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).

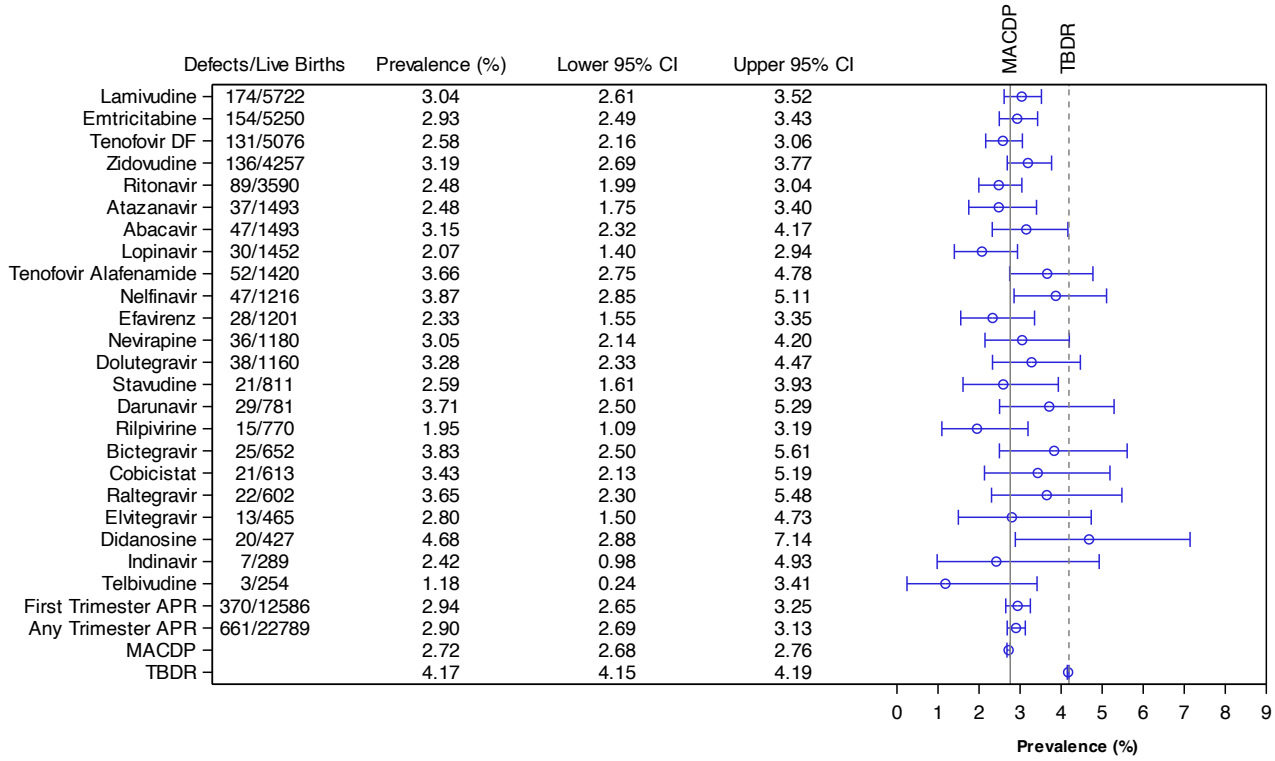
Of the 24,074 prospective Registry reports with outcomes, a total of 21,464 prospective reports are individuals living with HIV and 730 are individuals without HIV, including 464 prospective reports of Pre-Exposure Prophylaxis (PrEP)-exposed pregnancies (Table 2). Also included in the 24,074 prospective 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.