymidine triphosphate (K - 0.0083 to 0.032 μM) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases β and γ and markedly reduces the synthesis of mitochondrial DNA.

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

Stavudine was not mutagenic in the Ames *E. coli* reverse mutation or the CHO/HGPRT mammalian cell forward gene mutation assays with and without metabolic activation. Stavudine produced positive results in the *in vitro* human lymphocyte clastogenesis and mouse fibroblast assays and in the *in vivo* mouse micronucleus test. In the *in vitro* assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25 to 250 μg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 μg/mL, with and without metabolic activation). In the *in vivo* micronucleus assay, stavudine was clastogenic in bone marrow cells following oral stavudine administration to mice at dosages of 600 to 2000 mg/kg/day for three days. No evidence of impaired fertility was seen in rats with exposures (based on AUC) up to 137 times human exposure at the RHD.

Pregnancy Exposure Registry

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

Risk Summary

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome, which was also reported in non-pregnant individuals receiving nucleoside analogues. **The combination of stavudine (ZERIT) and didanosine is contraindicated.** Health care providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.
Prospective pregnancy data from APR are not sufficient to adequately assess the risk of major birth defects, miscarriage or adverse developmental outcomes. Available data from the APR show no increase in overall risk of major birth defects compared with 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. In the U.S. general population, the estimated background risks of miscarriage in clinically recognized pregnancies is 15 to 20%.

In animal reproduction studies, no adverse developmental effects were observed with oral administration of stavudine at clinically relevant exposures. No developmental toxicities were observed in rats and rabbits at systemic exposures 112 (AUC) and 183 (Cmax) times, respectively, the exposures in humans at the recommended human dose (RHD) of ZERIT (see Data).

Clinical Considerations

Maternal Adverse Reactions

Cases of lactic acidosis syndrome, sometimes fatal have occurred in pregnant individuals using ZERIT in combination with didanosine. ZERIT is associated with an increased risk of lactic acidosis syndrome/hepatic steatosis syndrome.

Data

Human Data

Based on prospective reports to the APR of live births following exposure to stavudine-containing regimens during pregnancy (including 811 exposed in the first trimester and 196 exposed in the second/third trimester); the prevalence of birth defects in live births for stavudine was 2.6% (95% CI: 1.6 % to 3.9%) with first trimester exposure, and 3.1% (95% CI: 1.1% to 6.5%) with second/third trimester exposure compared to the background birth defect rate of 2.7% in the U.S. reference population of the MACDP.

Prospective reports from the APR of overall major birth defects in pregnancies exposed to ZERIT is compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations, as well as confounding due to the underlying disease.

Animal Data

Stavudine was administered orally to pregnant rats (0, 50, 250, and 1000 mg/kg/day from gestation day 6 to 17) and rabbits (0, 60, 150, 300 and 600 mg/kg/day from gestation day 6 to 18). In rats, fetal skeletal variations, including increased unossified or incomplete ossification of sternebra, were observed at the highest dose (1000 mg/kg/day) (approximately 488 times human AUC exposure at the RHD). In rabbits, there were no developmental effects up to the highest dose of 600 mg/kg (approximately 183 times human Cmax exposure at the RHD).

In the pre/post-natal development study, stavudine was administered orally to rats at 0, 50, 250, and 1000 mg/kg/day from gestation day 17 to postnatal day 21. Post-implantation loss and an increase in early neonatal mortality was observed at 1000 mg/kg/day (approximately 488 times human AUC exposure at the RHD). No developmental effects were observed at 250 mg/kg/day (approximately 112 times human AUC exposure at the RHD).

Stavudine was transferred to the fetus through the placenta in rats with concentrations in fetal tissues approximately half the concentration detected in maternal plasma.

Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

Based on limited data, stavudine has been detected in human milk. No data are available regarding the effects of stavudine on the breastfed infant, or the effects on milk production.

Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) adverse reactions in breastfed infants similar to those seen in adults, instruct mothers not to breastfeed if they are receiving ZERIT.

(Last reviewed May 2021)

Telbivudine (SEBIVO®, TYZEKA®, LdT)

Telbivudine is no longer manufactured as of 2016. The latest product information can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022011s022,022154s019lbl.pdf

Tenofovir alafenamide (VEMLIDY®, TAF)

Tenofovir alafenamide, a hepatitis B virus (HBV) and HIV-1 nucleoside analog reverse transcriptase inhibitor, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. VEMLIDY® is the brand name of tenofovir alafenamide (TAF) indicated for the treatment of chronic HBV infection in adults and pediatric patients 12 years of age and older with compensated liver disease.

TAF is the component of the single tablet regimens indicated for HIV-1 treatment; Genvoya® (150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide), Descovy® (200 mg of emtricitabine and 25 mg of tenofovir alafenamide), Odefsey® (200 mg of emtricitabine, 25 mg of rilpivirine, and 25 mg of tenofovir alafenamide), Biktarvy® (50 mg of bictegravir, 200 mg of emtricitabine, and25 mg of tenofovir alafenamide). Descovy is also approved for pre-exposure prophylaxis (PrEP). Please refer to the local prescribing information for details.

There are no human data on the use of TAF in pregnant women to inform drug-associated risks of adverse fetal developmental outcomes. Embryonic fetal development studies performed in rats and rabbits with TAF administered though organogenesis revealed no evidence of impaired fertility or harm to the fetus. The embryo-fetal NOAELs (no observed adverse effect level) in rats and rabbits occurred at TAF exposures similar to and 51 times higher than, respectively, the exposure in humans at the recommended daily dose of TAF. Tenofovir alafenamide is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 54 (rats) and 85 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Since TAF is rapidly converted to tenofovir, and lower tenofovir exposure in rats and mice were observed after tenofovir alafenamide administration compared to TDF, a pre/postnatal development study in rats was conducted only with TDF; no adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 12 times the exposure at the recommended daily dosage of TAF.

It is not known whether TAF and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. It is not known if tenofovir alafenamide can be present in animal milk. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF (tenofovir disoproxil fumarate), another prodrug for tenofovir administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TAF and any potential adverse effects on the breastfed infant from TAF or from the underlying maternal condition.

Safety of VEMLIDY in HBV-infected pediatric patients less than 12 years of age has not been established. TAF-containing products for HIV-1 indication. Descovy® and Biktarvy® are approved for the pediatric patients weighing ≥ 14 kg, Genvoya® is approved for the pediatric patients weighing ⩾ 25 kg and Odefsey® is approved for the pediatric patients weighing at least 35 kg. Please refer to the local prescribing information for details.

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

female mice, liver adenomas were increased at tenofovir exposures approximately 151 times those observed after TAF administration in humans. In rats, the study was negative for carcinogenic findings.

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

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

(Last reviewed April 2023)

Tenofovir disoproxil fumarate (VIREAD®, TDF)

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

TDF is the component of the single tablet regimens indicated for HIV-1 treatment; Atripla® (600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF), Stribild® (150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir DF) , Truvada® (200 mg of emtricitabine and 25 mg of tenofovir DF), Complera® (200 mg of emtricitabine, 25 mg of rilpivirine, and 300 mg of tenofovir DF). Truvada® is also approved for pre-exposure prophylaxis (PrEP). Please refer to the local prescribing information for details.

VIREAD® is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and in pediatric patients ≥2 years of age and weighing at least 10 kg. It is also indicated for the treatment of chronic hepatitis B in adults and in pediatric patients ≥2 years of age and weighing at least 10 kg. Published studies in HBV-infected subjects do not report an increased risk of adverse pregnancy-related outcomes with the use of VIREAD during the third trimester of pregnancy.

In published data from three controlled clinical trials, a total of 327 pregnant women with chronic HBV infection were administered VIREAD from 28 to 32 weeks gestation through 1 to 2 months postpartum and followed for up to 12 months after delivery. There were no new safety findings in pregnant women compared with the known safety profile of VIREAD in HBV-infected adults. An increased risk of adverse pregnancy-related outcomes was not observed; 2 stillbirths were identified, and there was 1 major birth defect (talipes) and 1 occurrence of multiple congenital abnormalities (not further specified) in VIREAD-exposed infants. Infants were followed for up to 12 months after delivery; there were no clinically relevant drug-related safety findings in infants exposed to VIREAD during late gestation.

No significant toxicological effects were observed in embryo-fetal toxicity studies performed with TDF in reproductive studies conducted in rats and rabbits. In a pre/postnatal development study in rats, no adverse effects were observed in the offspring.

In a study of 50 HIV-uninfected, breastfeeding women on a tenofovir-containing regimen between 1 and 24 weeks postpartum (median 13 weeks), tenofovir was undetectable in the plasma of most infants after 7 days of treatment in mothers. There were no serious adverse events in mothers or infants. For the treatment of HIV-1 infection, because of the potential for HIV-1 transmission, developing viral resistance (in HIV-positive infants), and the potential for adverse reactions in a breastfed infant similar to those seen in adults, mothers should be

instructed not to breastfeed if they are receiving VIREAD. For the treatment of HBV infection, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIREAD and any potential adverse effects on the breastfed infant from VIREAD or from the underlying maternal condition.

The safety of VIREAD in pediatric patients with HIV-1 infection aged 2 to less than 18 years is supported by data from two randomized trials in which VIREAD was administered to HIV-1 infected treatment-experienced subjects. In addition, the pharmacokinetic profile of tenofovir in patients aged 2 to less than 18 years of age at the recommended doses was similar to that found to be safe and effective in adult clinical trials. The safety of VIREAD in pediatric patients with HBV infection aged 2 years to less than 18 years is supported by data from two randomized trials in which VIREAD was administered to HBV-infected treatment-experienced subjects. For treatment of both HIV-1 and HBV infection, the effects of VIREAD-associated changes in bone mineral density (BMD), biochemical markers on long-term bone health, and future fracture risk in pediatric patients 2 years and older are unknown. Additionally, the long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients 2 years and older, and in particular, the effects of long-duration exposure in younger children, is unknown. The safety of VIREAD in pediatric patients with either HIV-1 or chronic HBV infection younger than 2 years of age and weighing less than 10kg has not been established. TDF-containing products for HIV-1 indication (Atripla®, Stribild®, and Complera®) are approved in pediatric patients ≥ 12 years of age, and Truvada is approved in pediatric patients ≥ 6 years of age. Please refer to the local prescribing information for details.

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

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

There were no effects on fertility, mating performance or early embryonic development when TDF was administered to male rats.

(Last reviewed April 2023)

Tipranavir (APTIVUS®, TPV)

Pregnancy: Prospective pregnancy data from the APR and an Expanded Access program are not sufficient to adequately assess the risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Tipranavir use during pregnancy has been evaluated in a limited number of women as reported by the APR and an Expanded Access program, and available data show no birth defects in 13 first trimester exposures *(see Data)* compared with the background rate for major birth defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. The estimated 12 background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

In animal reproduction studies, fetal toxicities were observed with tipranavir at maternally toxic doses with systemic exposures (AUC) less than those in humans at the recommended human dose (RHD).

Data
Human Data
Based on prospective reports to the APR and an Expanded Access program for approximately 17 live births following exposure to tipranavir-containing regimens (including 13 live births exposed in the first trimester and 4 live births exposed in the second/third trimester), there were no birth defects reported in live-born infants.

Tipranavir has been shown to cross the placenta.

Animal Data
Tipranavir was administered orally to pregnant rats (at 0, 40, 400, or 1000 mg/kg/day from gestation day 6 to 17) and rabbits (at 0, 75, 150, or 375 mg/kg/day from gestation day 6 to 20). In rats, fetal toxicities including decreased body weight and sternebrae ossification occurred at maternally toxic doses (≥400 mg/kg/day) (approximately 0.8 times human exposure at the RHD). In rabbits, fetal toxicities including decreased fetal body weights, wavy ribs, and bent femurs occurred at a maternally toxic dose (375 mg/kg/day) (approximately 0.05 times human exposure at the RHD). Maternal toxicity included an increased incidence of abortions at doses ≥150 mg/kg/day (approximately 0.05 times human exposure at the RHD).

In the pre/post-natal development study, tipranavir was administered orally to rats at 0, 40, 400, 1000 mg/kg/day from gestation day 6 to lactation day 21. The only significant effect observed was growth inhibition of the offspring at maternally toxic doses (≥400 mg/kg/day) (approximately 0.8 times human exposure at the RHD).

Lactation

Risk Summary
The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers in the United States not breast-feed their infants to avoid risking postnatal transmission of HIV-1 infection. There is no information regarding the presence of tipranavir in human milk, the effects on the breastfed infant, or the effects on milk production. Tipranavir is present in rat milk *(see Data)*. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive patients), and (3) any possible adverse effects of APTIVUS, mothers should not breastfeed if they are receiving APTIVUS.

Data
In a lactation study, tipranavir was excreted into the milk of lactating rats following a single oral dose of tipranavir (10 mg/kg) on lactation/postpartum day 14, with a maximal milk concentration achieved 2 hours post-administration (milk concentration 0.13 times that of maternal plasma concentration).

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

WARNING: HEPATOTOXICITY and INTRACRANIAL HEMORRHAGE

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

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

Tipranavir (APTIVUS®, TPV) is a non-peptidic HIV-1 protease inhibitor that inhibits the virus-specific processing of the viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

APTIVUS®, co-administered with ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor.

Zalcitabine (HIVID®, ddC)

HIVID® no longer manufactured as of 2006 and has been discontinued globally. The latest product information can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019910s033lbl.pdf

Zidovudine (RETROVIR®, ZDV)

RETROVIR is the brand name for zidovudine (formerly called azidothymidine [AZT]), a pyrimidine nucleoside analogue active against HIV-1, and is indicated for the prevention of maternal-fetal HIV-1 transmission.

Pregnancy: In humans, treatment with RETROVIR during pregnancy reduced the rate of maternal-fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to 7.8% for infants born to mothers treated with RETROVIR. There were no differences in pregnancy-related adverse events between the treatment groups. A randomized, double-blind, placebo-controlled trial was conducted in HIV-1-infected pregnant women to determine the utility of RETROVIR for the prevention of maternal-fetal HIV-1-transmission [see Clinical Studies (14.3)]. Congenital abnormalities occurred with similar frequency between neonates born to mothers who received RETROVIR and neonates born to mothers who received placebo. The observed abnormalities included problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

Animal Data: Increased fetal resorptions occurred in pregnant rats and rabbits treated with doses of zidovudine that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg dose of zidovudine. There were no other reported developmental anomalies. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily exposure [AUC] in humans given 600 mg per day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose.

Human Data: Based on prospective reports to the APR of over 13,000 exposures to zidovudine during pregnancy resulting in live births (including over 4,000 exposed in the first trimester), there was no difference between the overall risk of birth defects for zidovudine compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.2% (95% CI: 2.7% to 3.8%) following first trimester exposure to zidovudine-containing regimens and 2.8% (95% CI: 2.5% to 3.1%) following second/third trimester exposure to zidovudine-containing regimens.

Pharmacokinetics and Transmission: The utility of RETROVIR for the prevention of maternal-fetal HIV-1 transmission was demonstrated in a randomized, double-blind, placebo-controlled trial (ACTG 076) conducted in HIV-1-infected pregnant women with CD4+ cell counts of 200 to 1,818 cells per mm^3 (median in the treated group: 560 cells per mm^3) who had little or no previous exposure to RETROVIR. Oral RETROVIR was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by IV administration of RETROVIR during labor and delivery. Following birth, neonates received oral RETROVIR syrup for 6 weeks. The trial showed a statistically significant difference in the incidence of HIV-1 infection in the neonates (based on viral culture from peripheral blood) between the group receiving RETROVIR and the group receiving placebo. Of 363 neonates evaluated in the trial, the estimated risk of HIV-1 infection was 7.8% in the group receiving RETROVIR and 24.9% in the placebo group, a relative reduction in transmission risk of 68.7%. RETROVIR was well tolerated by mothers and infants. There was no difference in pregnancy-related adverse events between the treatment groups.

Animal Data: Increased fetal resorptions occurred in pregnant rats and rabbits treated with doses of zidovudine that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg dose of zidovudine. There were no other reported developmental anomalies. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily exposure [AUC] in humans given 600 mg per day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose.

Lactation: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving RETROVIR.

Pediatric Use: RETROVIR has been studied in HIV-1-infected pediatric subjects aged at least 6 weeks who had HIV-1-related symptoms or who were asymptomatic with abnormal laboratory values indicating significant HIV-1-related immunosuppression. RETROVIR has also been studied in neonates perinatally exposed to HIV-1.

Carcinogenicity: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg per kg per day in mice and 80, 220, and 600 mg per kg per day in rats. The doses in mice were reduced to 20, 30, and 40 mg per kg per day after Day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg per kg per day on Day 91 and then to 300 mg per kg per day on Day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

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

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg per kg per day or 40 mg per kg per day from gestation Day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine administered in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg per day or 25 mg per day (approximately 1,000 mg per kg nonpregnant body weight or approximately 450 mg per kg of term body weight) to pregnant mice from Days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

Mutagenesis: Zidovudine was mutagenic in a 5178Y/TK+/- mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in

mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Impairment of Fertility: Zidovudine, administered to male and female rats at doses up to 450 mg per kg per day, which is 7 times the recommended adult dose (300 mg twice daily) based on body surface area, had no effect on fertility based on conception rates.

Patient Counseling Information

Pregnancy: Inform pregnant women considering the use of RETROVIR during pregnancy for prevention of HIV-1 transmission to their infants that transmission may still occur in some cases despite therapy.

Pregnancy Registry: Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to RETROVIR during pregnancy.

Lactation: Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk.

(Last reviewed May 2023)

Appendix F: Methods

In an effort to assure that the Registry collects, analyzes, and presents information which is accurate and useful to the health care provider, the Registry continues to review and update its processes and procedures. These methods are presented in detail in the Registry's Monitoring, Analysis, and Termination plan (30) and are summarized here for reference.

The Registry conforms to the FDA Guidance for Industry: Establishing Pregnancy Exposure Registries (31, 32), the Guidelines for Good Pharmacoepidemiology Practices (GPP) (33), and the FDA Guidance on Pharmacovigilance (34).

In order to permit comparisons with population-expected rates, the Registry adopts definitions and best practices from two primary reference Registries, the Metropolitan Atlanta Congenital Defects Registry (MACDP) and the Texas Birth Defects Registry (TBDR) (4,5,6,7,8). Because population representativeness is a concern with any external comparison group, the use of multiple complimentary comparators is advisable. The TBDR covers the state of Texas which has a large population with a demographic distribution similar to that of the US overall. Therefore, the TBDR was added as a second external comparison group in addition to the MACDP.

Institutional Review Board (IRB) Review

The Registry is committed to the highest standards of ethical conduct; assuring patient rights, including protection of patient privacy, is a very high priority for the Registry. For this reason, the Registry sought and obtained IRB approval from Western IRB (WIRB®) in March 2000. With the IRB approval of the protocol, the Registry was granted a waiver from having to obtain patient informed consent. The IRB reviews the Registry protocol annually with annual status reports required. Additionally, the Registry reviews data privacy issues on a regular basis.

HIPAA Privacy Rule: Protecting Personal Health Information in Research

The HIPAA Privacy Rule allows covered entities (e.g., health care providers) to disclose protected health information (PHI) without subject authorization if the covered entity obtains documentation that an Institutional Review Board has waived the requirement for authorization (35).

On April 29, 2003, Western Institutional Review Board (WIRB) approved a request for a waiver of authorization for use and disclosure of PHI. WIRB determined that documentation received from this Registry satisfies the three requirements for a waiver of authorization. These requirements are:

1. The use or disclosure of the PHI involves no more than minimal risk to the individuals, based on the following elements:

    a. an adequate plan to protect identifiers from improper use and disclosure;

    b. an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law); and

    c. adequate written assurances that the PHI will not be reused or redisclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use of disclosure of PHI would be permitted by HIPAA.

2. The research could not be practicably conducted without access to and use of the PHI; and

3. The research could not practicably be conducted without the waiver.

The Board determined that a waiver of authorization for use of the following PHI is needed and approved for this research:

> Information about subjects on antiretroviral drugs during pregnancy, including dates of services, estimated date of delivery, date of last menstrual period, dates of exposure to antiretroviral drugs and date of pregnancy outcome.

Registration and Follow-up

The Antiretroviral Pregnancy Registry collects data on use of abacavir, abacavir/dolutegravir/lamivudine, abacavir/lamivudine, abacavir/lamivudine/zidovudine, adefovir dipivoxil, amprenavir, atazanavir, atazanavir/cobicistat, bictegravir/tenofovir alafenamide, cabotegravir, cobicistat, darunavir, darunavir/cobicistat, darunavir/cobicistat/emtricitabine/tenofovir alafenamide, delavirdine mesylate, didanosine, dolutegravir, dolutegravir/lamivudine, dolutegravir/lamivudine/tenofovir disoproxil fumarate, dolutegravir/rilpivirine, doravirine, doravirine/lamivudine/tenofovir disoproxil fumarate, efavirenz, efavirenz/tenofovir disoproxil fumarate/emtricitabine, efavirenz/lamivudine/tenofovir disoproxil fumarate, elvitegravir, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, emtricitabine/tenofovir alafenamide, emtricitabine/tenofovir disoproxil fumarate, enfuvirtide, entecavir, etravirine, fosamprenavir calcium, fostemsavir, indinavir, lamivudine, lamivudine/raltegravir, lamivudine/tenofovir disoproxil fumarate, lamivudine/zidovudine, lenacapavir, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpivirine, rilpivirine/emtricitabine/tenofovir alafenamide, rilpivirine/emtricitabine/tenofovir disoproxil fumarate, ritonavir, saquinavir, stavudine, telbivudine, tenofovir alafenamide, tenofovir disoproxil fumarate, tipranavir, zalcitabine, and zidovudine during pregnancy. There are risks associated with any new chemical entity or combination therapy and the historic precedent of less specific antiviral agents causing genetic damage. The Registry requests information on antiretroviral therapy, though there may be other exposures to other drugs, which are not systematically collected. As more data are collected in the Registry, clinicians will be provided with updated information on the use of these drugs during pregnancy.

Registration is voluntary. Health professionals are strongly encouraged to enroll their antiretroviral-exposed pregnant people 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.

People 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 emailing completed forms. Copies of the current forms are included in this report and are also available on the website.

In an attempt to limit the bias in the analysis, the Registry has begun assembling a group of providers who have committed in writing to report to the Registry every prospective antiretroviral therapy exposure during pregnancy that comes to their site. This will allow the Registry to include every report from that site as an evaluable case. As the number of cases from these sites increases, the Registry will be able to analyze these cases separately. Providers are encouraged to participate in this group.

Registration Process

The minimum requirements for an evaluable case are: a prospective report with clear information on the antiretroviral therapy exposure during pregnancy, source of the report, enough information to search for duplicate reporting of a case (e.g., LMP, EDD, maternal age). If follow-up information on the outcome of the pregnancy is unavailable, a case may be considered lost to follow-up. Cases were rendered unevaluable or lost to follow-up if the reporting health care provider could no longer locate the patient to provide pregnancy outcome data, if after numerous attempts, there are no follow-up data forthcoming from the health care provider, or if the birth outcome is missing or indication of a defect is marked as unknown. **Only data from evaluable prospective cases with known outcomes were summarized in this report.**

To preserve the patient's confidentiality, registration is conducted through the health care provider rather than the patient. The Registry *assigns* patient LOG ID numbers rather than using a patient ID chosen by the provider. This is the ID with which the Registry communicates to the site regarding a patient. To obtain a Registry-assigned LOG ID:

- **Notify the Registry:** The health care provider should notify the Registry of the pregnancy exposure by phone, email or fax (as early in pregnancy as possible, preferably before prenatal testing for defects is done). The Registry will assign a sequential number to the provider for that patient. This number is used to identify the patient when communicating with the Registry for follow-up.

  (If necessary, a block of numbers may be obtained by providers who enroll people into the Registry on a regular basis.)

- **Patient Log:** The Registry provides a patient log sheet as a possible way a provider might cross-reference the identity of the patient at the site to the Registry LOG ID. (This log sheet is for the provider's use only and must be kept in a secure place separate from the patient charts to protect patient confidentiality at the site.)

The Registry prefers and encourages prospective registration, which is defined as registration of a pregnancy prior to knowledge of the pregnancy outcome. The outcome of pregnancy is defined at the time of delivery or fetal loss, or when a defect reported at enrollment is detected on a prenatal test (e.g., structural defect noted on an ultrasound). Retrospective reports (i.e., reports made after the pregnancy outcome is known), are welcomed and carefully reviewed by the Registry. However, retrospective reports may be biased toward more abnormal outcomes and are less likely to be representative of the general population experience. Therefore, the retrospective outcomes are summarized independent of the prospective outcomes. Due to difficulty in obtaining follow-up, retrospective reports with outcomes without defects over two years prior to receipt by the Registry are not included. Retrospective reports of exposed infants with defects can be useful in the identification of patterns of defects suggestive of common etiology.

*The Registry is interested in identifying and receiving written commitment from providers who are willing to report **all** of their site's antiretroviral pregnancy exposures to the Registry. The Registry encourages providers to become part of this special group. Please contact the Registry by email, phone, or fax to receive more information on how to participate. Emails can be sent to SM_APR@APRegistry.com. Call 1-800-258-4263 or Fax 1-800-800-1052 (or Fax to 1-910-256-0637 for International). 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 email (SM_APR@APRegistry.com), fax transmission to +1-800-800-1052 (US, Canada), +1-910-256-0637 (International), or by calling the Registry at +1-800-258-4263. After receipt of the registration information, the Registry will send a follow-up form and a copy of the antiretroviral therapy information reported at registration to ascertain the outcome of the pregnancy and additional therapy information.

Review of Birth Defects Identified

The Advisory Committee reviews all reports of birth defects. Initial review, request for further information (as necessary), and assessment are conducted by a consultant geneticist trained on MACDP classification and the Registry evaluation process by staff at the CDC, Division of Birth Defects and Developmental Disabilities (36). At the semi-annual Steering Committee meeting, the Advisory Committee reviews each of the defect reports with the consultant's evaluations and reaches a consensus on the final assessment.

Classification of Outcomes

The Registry is intended to provide an early signal of teratogenicity associated with prenatal use of antiretroviral therapy for those drugs monitored in the Registry. This is accomplished through monitoring the pregnancy and birth outcomes following pregnancy exposure to an antiretroviral drug. Pregnancy outcomes are mutually exclusive and include spontaneous pregnancy loss, induced abortion, stillbirth, fetal death due to maternal death, and live birth. Stillbirth refers to fetuses born dead at or after 20 weeks gestation or weighing greater than 500 grams. However, the Registry will accept the health care provider's determination for spontaneous pregnancy loss or stillbirth. From time to time, the Registry receives cases resulting in induced abortion and the reporter is reluctant to code the outcome as such because induced abortions are illegal in the particular country. The Registry is sensitive to such cultural issues. For the purposes of reporting, unspecified abortions are coded as induced when they are received from countries in which induced abortions are illegal.

The Registry defines a birth defect as any major structural or chromosomal defect diagnosed by six years of age, or any cluster of two or more conditional abnormalities. In addition, any structural or chromosomal defect detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, fetus, or deceased infant is evaluated. All birth defects are reviewed and classified by the consultant geneticist using a widely-recognized system for standardized public health surveillance of birth defects (4). The Registry's definition of birth defects is consistent with, but not restricted to this list. Clusters of conditional abnormalities (defects of secondary importance) and data from abortuses of ≥20 weeks, when available, have been included to increase the sensitivity of Registry monitoring. Public health surveillance cases have at least one major defect, regardless of whether conditional defects are also present. The Registry includes these cases, but differs from the public health protocols by additionally considering reports of two (2) or more conditional defects alone as a "defect case", so as to cast as broad a net as possible for outcomes that may be associated with antiretroviral medication use.

The Registry focuses on birth defect data detected and reported during the perinatal period. To protect the privacy of the mother, the Registry limits contact to the health care provider who initiated the report, which is usually the mother's health care provider. Most major structural defects and clusters of conditional abnormalities are readily apparent at birth. However, underascertainment of other birth defects is possible since follow-up is usually obtained from the mother's health care provider in the immediate postnatal period and not by the infant's pediatrician who is more likely to observe defects not easily detected during the neonatal period (such as some cardiac or intestinal abnormalities). The Registry does update case reports if information is received on any birth defect diagnosed or with signs/symptoms occurring up to six years of age, however, this information is not systematically collected.

Certain conditions, such as hepatomegaly and/or splenomegaly, are considered conditional birth defects if they occur at birth. These conditions can also be acquired after birth. To attempt to avoid misclassifying

conditions that are acquired after birth as congenital birth defects, such conditions are not coded as birth defects if they are clearly diagnosed after one week of birth.

The Registry differentiates “conditional” defects, the terminology and classification used by MACDP and TBDR, from “minor” defects, a medical term sometimes applied but which lacks the required specificity for population monitoring. The Registry does not systematically collect, but accepts information on minor abnormalities, as well as transient or infectious conditions or biochemical abnormalities that reporting clinicians deem important. Since these data are not systematically collected, their utility is very limited. It is therefore out of the scope of this Registry to evaluate information on other clinical conditions associated with pregnancy or events at outcome which are not considered defects. These other events are subject to monitoring and evaluation by other sources. Providers are encouraged to report information on events not monitored by the Registry to the manufacturer of the drug and/or the FDA.

Organ System Classification

To facilitate the ability to identify a potential signal, the Registry uses an organ system classification based on the British Pediatric Association (BPA) (37), World Health Organization, and MACDP (4, 5, 6) systems that are in common use in public health birth defect surveillance (13). The classification of similar defects or defects with similar etiology into groups reduces granularity and increases the possibility of identifying a potential signal. Once a potential signal is identified, the individual defect cases can be evaluated.

What follows is the scheme used to place specific defects within an organ system.

The purpose of the list is two-fold. The organ system categories represent groups of defects with presumed common embryologic pathogenesis. Defects are not grouped by genetic or environmental etiology. Syndromes are listed within the organ system categories when all components of the syndrome can be found in that category.

Individual defect terms are the most common in current use. Defects are passively reported using various terminologies, even when the defects themselves are the same. Upon case review, the reported defects are given the standard terminology from the organ system list. This eliminates artifactual variation and facilitates analysis.

The result is a three-level hierarchy of defect classification:

Organ System Classification	***Defect Std Terminology***	***Reported Defect***
Cleft lip and/or palate	Cleft lip of any type without cleft palate	• L cleft lip • Unilateral cleft alveolus • Cleft lip

The value of the system is its ability to decrease granularity to facilitate detection of a potential cluster of events identifying a potential signal. Once the potential signal is identified, reanalysis of the individual components within the cluster can be conducted to determine whether or not the signal is cause for concern.

Medical terminology and knowledge of embryogenesis does evolve over time. This list will be reviewed intermittently and updated as needed. Also, the standard defect terminology and organ system classifications are relatively general. If a general defect term is used frequently, it will be evaluated to see if more specific terminology is warranted for that defect.

Analysis

An important aspect of the Registry is the Registry Steering Committee comprising the Advisory Committee and Sponsor representatives. The Registry Advisory Committee consists of members from the CDC, FDA, NIH, and private sector. Membership consists of specialists in maternal and fetal medicine, infectious disease, teratology, epidemiology, and biostatistics. The Sponsor Company members are from AbbVie, Alvogen Inc, Amneal Pharmaceuticals LLC, Apotex Inc, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb

Company, Cipla Ltd, Dr. Reddy's Laboratories Inc, Gilead Sciences Inc, Hetero Labs Ltd, Hikma Pharmaceuticals USA Inc., i3 Pharmaceuticals, Janssen Scientific Affairs, LLC, Lannett Company, Inc., Laurus Labs, Lupin Pharmaceuticals, Macleods Pharmaceuticals Ltd., Merck & Co. Inc, Mylan Inc., a Viatris Company, Pharmascience, Qilu Pharmaceuticals Company Ltd., SigmaPharm Laboratories, Strides Pharma Science Limited, Teva Pharmaceuticals USA Inc, ViiV Healthcare, Yung Shin Pharm., and Zydus Pharmaceuticals. This Steering Committee oversees the Registry process and reviews the results from the Registry data. The Antiretroviral Pregnancy Registry Interim Report is prepared semi-annually, summarizing the aggregate data collected by the Registry. Since the report contains historical information as well as new data, each report completely supercedes all previous reports. This report is available to health care providers who treat this specialized population or to any health care provider who requests a report.

Data analysis is conducted on prospective, closed cases for which adequate follow-up exists. In addition, these cases must meet the following minimum criteria for evaluation:

- Documentation that a Registry drug was taken during pregnancy
- Timing of the prenatal exposure to the Registry medication (no broader than which trimester)
- Source of report (patient or health care provider, self-reported or through Sponsor Companies)
- Documentation on whether the patient was enrolled in a study conducted in pregnancy, during the reported pregnancy

As patients participating in a clinical study involving use of antiretrovirals in pregnancy must meet certain selection criteria and may be followed more closely than people 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 (6). The prevalence of birth defects is calculated by dividing the number of outcomes with reported birth defects by the total number of live births. Spontaneous losses and induced abortions with or without birth defects are excluded from the denominator to be consistent with the calculation used by the MACDP, which is the primary comparator for the Registry. Defects reported in pregnancies terminating before 20 weeks are included in this report (Appendix C) and reviewed with other related defects, but not included in rate calculations. MACDP birth defect rates published in 2007 differ from previously published rates in part due to re-classification of congenital cardiac defects that resulted in improved specificity of cardiac diagnoses and elimination of normal physiologic variants and obligatory shunt lesions (7). Beginning with 2001 data, the TBDR case definition includes all major defects in the calculation of birth defect rates regardless of the gestational age at outcome (8). Prior to then, only pregnancy outcomes occurring at 20 weeks gestation or greater were actively identified. As the behavior of a specific antiretroviral may differ widely from others in its drug classification, it is reasonable to prepare an

analysis that would highlight potential increased risk for a given compound. For such an analysis, exposures to a given antiretroviral will be summarized according to the earliest trimester of that exposure.

Studies have shown that risk of spontaneous pregnancy loss in the general population is high early in pregnancy and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 14-22% (38). Although the Steering Committee carefully reviews each pregnancy outcome, calculation of risk of spontaneous pregnancy losses attributable to drug intervention overall is outside the scope of the Registry and should not be attempted because pregnancies in this Registry may be reported at variable and imprecise times during gestation. Further, the reader is reminded of the context in which this Registry is conducted, i.e., generally an HIV-positive population, often with advanced disease, at possibly increased risk of adverse outcomes of pregnancy unrelated to teratology. This Registry is not designed to monitor these unrelated effects.

The Advisory Committee uses the following concepts to review the data: The general population risk of birth defects meeting the CDC criteria is approximately 3% of live births (39, 40). The overall prevalence of birth defects by year (1968-1999 ranges from 2% to 5%). The baseline risk of a specific birth defect may be as low as 1-2 per 1000 live births or less.

Given the inherent difficulties in identifying a comparison group, three different methods are used to review the data for signals of teratogenicity. First, the prevalence of birth defects in the Registry is compared to the prevalence observed in population-based birth defect surveillance systems including the MACDP and TBDR. The MACDP reports a total prevalence of birth defects identified among births from 1968 through 2003 of 2.67%; the prevalence of birth defects identified among births in the years that most closely mirror the years APR has been in operation (1989-2003) was 2.72% (95% CI 2.68, 2.76)[*] (6). The TBDR reports an overall prevalence of birth defects of 4.17% (95% CI 4.15, 4.19) for deliveries during 2000 through 2009 among people who were residents of Texas at the time of delivery (8). The prevalence of “early diagnoses” is important for Registry comparisons since the majority of outcome reports are from obstetricians who may have limited access to diagnoses made after the day of birth. The MACDP, TBDR, and other population-based registries ascertain defect cases by active review of medical records. This Registry’s methods differ by using voluntary registration with active solicitation of outcome data.

As a second method of analysis, an internal comparison is made between the risk of birth defects among people with first trimester exposures to antiretroviral medications and the risk of birth defects among people with second or third trimester exposures to antiretroviral medications. Prevalence ratios and 95% confidence intervals (41) are calculated to assess the presence or absence of any excess risk associated with timing of the exposure. A third is a qualitative analysis of cases for the emergence of any unique defects or patterns of defects.

For all birth defects combined, a cohort of 200 newborns exposed to antiretroviral drugs in the first trimester is sufficient to detect a 2.2 fold increased risk of birth defects compared to a general US population prevalence of 3% (40), with 80% power and a Type I error rate of 5%. Once the Registry experience with an individual drug reaches this threshold of 200 first trimester exposures, the drug specific overall birth defect rate and 95% CI is calculated and reported. A cohort of 1000 is sufficient to detect a 1.5 fold increased risk of birth defects. For specific defects, the power to detect an increased risk varies depending on the frequency of the defect in the population and the evolving size of the exposed group.

Defect Monitoring Plan

The intent of the Registry is to provide useful information to health care providers on the outcomes of pregnancy following prenatal exposure to antiretroviral therapy, including determination if there is a signal that might indicate a potential risk of a major defect in the offspring. Therefore, it is necessary to determine in the

[*] 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.

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 (30) (monograph available upon request).

Information about the Registry can be found in other Registry publications and presentations (42 - 93).

Appendix G: Data Collection Forms

Registry Enrollment / Patient Enrollment Forms

The case-registration approach for collecting information depends on the continued participation of health care providers who register people 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 products being followed in this Registry include:

Product Name:	**Manufactured by:**
abacavir (ZIAGEN®, ABC)	ViiV HealthCare
abacavir (generic)	Apotex, Aurobindo Pharma*, Cipla, Hetero Labs, Mylan Inc., Strides Pharma Science
abacavir+dolutegravir+lamivudine (TRIUMEQ®, TRI)	ViiV HealthCare
abacavir+dolutegravir+lamivudine (generic)	Hetero Labs
abacavir+lamivudine (EPZICOM®, KIVEXA®, EPZ)	ViiV HealthCare
abacavir+lamivudine (generic)	Apotex, Aurobindo Pharma*, Cipla, Dr. Reddys*, Hetero Labs, Laurus Labs, Lupin Pharmaceuticals, Mylan Inc.*, Pharmascience, Teva Pharmaceuticals USA*
abacavir+lamivudine+zidovudine (TRIZIVIR®, TZV)	ViiV HealthCare
abacavir+lamivudine+zidovudine (generic)	Apotex, Hetero Labs, Lupin Pharmaceuticals
adefovir dipivoxil (HEPSERA®, ADV)	Gilead Sciences
adefovir dipivoxil (generic)	Apotex, SigmaPharm Laboratories
amprenavir (AGENERASE®, APV)*	ViiV HealthCare
atazanavir (REYATAZ®, ATV)	Bristol-Myers Squibb Company
atazanavir (generic)	Aurobindo Pharma*, Amneal Pharmaceuticals, Cipla, Hetero Labs, Laurus Labs
atazanavir+cobicistat (EVOTAZ®, EVO)	Bristol-Myers Squibb Company
bictegravir+emtricitabine+tenofovir alafenamide (BIKTARVY®, BVY)	Gilead Sciences
bictegravir+emtricitabine+tenofovir alafenamide (generic)	Hetero Labs
cabotegravir (VOCABRIA®, CABENUVA®, APRETUDE®, CAB)	ViiV HealthCare
cobicistat (TYBOST®, COBI)	Gilead Sciences
darunavir (PREZISTA®, DRV)	Janssen Scientific Affairs
darunavir (generic)	Amneal Pharmaceuticals, Apotex, Dr. Reddy's, Hetero Labs, Lupin Pharmaceuticals, Sandoz Canada*, Teva Pharmaceuticals USA, Zydus Pharmaceuticals
darunavir+cobicistat (PREZCOBIX™, REZOLSTA™, PCX)	Janssen Scientific Affairs
darunavir+cobicistat+emtricitabine+tenofovir alafenamide (SYMTUZA®, DCF TAF)	Janssen Scientific Affairs
delavirdine mesylate (RESCRIPTOR®, DLV)*	ViiV HealthCare
didanosine (VIDEX®, VIDEX® EC, ddI)	Bristol-Myers Squibb Company
didanosine (generic)	Aurobindo Pharma*, Mylan Inc.*, Teva Pharmaceuticals USA*
dolutegravir (TIVICAY®, DTG)	ViiV HealthCare

Product Name:	Manufactured by:
dolutegravir (generic)	Hetero Labs, Mylan Inc.
dolutegravir+lamivudine (DOVATO®, DTG+3TC)	ViiV HealthCare
dolutegravir+lamivudine+tenofovir disoproxil fumarate (ACRIPTEGA/TELADOMYL/TENDOLA™, TLD)	Mylan Inc.
dolutegravir+lamivudine+tenofovir disoproxil fumarate (generic)	Hetero Labs
dolutegravir+rilpivine (JULUCA®, DTG+RPV)	ViiV HealthCare
doravirine (PIFELTRO™, PIF)	Merck & Co.
doravirine+lamivudine+tenofovir disoproxil fumarate (DELSTRIGO™, DEL)	Merck & Co.
efavirenz (SUSTIVA® / STOCRIN®, EFV)	Bristol-Myers Squibb Company / Merck & Co.
efavirenz (generic)	Aurobindo Pharma*, Cipla, Hetero Labs, MacLeods Pharmaceuticals, Mylan Inc.*, Strides Pharma Science
efavirenz+emtricitabine+tenofovir disoproxil fumarate (ATRIPLA®, ATR)	Gilead Sciences
efavirenz+emtricitabine+tenofovir disoproxil fumarate (generic)	Apotex, Aurobindo Pharma*, Hetero Labs, Laurus Labs, MacLeods Pharmaceuticals, Mylan Inc., Pharmascience, Sandoz Canada*, Teva Pharmaceuticals USA, Zentiva*
efavirenz+lamivudine+tenofovir disoproxil fumarate (SYMFI™ / SYMFI LO™, EFV/3TC/TDF)	Mylan Inc.
efavirenz+lamivudine+tenofovir disoproxil fumarate (generic)	Aurobindo Pharma*, Hetero Labs, Laurus Labs, Macleods Pharmaceuticals
elvitegravir (VITEKTA®, EVG)	Gilead Sciences
elvitegravir+cobicistat+emtricitabine+tenofovir alafenamide (GENVOYA®, GEN)	Gilead Sciences
elvitegravir+cobicistat+emtricitabine+tenofovir disoproxil fumarate (STRIBILD®, STB)	Gilead Sciences
emtricitabine (EMTRIVA®, FTC)	Gilead Sciences
emtricitabine (generic)	Cipla, Hetero Labs
emtricitabine+tenofovir alafenamide (DESCOVY®, DVY)	Gilead Sciences
emtricitabine+tenofovir alafenamide (generic)	Hetero Labs, Mylan Inc.
emtricitabine+tenofovir disoproxil fumarate (TRUVADA®, TVD)	Gilead Sciences
emtricitabine+tenofovir disoproxil fumarate (generic)	Apotex, Amneal Pharmaceuticals, Aurobindo Pharma*, Dr. Reddy's*, Hetero Labs, Laurus Labs, Lupin Pharmaceuticals, Macleods Pharmaceuticals, Mylan Inc., Pharmascience, Sandoz Canada*, Teva Pharmaceuticals USA, Zentiva*
emtricitabine+tenofovir disoproxil maleate (generic)	Mylan Inc.
enfuvirtide (FUZEON®, T-20)	F.Hoffman-La Roche*
entecavir (BARACLUDE®, ETV)	Bristol-Myers Squibb Company
entecavir (generic)	Accord Healthcare*, Amneal Pharmaceuticals, Apotex, Aurobindo Pharma*, Cipla, Hetero Labs, Pharmascience, Prinston*, Teva Pharmaceuticals USA*, Yung Shin Pharm.
etravirine (INTELENCE®, ETR)	Janssen Scientific Affairs
etravirine (generic)	Amneal Pharmaceuticals

Product Name:	Manufactured by:
fosamprenavir calcium (LEXIVA®, FOS)	ViiV HealthCare
fosamprenavir calcium (generic)	Mylan Inc.
fostemsavir (RUKOBIA®, FTR)	ViiV HealthCare
indinavir (CRIXIVAN®, IDV)	Merck & Co.
indinavir (generic)	Hetero Labs
lamivudine (EPIVIR®, ZEFFIX®, HEPITEC, HEPTODIN, HEPTOVIR, 3TC)	ViiV HealthCare
lamivudine (generic)	Apotex, Aurobindo Pharma*, Cipla, Lannett Company*, Hetero Labs, Lupin Pharmaceuticals, Macleods Pharmaceuticals, Mylan Inc.*, Strides Pharma Science
lamivudine+raltegravir (DUTREBIS™, DUT)*	Merck & Co.
lamivudine+tenofovir disoproxil fumarate (CIMDUO™, 3TC+TDF)	Mylan Inc.
lamivudine+tenofovir disoproxil fumarate (generic)	Aurobindo Pharma*, Celltrion*, Hetero Labs
lamivudine+zidovudine (COMBIVIR®, CBV)	ViiV HealthCare
lamivudine+zidovudine (generic)	Apotex, Aurobindo Pharma*, Cipla, Hetero Labs, Lupin Pharmaceuticals, MacLeods Pharmaceuticals, Mylan Inc.*, Strides Pharma Science, Teva Pharmaceuticals USA*
lenacapavir (SUNLENCA®, LEN)	Gilead Sciences
lopinavir+ritonavir (KALETRA®, ALUVIA®, LPV/r)	AbbVie
lopinavir+ritonavir (generic)	Hetero Labs, Lannett Company, Laurus Labs
maraviroc (SELZENTRY®, CELSENTRI®, MVC)	ViiV HealthCare
maraviroc (generic)	Hetero Labs, i3 Pharmaceuticals
nelfinavir (VIRACEPT®, NFV)	Pfizer Inc (distributed by ViiV HealthCare)
nevirapine (VIRAMUNE®, VIRAMUNE XR®, NVP)	Boehringer Ingelheim Pharmaceuticals Inc
nevirapine/nevirapine ER (generic)	Alvogen, Apotex*, Aurobindo Pharma*, Cipla, Hetero Labs, MacLeods Pharmaceuticals, Mylan Inc., Prinston*, Sandoz*, Sciegen*, Strides Pharma Science, Teva Pharmaceuticals USA*
raltegravir (ISENTRESS®, RAL)	Merck & Co.
raltegravir (generic)	Hetero Labs
rilpivirine (EDURANT®, REKAMBYS®, CABENUVA®, RPV)	Janssen Scientific Affairs
rilpivirine+emtricitabine+tenofovir alafenamide (ODEFSEY®, ODE)	Gilead Sciences
rilpivirine+emtricitabine+tenofovir disoproxil fumarate (COMPLERA®, CPA; EVIPLERA®, EPA)	Gilead Sciences
ritonavir (NORVIR®, RTV)	AbbVie
ritonavir (generic)	Amneal Pharmaceuticals, Aurobindo Pharma*, Hetero Labs, Hikma Pharmaceuticals USA
saquinavir mesylate (INVIRASE®, SQV-HGC) / saquinavir soft gel (FORTOVASE®, SQV-SGC)*	F.Hoffman-La Roche*
saquinavir mesylate (generic)	Hetero Labs
stavudine (ZERIT®, d4T)	Bristol-Myers Squibb Company
stavudine (generic)	Aurobindo Pharma*, Cipla, Hetero Labs, Mylan Inc.*
telbivudine (SEBIVO®, TYZEKA®, LdT)*	Sandoz*
tenofovir alafenamide (VEMLIDY®, TAF)	Gilead Sciences
tenofovir alafenamide (generic)	Hetero Labs
tenofovir disoproxil fumarate (VIREAD®, TDF)	Gilead Sciences

Product Name:	Manufactured by:
tenofovir disoproxil fumarate (generic)	Apotex, Aurobindo Pharma*, Cipla, Dr. Reddys*, Hetero Labs, Laurus Labs*, Macleods Pharmaceuticals, Mylan Inc.*, Pharmascience, Qilu Pharmaceuticals, Strides Pharma Science, Zentiva*
tipranavir (APTIVUS®, TPV)	Boehringer Ingelheim Pharmaceuticals
zalcitabine (HIVID®, ddC)*	F.Hoffman-La Roche*
zidovudine (RETROVIR®, ZDV)	ViiV HealthCare
zidovudine (generic)	Apotex, Aurobindo Pharma*, Cipla, Hetero Labs, Hikma Pharmaceuticals, Ipca*, Mylan Inc.*, Ranbaxy*, Sunshine Lake*, ViiV HealthCare

***** Either no longer manufactured or no longer participating in the Registry

The Registry encourages the reporting of all known pregnancy exposures to a Registry drug, but prospectively reported cases are preferred. Registry enrollment and follow-up forms may be obtained by contacting the Pregnancy Registry or the included data forms may be photocopied. Prospective or retrospective notifications of prenatal exposures to therapies followed by the Registry can be registered by contacting the Registry via email, phone, or fax.

Instructions for Completing Forms

Patient Anonymity and Patient Identifiers

The Registry makes every effort to assure patient confidentiality within the Registry. The Registry does not collect identifying information such as maternal date of birth, initials, or chart number. The patient identifier is a Registry-assigned number provided to the reporter at the time the patient is enrolled (patient LOG ID).

Patient LOG ID numbers can be obtained by calling, emailing, or faxing the Registry Office for a number (or a block of numbers, for providers who register people on a regular basis). The Registry also provides a Patient Log as a possible way the reporter might cross-reference the patient with the Registry ID number. Whatever method is used, this record must be kept in a secure place separate from patient charts to assist in protecting patient confidentiality at your site.

Prospective Registration

Registration and Therapy Forms (To be completed when notifying Registry of prenatal exposure while patient is still pregnant.)

- Contact the Registry via phone, email or fax to obtain a patient ID number

Telephone:
+1-800-258-4263

Fax:
+1-800-800-1052 (toll free US, Canada)
+1-910-256-0637 (International)

Email: SM_APR@APRegistry.com

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

- Track the Registry-assigned patient ID number with your own identification of the patient
  - Secure the tracking log to protect patient confidentiality
- Photocopy the Registration Form pages from the report or print from the APR Website
- Complete as much information as is available at the time of reporting
- Report as early as possible after the pregnancy exposure is known
- Return the Registration Forms to the Registry by email or fax

Follow-up: In the month of the estimated date of delivery, the reporter will be sent a two-page Follow-Up Form with a copy of the originally submitted Antiviral Therapy during Pregnancy Form. Please complete the information on the Follow-up Form and update the Antiviral Therapy during Pregnancy Form with any therapy modifications or additions since registration.

Retrospective Registration

Registration and Follow-Up Forms (To be completed when notifying Registry of prenatal exposure *after* the pregnancy outcome is known.)

- Contact the Registry via phone, email or fax to obtain a patient ID number

Telephone:
+1-800-258-4263

Fax:
+1-800-800-1052 (toll free US, Canada)
+1-910-256-0637 (International)

Email: SM_APR@APRegistry.com
***Website*:** www.APRegistry.com (for data forms and information)

- Track the Registry-assigned patient ID number with your own identification of the patient
  - Secure the tracking log to protect patient confidentiality
- Photocopy both the Registration, Therapy and Follow-Up Forms pages or print from the APR Website
- Complete as much information as is available to you
- Return the Registration, Therapy and Follow-Up Forms to the Registry (by email or fax)

Data Forms included (see next 10 pages)

KEEP IN A SECURE PLACE TO PROTECT PATIENT CONFIDENTIALITY

HCP: <INSERT>

THE ANTIRETROVIRAL PREGNANCY REGISTRY
PATIENT LOG

Call or Email the Registry for Additional Patient ID Numbers
(Contact information below)

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 Log ID number.

This log is provided for your convenience. You should use this to track your Registry enrollments and to easily cross-reference the APR Registry assigned Log ID with your patient.

THIS IS FOR YOUR USE ONLY.

PLEASE DO NOT RETURN THIS TO THE REGISTRY.

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 Registration form completed**	**Date APR Outcome form completed**
Ex.) 03000	*Jane Doe*	*123656*	*Jun. 1, 2015*	*Dec. 3, 2014*	*Jun. 15, 2015*

Email:	SM_APR@APRegistry.com
Phone:	800-258-4263 (US/Canada toll-free)
Fax:	800-800-1052 (US/Canada toll-free) +1-910-256-0637 (International)
Website:	www.APRegistry.com

CONFIDENTIAL

The Antiretroviral Pregnancy Registry

Instructions for Completing the REGISTRATION FORM

General Guideline: Date format should always be entered as *DD/MMM/YYYY* (e.g., 14Oct2024)

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

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

1. Maternal Information

1.1 Clinical Study: Indicate if the patient is participating in a clinical study by checking "Yes", "No", or "Unknown".

- If no, move to Subsection 1.2
- If yes, provide the study protocol number and indicate whether the study was conducted in pregnant people by checking "Yes" or "No"

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

1.3 Was a Dating Ultrasound performed: Indicate if a dating ultrasound was performed on the patient.

- If no, move to Subsection 1.4
- If yes, provide the date of the ultrasound and the Corrected Estimated Date of Delivery (CEDD) from the test.

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

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

2. Prenatal Tests

2.1 Prenatal Test Done: Indicate if a prenatal test was done by checking "Yes", "No", or "Unknown".

- If no, move to Section 3: Clinical Indicators.
- If yes, check the prenatal test performed and provide the date in *DD/MMM/YYYY* format, or the gestational age. If "Other (specify)" is selected list the name of the prenatal test (i.e., Ultrasound, Amniocentesis, MSAFP).

2.2 Evidence of a Structural Defect or genetic abnormality: Indicate if a structural defect(s) and/or a genetic abnormality was identified on a prenatal test by checking "Yes", "No" or "Unknown" by each prenatal test done.

- If no, move to Section 3: Clinical Indicators.
- If yes, specify the structural and/or chromosomal defect(s).

3. Clinical Indicators (at the START of pregnancy)

3.1 Indication for ARV/AV (Check all that apply)

3.2 Earliest CD4 + T-cell Categories (in this pregnancy): Check the appropriate range for the counts as they were as close to the beginning of the pregnancy (not applicable should be marked if the patient is not HIV infected).

Instructions for Completing the Antiviral Therapy During Pregnancy Form

4. Antiretroviral therapy exposures

- Indicate if the patient has received any long-acting injectable antiretroviral in the 24 months prior to conception by checking "Yes" or 'No".
  - If no, move to subsection 4.1.
  - If yes, provide
    - **Med Code:** Indicate the code number from the list provided in subsection 4.2
    - **Date of Injection:** Provide the dates of the **two** most recent injections prior to conception in the DD/MMM/YYYY format.
  - Long-acting injections administered during pregnancy should be reported in subsection 4.1.

4.1 Medications during pregnancy

- **Med Code:** Indicate the code number from the list provided in subsection 4.2. If a drug is not listed, provide the name of the drug.
- **Total Daily Dose:** Provide the total daily dose with units (e.g., 80 mg, 2 tabs, 2 mg/kg/hr, etc.).
- **Route:** Provide the code "1" for oral, "2" for IV, and "3" for subcutaneous (sub-Q).
- **Pt taking Meds at Conception?:** "1" if yes at conception, "2" if during pregnancy, "3" if unknown.
- **Date Treatment Began or Gestational Age Course Began:**
  - Provide start date in *DD/MMM/YYYY* format, ***OR*** provide gestational age course began.
- **Date Treatment Stopped or Ongoing:**
  - Provide date or gestation week treatment stopped in *DD/MMM/YYYY* format, ***OR***
  - Check "Ongoing" if treatment continues following outcome of pregnancy.

4.2 Medication codes

- **Medication codes**: List of registered antiretroviral/ antiviral products with correlating code. If a drug is not listed, provide the name of the drug in subsection 4.1.

Please write "unk" or "N/A" on the forms if any information is unknown or not applicable.

The Registry is not designed to monitor all types of events that might occur during pregnancy, labor and delivery, or other neonatal or post-natal events other than defects. If such events occur the provider is encouraged to contact the manufacturer of the individual drug and/or the FDA. FDA can be reached by faxing the information to 800-FDA-0178 or at http://www.fda.gov/Safety/MedWatch/default.htm

ANTIRETROVIRAL PREGNANCY REGISTRY

REGISTRATION FORM

Fax to: 1-800-800-1052 (US, Canada)
+1-910-256-0637 (International)

Email to: SM_APR@APRegistry.com

FOR OFFICE USE ONLY

Registry Patient ID _____ HCP ID _____

Prospective ☐ Retrospective ☐ 100% Provider ☐

Registry date of notification _____ _____ _____ ☐ Phone
DD MMM YYYY

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

Country of report origin_____ **State *(U.S. only)***_____

Date patient first seen during this pregnancy or Sponsor date of notification of pregnancy
Date: _____ _____ _____
DD MMM YYYY

1. MATERNAL INFORMATION

1.1 Is the patient enrolled in a clinical study? *(treatment or observational study)* ☐ Yes ☐ No ☐ Unknown

If yes, provide the protocol number _____

Was the clinical study conducted in pregnant people? ☐ Yes ☐ No ☐ Unknown

1.2 Last Menstrual Period _____ _____ _____
DD MMM YYYY

1.3 Was a Dating Ultrasound performed? ☐ Yes ☐ No ☐ Unknown

If yes, provide the date of ultrasound _____ _____ _____
DD MMM YYYY

Corrected EDD from test _____ _____ _____ *(e.g., by ultrasound)*
DD MMM YYYY

1.4 Patient Age: _____ *(at conception)*

1.5 Race: ☐ White ☐ Black ☐ Hispanic ☐ Asian ☐ Other (specify) _____

2. PRENATAL TESTS*

2.1 Was a prenatal test done?

☐ No *(go to section 3)*
☐ Yes
☐ Unknown *(go to section 3)*

Date OR Gestational Age when test(s) done:

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

(✓) test(s)

☐ Ultrasound _____ date	☐Yes ☐No ☐Unknown. If yes, Specify finding _____
☐ Ultrasound _____ date	☐Yes ☐No ☐Unknown. If yes, Specify finding _____
☐ Ultrasound _____ date	☐Yes ☐No ☐Unknown. If yes, Specify finding _____
☐ Cell-free DNA_____ date	☐Yes ☐No ☐Unknown. If yes, Specify finding _____
☐ Amniocentesis _____ date	☐Yes ☐No ☐Unknown. If yes, Specify finding _____
☐ Fetal Echo _____ date	☐Yes ☐No ☐Unknown. If yes, Specify finding _____
☐ Other (specify):_____ date	☐Yes ☐No ☐Unknown. If yes, Specify finding _____
☐ Other (specify):_____ date	☐Yes ☐No ☐Unknown. If yes, Specify finding _____
☐ Other (specify):_____ date	☐Yes ☐No ☐Unknown. If yes, Specify finding _____

*Note the APR is no longer collecting prenatal tests that do not indicate a true structural or genetic defect.

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

3.1 Indication for ARV/AV *(√all that apply)*:

☐ HIV Treatment
☐ HIV Prevention
  ☐ Post-Exposure Prophylaxis (PEP)
  ☐ Pre-Exposure Prophylaxis (PrEP)
☐ Hepatitis B
☐ Hepatitis C

3.2 Earliest CD4+ T-cell Category *(in this pregnancy)*

☐ ≥ 500 cells/μL
☐ 200-499 cells/μL
☐ <200 cells/μL
☐ Not applicable

Complete applicable information on: ANTIVIRAL THERAPY DURING PREGNANCY Form

HEALTH CARE PROVIDER INFORMATION

Name	_____	Specialty	_____
Address	_____	Phone	_____
	_____	Fax	_____
Alternate Contact	_____	Email	_____
Provider's Signature	_____	Date	_____ _____ _____ DD MMM YYYY

CONFIDENTIAL

ANTIRETROVIRAL PREGNANCY REGISTRY

ANTIRETROVIRAL/ANTIVIRAL THERAPY EXPOSURE FORM

(Initiated at registration and completed at follow-up)

FOR OFFICE USE ONLY
Registry ID_____
HCP ID_____
☐ Update

Complete as much of this page as applicable at Registration. A copy of this form will be sent to you in the expected month of delivery for completion.

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

4. ANTIRETROVIRAL THERAPY EXPOSURES

*Has the patient previously been exposed to any long-acting injectable antiretroviral during 24 months **PRIOR TO CONCEPTION**?*

☐ *Yes* ☐ *No*

*If yes, provide the dates of the last **two** injections **PRIOR TO CONCEPTION** (Injections administered **DURING PREGNANCY** should be entered in 4.1 below):*

Med. Code #: _____ Date of Injection: _____ (DD-MMM-YYYY)

Date of Injection: _____ (DD-MMM-YYYY)

Med. Code #: _____ Date of Injection: _____ (DD-MMM-YYYY)

Date of Injection: _____ (DD-MMM-YYYY)

Calculation Source (FOR OFFICE USE ONLY)
☐***LMP*** ☐***corrected EDD***

4.1. MEDICATIONS DURING PREGNANCY

*In the following table, describe each course or change in route for each applicable therapy taken DURING PREGNANCY. Any **changes to frequency** of antiretroviral injections administered during pregnancy should be listed separately. All registered therapies are listed in section 4.2 for your reference. If the therapy is missing from list, please specify medication name and manufacturer in table below.*

Course *(FOR OFFICE USE ONLY)*	***Med. Code*** ***if no code indicated, please write medication name and indicate if generic***	***Blinded therapy?***	***Dose***	***Unit*** ***- mg*** ***- tab./cap.*** ***- mg/kg*** ***- mL***	***Frequency*** ***1 = hourly*** ***2 = daily*** ***3 = weekly*** ***4 = monthly*** ***5 = bimonthly***	***Route*** ***1 = Oral*** ***2 = IV*** ***3 = SubQ/IM***	***Pt Taking Med. Prior to Conception?*** ***1 = Yes*** ***2 = No*** ***3 = Unknown***	***Date Treatment Course Began*** *(DD-MMM-YYYY)* ***OR*** ***Gestational Age Course Began*** (0 weeks = prior to conception)	***Date Treatment Stopped*** *(DD-MMM-YYYY),* ***Gestational Week Course stopped*** ***OR*** ***Ongoing following delivery?***
		☐							**or ☐ ongoing**
		☐							**or ☐ ongoing**
		☐							**or ☐ ongoing**
		☐							**or ☐ ongoing**
		☐							**or ☐ ongoing**
		☐							**or ☐ ongoing**
		☐							**or ☐ ongoing**
		☐							**or ☐ ongoing**
		☐							**or ☐ ongoing**
		☐							**or ☐ ongoing**
		☐							**or ☐ ongoing**

Complete as much of this page as applicable at Registration. A copy of this form will be sent to you in the expected month of delivery for completion.

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

4.2 Use the medication codes below for antiviral medication taken during pregnancy (see section 4.1). If not coded, Specify medication name and manufacturer in table above.

1. Abacavir (ZIAGEN®, ABC) – ViiV
1.1 Abacavir generic – Hetero
1.2 Abacavir generic – Apotex
1.3 Abacavir generic – Mylan
1.4 Abacavir generic – Strides
1.5 Abacavir generic – Aurobindo (no longer partic.)
1.6 Abacavir generic – Cipla
1.99 Abacavir generic (unknown manufacturer)
2. Didanosine (VIDEX®, VIDEX® EC, ddI) – BMS
2.1 Didanosine generic – Teva (no longer manuf.)
2.2 Didanosine generic – Aurobindo (no longer manuf.)
2.3 Didanosine generic – Mylan (no longer manuf.)
2.99 Didanosine (unknown manufacturer)
3. Efavirenz (SUSTIVA®, EFV) – BMS
3.1 Efavirenz (STOCRIN™, EFV) – Merck
3.2 Efavirenz generic – Hetero
3.3 Efavirenz generic – Aurobindo (no longer partic.)
3.4 Efavirenz generic – Mylan (no longer manuf.)
3.5 Efavirenz generic – Strides
3.6 Efavirenz generic – Cipla
3.7 Efavirenz generic – Macleods
3.99 Efavirenz (unknown manufacturer)
4. Lamivudine (EPIVIR®, ZEFFIX®, 3TC, HEPITEC, HEPTODIN, HEPTOVIR) – ViiV
4.1 Lamivudine generic – Hetero
4.2 Lamivudine + tenofovir dispoproxil fumarate generic – Hetero (no longer manuf.)
4.3 Lamivudine generic – Apotex
4.4 Lamivudine generic – Aurobindo (no longer partic.)
4.5 Lamivudine generic – Lannett (no longer manuf.)
4.6 Lamivudine generic – Lupin
4.7 Lamivudine generic – Mylan (no longer manuf.)
4.8 Lamivudine generic – Cipla
4.9 Lamivudine generic – Strides
4.10 Lamivudine generic – Macleods
4.99 Lamivudine (unknown manufacturer)
5. Lamivudine+zidovudine (COMBIVIR®, CBV) – ViiV
5.1 Lamivudine+zidovudine generic – Hetero
5.2 Lamivudine+zidovudine generic – Teva (no longer manuf.)
5.3 Lamivudine+zidovudine generic – Aurobindo (no longer partic.)
5.4 Lamivudine+zidovudine generic – Lupin
5.5 Lamivudine+zidovudine generic – Strides
5.6 Lamivudine+zidovudine generic – Mylan (no longer manuf.)
5.7 Lamivudine+zidovudine generic – Macleods
5.8 Lamivudine+zidovudine generic – Cipla
5.9 Lamivudine+zidovudine generic – Apotex
5.99 Lamivudine+zidovudine generic (unknown manufacturer)
6. Nelfinavir (VIRACEPT®, NFV) – ViiV/Pfizer
7. Nevirapine (VIRAMUNE®, VIRAMUNE® XR™, NVP) – BI
7.1 Nevirapine generic – Hetero
7.2 Nevirapine generic – Prinston (no longer partic.)
7.3 Nevirapine/nevirapine ER generic – Sciegen (no longer manuf.)
7.4 Nevirapine/nevirapine ER generic – Apotex (no longer manuf.)
7.5 Nevirapine/nevirapine ER generic – Aurobindo (no longer partic.)
7.6 Nevirapine generic – Strides
7.7 Nevirapine ER generic – Sandoz (no longer partic.)
7.8 Nevirapine/nevirapine ER generic – Cipla
7.9 Nevirapine ER generic – Alvogen
7.10 Nevirapine ER generic – Teva (no longer manuf.)
7.11 Nevirapine/nevirapine ER generic – Mylan
7.12 Nevirapine/Nevirapine ER generic – Macleods
7.99 Nevirapine (unknown manufacturer)
8. Ritonavir (NORVIR®, RTV) – AbbVie
8.1 Ritonavir generic – Hikma
8.2 Ritonavir generic – Amneal
8.3 Ritonavir generic – Aurobindo (no longer partic.)
8.4 Ritonavir generic – Hetero
8.99 Ritonavir (unknown manufacturer)
9. Saquinavir (FORTOVASE®, SQV-SGC) – Roche (no longer manuf./ no longer partic.)
9.1 Saquinavir generic – Hetero
9.99 Saquinavir (unknown manufacturer)
10. Saquinavir mesylate (INVIRASE®, SQV-HGC) – Roche (no longer partic.)
11. Stavudine (ZERIT®, d4T) – BMS
11.1 Stavudine generic – Mylan (no longer manuf.)
11.2 Stavudine generic – Aurobindo (no longer manuf.)
11.3 Stavudine generic – Cipla
11.4 Stavudine generic – Hetero
11.99 Stavudine generic (unknown manufacturer)
12. Zalcitabine (HIVID®, ddC) – Roche (no longer manuf./ no longer partic.)
13. Zidovudine (RETROVIR®, ZDV) – ViiV
13.1 Zidovudine oral generic – Ranbaxy (no longer manuf.)
13.2 Zidovudine oral generic – ViiV
13.3 Zidovudine oral generic – Hikma
13.4 Zidovudine oral generic – Aurobindo (no longer partic.)
13.5 Zidovudine oral generic – Cipla
13.6 Zidovudine oral generic – Mylan (no longer manuf.)
13.7 Zidovudine oral generic – Hetero
13.8 Zidovudine oral generic – Sunshine Lakes (no longer manuf.)
13.9 Zidovudine oral generic – Ipca (no longer manuf.)
13.10 Zidovudine oral generic – Apotex
13.99 Zidovudine oral (unknown manufacturer)
14. Amprenavir (AGENERASE®, APV) – ViiV (no longer manuf.)
15. Indinavir (CRIXIVAN®, IDV) – Merck
15.1 Indinavir generic – Hetero
15.99 Indinavir (unknown manufacturer)
16. Delavirdine mesylate (RESCRIPTOR®, DLV) – ViiV (no longer manuf.)
17. Lopinavir+ritonavir (KALETRA®, ALUVIA®, LPV/r) – Abbvie
17.1 Lopinavir+ritonavir generic – Lannett
17.2 Lopinavir+ritonavir generic – Laurus Labs
17.3 Lopinavir+ritonavir generic – Hetero
17.99 Lopinavir+ritonavir (unknown manufacturer)
18. Abacavir+lamivudine+zidovudine (TRIZIVIR®, TZV) – ViiV
18.1 Abacavir+lamivudine+zidovudine generic – Lupin
18.2 Abacavir+lamivudine+zidovudine generic – Apotex
18.3 Abacavir+lamivudine+ zidovudine generic – Hetero
18.99 Abacavir+lamivudine+zidovudine (unknown manufacturer)
19. Tenofovir disoproxil fumarate (VIREAD®, TDF) – Gilead
19.1 Tenofovir disoproxil fumarate generic – Hetero
19.2 Tenofovir disoproxil fumarate generic – Apotex
19.3 Tenofovir disoproxil maleate generic – Mylan
19.4 Tenofovir disoproxil phosphate generic – Zentiva (no longer partic.)
19.5 Tenofovir disoproxil succinate generic – Dr. Reddys (no longer partic.)
19.6 Tenofovir disoproxil fumarate generic – Aurobindo (no longer partic.)
19.7 Tenofovir disoproxil fumarate generic – Macleods
19.8 Tenofovir disoproxil fumarate generic – Strides
19.9 Tenofovir disoproxil fumarate generic – Zentiva (no longer partic.)
19.10 Tenofovir disoproxil fumarate generic – Qilu
19.11 Tenofovir disoproxil fumarate generic – Laurus Labs (no longer manuf.)
19.12 Tenofovir disoproxil fumarate generic – Mylan (no longer manuf.)
19.13 Tenofovir disoproxil fumarate generic – Cipla
19.14 Tenofovir disoproxil fumarate generic – Pharmascience
19.99 Tenofovir disoproxil fumarate (unknown manufacturer)
20. Adefovir dipivoxil (HEPSERA®, ADV) – Gilead
20.1 Adefovir dipivoxil generic – SigmaPharm
20.2 Adefovir dipivoxil generic – Apotex
20.99 Adefovir dipivoxil (unknown manufacturer)
21. Enfuvirtide (FUZEON®, T-20) – Roche (no longer partic.)
22. Atazanavir (REYATAZ®, ATV) – BMS
22.1 Atazanavir generic – Aurobindo (no longer partic.)
22.2 Atazanavir generic – Cipla
22.3 Atazanavir generic – Amneal
22.4 Atazanavir generic – Laurus Labs
22.5 Atazanavir generic – Hetero
22.99 Atazanavir (unknown manufacturer)
23. Emtricitabine (EMTRIVA®, FTC) – Gilead
23.1 Emtricitabine generic – Cipla
23.2 Emtricitabine generic – Hetero
23.99 Emtricitabine (unknown manufacturer)
24. Fosamprenavir calcium (LEXIVA®, FOS) – ViiV
24.1 Fosamprenavir calcium generic – Mylan

ANTIRETROVIRAL PREGNANCY REGISTRY

ANTIRETROVIRAL/ANTIVIRAL THERAPY EXPOSURE FORM

(Initiated at registration and completed at follow-up)

FOR OFFICE USE ONLY

Registry ID_____

HCP ID_____

☐ Update

Complete as much of this page as applicable at Registration. A copy of this form will be sent to you in the expected month of delivery for completion.

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

24.99 Fosamprenavir calcium (unknown manufacturer)
25. Abacavir+lamivudine (EPZICOM®, KIVEXA®, EPZ) – ViiV
25.1 Abacavir+lamivudine generic – Teva (no longer manuf.)
25.2 Abacavir+lamivudine generic – Dr. Reddy's (no longer partic.)
25.3 Abacavir+lamivudine generic – Aurobindo (no longer partic.)
25.4 Abacavir+lamivudine generic – Cipla
25.5 Abacavir+lamivudine generic – Lupin
25.6 Abacavir+lamivudine generic – Mylan (no longer manuf.)
25.7 Abacavir+lamivudine generic – Pharmascience
25.8 Abacavir+lamivudine generic – Apotex
25.9 Abacavir+lamivudine generic – Laurus Labs
25.10 Abacavir+lamivudine generic – Hetero
25.99 Abacavir+lamivudine (unknown manufacturer)
26. Tenofovir disoproxil fumarate+emtricitabine (TRUVADA®, TVD) – Gilead
26.1 Tenofovir disoproxil fumarate+emtricitabine generic – Apotex
26.2 Tenofovir disoproxil maleate+emtricitabine generic – Mylan
26.3 Tenofovir disoproxil fumarate+emtricitabine generic – Dr. Reddy's (no longer partic.)
26.4 Tenofovir disoproxil fumarate+emtricitabine generic – Zentiva (no longer partic.)
26.5 Tenofovir disoproxil fumarate+emtricitabine generic – Aurobindo (no longer partic.)
26.6 Tenofovir disoproxil fumarate+emtricitabine generic – Zentiva (no longer partic.)
26.7 Tenofovir disoproxil fumarate+emtricitabine generic – Amneal
26.8 Tenofovir disoproxil phosphate+emtricitabine generic – Teva
26.9 Tenofovir disoproxil phosphate+emtricitabine generic – Macleods
26.10 Tenofovir disoproxil fumarate+emtricitabine generic – Laurus Labs
26.11 Tenofovir disoproxil fumarate+emtricitabine generic – Pharmascience
26.12 Tenofovir disoproxil fumarate+emtricitabine generic – Sandoz (no longer partic.)
26.13 Tenofovir disoproxil fumarate+emtricitabine generic – Lupin
26.14 Tenofovir disoproxil fumarate+emtricitabine generic – Hetero
26.15 Tenofovir disoproxil fumarate+emtricitabine generic – Mylan
26.99 Tenofovir disoproxil fumarate+emtricitabine generic – (unknown manuf.)
27. Entecavir (BARACLUDE®, ETV) – BMS
27.1 Entecavir generic – Teva (no longer manuf.)
27.2 Entecavir generic – Aurobindo (no longer partic.)
27.3 Entecavir generic – Amneal
27.4 Entecavir generic – Cipla
27.5 Entecavir generic – Accord (no longer partic.)
27.6 Entecavir generic – Prinston (no longer partic.)
27.7 Entecavir generic – Pharmascience
27.8 Entecavir generic – Hetero
27.9 Entecavir generic – Apotex
27.10 Entecavir generic – Yung Shin Pharm
27.99 Entecavir (unknown manufacturer)
28. Tipranavir (APTIVUS®, TPV) – BI
29. Efavirenz+tenofovir disoproxil fumarate+emtricitabine (ATRIPLA®, ATR) – Gilead
29.1 Efavirenz+tenofovir disoproxil phosphate+emtricitabine generic – Teva
29.2 Efavirenz+tenofovir disoproxil phosphate+emtricitabine generic – Zentiva (no longer partic.)
29.3 Efavirenz+tenofovir disoproxil maleate+emtricitabine generic – Mylan
29.4 Efavirenz+tenofovir disoproxil maleate+emtricitabine generic – Aurobindo (no longer partic.)
29.5 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Macleods
29.6 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Pharmascience
29.7 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Sandoz (no longer partic.)
29.8 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Laurus Labs
29.9 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Apotex
29.10 Efavirenz+tenofovir disoproxil fumarate+emtricitabine generic – Hetero
29.99 Efavirenz+ tenofovir disoproxil fumarate+emtricitabine (unknown manufacturer)
30. Telbivudine (TYZEKA®, LdT) – Novartis/Sandoz (no longer manuf.)
30.1 Telbivudine (SEBIVO®, LdT) – Novartis/Sandoz (no longer manuf.)
31. Darunavir (PREZISTA®, DRV) – Janssen
31.1 Darunavir generic – Teva
31.2 Darunavir generic – Sandoz Canada (no longer partic.)
31.3 Darunavir generic – Apotex
31.4 Darunavir generic – Lupin
31.5 Darunavir generic – Hetero
31.6 Darunavir generic – Amneal
31.7 Darunavir generic – Dr. Reddy's
31.8 Darunavir generic – Zydus Pharmaceuticals (USA) Inc
31.99 Darunavir (unknown manufacturer)
32. Raltegravir (ISENTRESS®, RAL) – Merck
32.1 Raltegravir generic – Hetero
32.99 Raltegravir (unknown manufacturer)
33. Maraviroc (SELZENTRY®, CELSENTRI®, MVC) – ViiV
33.1 Maraviroc generic – i3 Pharmaceuticals
33.2 Maraviroc generic – Hetero
33.99 Maraviroc (unknown manufacturer)
34. Etravirine (INTELENCE®, ETR) – Janssen
34.1 Etravirine generic – Amneal
34.99 Etravirine (unknown manufacturer)
35. Rilpivirine (EDURANT®, RPV) – Janssen
36. Rilpivirine+emtricitabine+tenofovir disoproxil fumarate (COMPLERA®, CPA; EVIPLERA® EPA) – Gilead
37. Elvitegravir+cobicistat+emtricitabine+tenofovir disoproxil fumarate (STRIBILD®, SB) – Gilead
38. Dolutegravir (TIVICAY®, DTG) – ViiV
38.1 Dolutegravir generic – Mylan
38.2 Dolutegravir generic – Hetero
38.99 Dolutegravir (unknown manufacturer)
39. Elvitegravir (VITEKTA®, EVG) – Gilead
40. Cobicistat (TYBOST®, COBI) – Gilead
41. Abacavir+dolutegravir+lamivudine (TRIUMEQ®, TRI) – ViiV
41.1 Abacavir+dolutegravir+lamivudine generic – Hetero
41.99 Abacavir+dolutegravir+lamivudine (unknown manufacturer)
42. Darunavir+cobicistat (PREZCOBIX™, REZOLSTA™, PCX) – Janssen
43. Atazanavir+cobicistat (EVOTAZ™, EVO) – BMS
44. Lamivudine+raltegravir (DUTREBIS™, DUT) – Merck (no longer manuf.)
45. Elvitegravir+cobicistat+emtricitabine+tenofovir alafenamide (GENVOYA®, GEN) – Gilead
46. Rilpivirine+emtricitabine+tenofovir alafenamide (ODEFSEY®, ODE) – Gilead
47. Emtricitabine+tenofovir alafenamide (DESCOVY®, DVY) – Gilead
47.1 Emtricitabine+tenovfovir alafenamide generic – Mylan
47.2 Emtricitabine+tenovfovir alafenamide generic – Hetero
47.99 Emtricitabine+tenovfovir alafenamide (unknown manufacturer)
48. Tenofovir alafenamide (VEMLIDY®, VEM) – Gilead
48.1 Tenovfovir alafenamide generic – Hetero
48.99 Tenovfovir alafenamide (unknown manufacturer)
49. Dolutegravir+ rilpivirine (JULUCA®, DTG+RPV) – ViiV
50. Efavirenz+lamivudine+tenofovir disoproxil fumarate (SYMFI LO™, SYMFI™, EFV+3TC+TDF) – Mylan
50.1 Efavirenz+lamivudine+tenofovir disoproxil fumarate – Aurobindo (no longer partic.)
50.2 Efavirenz+lamivudine+tenofovir disoproxil fumarate – Macleods
50.3 Efavirenz+lamivudine+tenofovir disoproxil fumarate – Laurus Labs
50.4 Efavirenz+lamivudine+tenofovir disoproxil fumarate – Hetero
50.99 Efavirenz+lamivudine+tenofovir disoproxil fumarate (unknown manufacturer)
51. Lamivudine+tenofovir disoproxil fumarate (CIMDUO™, 3TC+TDF) – Mylan
51.1 Lamivudine+tenofovir disoproxil fumarate generic – Hetero
51.2 Lamivudine+tenofovir disoproxil fumarate generic – Aurobindo (no longer partic.)
51.3 Lamivudine+tenofovir disoproxil fumarate (TEMIXYS™) – Celltrion (no longer partic.)
51.99 Lamivudine+tenofovir disoproxil fumarate (unknown manufacturer)
52. Bictegravir+emtricitabine+tenofovir alafenamide (BIKTARVY®, BVY) – Gilead
52.1 Bictegravir+ Emtricitabine+Tenofovir alafenamide generic – Hetero
52.99 Bictegravir+ Emtricitabine+Tenofovir alafenamide (unknown manufacturer)
53 Doravirine (PIFELTRO™, PIF) – Merck
54. Doravirine+lamivudine+tenofovir disoproxil fumarate (DELSTRIGO™, DEL) – Merck
55. Dolutegravir+lamivudine+tenofovir disoproxil fumarate (ACRIPTEGA™, TLD) – Mylan
55.1 Dolutegravir+lamivudine+Tenofovir disoproxil fumarate generic – Hetero
55.99 Dolutegravir+lamivudine+Tenofovir disoproxil fumarate (unknown manufacturer)
56. Dolutegravir+lamivudine (DOVATO®) – ViiV
57. Darunavir+cobicistat+emtricitabine+tenofovir alafenaminde (SYMTUZA®, DCF TAF) – Janssen
58. Fostemsavir (RUKOBIA®, FTR) – ViiV
59. Cabotegravir (VOCABRIA®, CABENUVA®, APRETUDE®, CAB) – ViiV
60. Rilpivirine (REKAMBYS®, CABENUVA®, RPV) – Janssen
61. Lenacapavir (SUNLENCA®, LEN) – Gilead

The Antiretroviral Pregnancy Registry

Instructions for completing the FOLLOW-UP FORMS

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

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

Please indicate **UNK** or **N/A** for any data points where the information is unknown or not applicable.

1. Maternal Information

1.1 **Clinical Study:** Indicate if the patient is participating in a clinical study by checking "Yes", "No", or "Unknown".

- If no, move to Subsection 2 and do not check a response for "Was the clinical study conducted in pregnant women?"
- If yes, provide the study protocol number and check "Yes," "No" or "Unknown" for "Was the clinical study conducted in pregnant women?"

2.1 Clinical Indication:

- Indication for ARV/AV (select all that appl at time of outcome)

2. Fetal Outcome

If there are multiple outcomes (e.g., twins, triplets) complete a Follow-up Form for each baby.

2. 1 **Birth Defect Noted:** *Was a structural birth defect noted?* Check "Yes", "No", or "Unknown".

- If no, move to section 2.2: Outcome.
- If yes, list each specific defect in Section 3: Birth Defects.
- If unknown, the case will not be included in the Registry analysis.

2.2 **Outcome:** Check the applicable outcome: "Live Infant", "Spontaneous abortion*", "Induced abortion", or "Stillbirth*".

*(A **spontaneous abortion** is defined by the Registry as a fetal loss occurring earlier than 20 weeks. A **stillbirth** is a fetal death occurring greater than or equal to 20 weeks, or if the fetus weighs 500 grams or more.)

- If either Spontaneous or Induced abortion or Stillbirth is checked, list the factors that may have had an impact on the fetal loss in Section 4: Fetal Loss.

2.3 **Date of Outcome:** Provide the outcome date of the live infant or date the fetal loss occurred in *DD/MMM/YYYY* format.

2.4 **Gender:** Check the appropriate gender: "Male" or "Female".

2.5 **Length:** Provide the length of the infant at outcome and the appropriate metric used ("centimeter" or "inch").

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

2.7 **Birth Weight:** Provide the birth weight of the infant at outcome and the appropriate metric used (grams or pounds/ounces).

2.8 **Head Circumference:** Provide the infant's head circumference at outcome and the appropriate metric used ("centimeter" or "inch").

3. Birth Defects

- List the structural birth defect(s)
- Indicate if the defect(s), was attributed to the antiviral therapy by recording:
  - 1 for Yes
  - 2 for No
  - 3 for Unknown
- Indicate other factors that might have contributed to this outcome by recording:
  - 1 for Maternal Age
  - 2 for Unknown
  - 3 for Other, specify. *If other, please specify the contributing factor.*

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

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

****ANTIVIRAL THERAPY DURING PREGNANCY FORM**

Update the "Antiviral Therapy During Pregnancy" data form provided at Registration once outcome is obtained.

The Registry is not designed to monitor all types of events that might occur during pregnancy, labor and delivery, or other neonatal or post-natal events other than defects. If such events occur the provider is encouraged to contact the manufacturer of the individual drug and/or FDA. FDA can be reached by faxing the information to 800-FDA-0178 or at http://www.fda.gov/medwatch/.

ANTIRETROVIRAL PREGNANCY REGISTRY FOLLOW-UP FORM

Fax to: 1-800-800-1052 (US, Canada)
+1-910-256-0637 (International)
Email to: SM_APR@APRegistry.com

FOR OFFICE USE ONLY (3)
Registry Patient ID _____ HCP ID _____
Date Case Closed _____ _____ _____ ☐ Phone
DD MMM YYYY

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

1. MATERNAL INFORMATION

1.1 Is the patient enrolled in a clinical study? *(treatment or observational study)* ☐ Yes ☐ No ☐ Unknown

If yes, provide the protocol number _____

Was the clinical study conducted in pregnant women? ☐ Yes ☐ No ☐ Unknown

1.2 Please confirm clinical indication for current ARV/AV exposure (select all that apply at time of outcome)

- ☐ HIV Treatment
- ☐ HIV Prevention
  - ☐ Post-Exposure Prophylaxis (PEP)
  - ☐ Pre-Exposure Prophylaxis (PrEP)
- ☐ Hepatitis B
- ☐ Hepatitis C

2. FETAL OUTCOME

2.1 Birth Defect Noted? ☐ Yes *(If yes, list on page 4)* ☐ No ☐ Unknown

2.2 Outcome:

- ☐ Live Infant
- ☐ Abortion, Spontaneous
- ☐ Abortion, Induced
- ☐ Stillbirth
- ☐ Fetal loss due to maternal death

FOR REGISTRY USE ONLY
Baby ID: _____

If a fetal loss, go to page 4: Birth Defects (section 3) and/or other factors that may have contributed to the fetal loss (section 4)

2.3 Date of Outcome: _____ _____ _____ (DD MMM YYYY)

2.4 Gender: ☐ Male ☐ Female

2.5 Length: _____ ☐ cm. ☐ in.

2.6 Gestational Age: _____ weeks

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

2.8 Head Circumference: _____ ☐ cm. ☐ in.

NOTES:

- **If DEFECT or FETAL LOSS, go to page 4**
- **Please update the ANTIVIRAL THERAPY DURING PREGNANCY FORM when reporting pregnancy outcome. The form includes the initial information provided to the Registry at registration.**

HEALTH CARE PROVIDER INFORMATION

Name _____ Specialty _____
Address _____ Phone _____
_____ Fax _____
_____ Email _____
Alternate Contact _____
Provider's Signature _____ Date _____ _____ _____ (DD MMM YYYY)

ANTIRETROVIRAL PREGNANCY REGISTRY FOLLOW-UP FORM

FOR OFFICE USE ONLY (4)

Registry Patient ID _____

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

Complete this page ONLY if there is a <u>birth defect</u> or information on a <u>fetal loss</u> (stillbirth, spontaneous or induced abortion)

3. BIRTH DEFECTS – *List birth defects below.*

	Birth defect *(list birth defect)*	***Was the defect attributed to antiviral therapy?*** *1 = Yes* *2 = No* *3 = Unknown*	***Other factors that might contribute to this outcome*** *1 = Maternal age* *2 = Unknown* *3 = Other, specify*
1.			
2.			
3.			
4.			
5.			
6.			

4. FETAL LOSS (STILLBIRTH, SPONTANEOUS, INDUCED ABORTION, OR FETAL LOSS DUE TO MATERNAL DEATH)

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

1.	
2.	
3.	
4.	

Please <u>update</u> the ANTIVIRAL THERAPY DURING PREGNANCY FORM when reporting pregnancy outcome. The form includes the initial information provided to the Registry at registration.

Thank you for your participation in the Antiretroviral Pregnancy Registry