

Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 – 31 January 2021

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 reproductive-age women 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 women are exposed (1). Registration is voluntary and confidential with information obtained from the healthcare 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 healthcare provider, with follow-up obtained from the healthcare provider after the outcome is determined. (For more details, see Appendix F: Methods beginning on page 149.) Providers are strongly urged to enroll their patients as early in pregnancy as possible to maximize the validity of the data. In addition, the Registry is very interested in assembling a group of providers who are willing to make a commitment to report all of their site's antiretroviral pregnancy exposures to the Registry, thereby assuring all cases can be considered prospective. Providers are encouraged to contact the Registry for more information about this group. The Registry is informed in its analysis by other data, for example, retrospective reports and clinical studies.

Annually, the Registry enrolls approximately 1,300-1,700 pregnant women 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. This number includes approximately 1300 (25%) of the estimated 5,000 HIV infected women who give birth to live infants annually in the US and approximately 350 pregnant women from other countries (2)†. Approximately 1,000 of these cases are prospectively reported and included in the analysis. 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. Healthcare providers are strongly encouraged to continue reporting eligible patients to the Registry.

*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[®], CAB), cobicistat (TYBOST[®], COBI), darunavir (PREZISTA[®], DRV), darunavir/cobicistat (PREZCOBIX[™], REZOLSTA[™], PCX), darunavir/cobicistat/emtricitabine/tenofovir alafenamide (SYM TUZA[®], 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), emtricitabine/tenofovir alafenamide (DESCOVY[®], DVY), efavirenz (SUSTIVA[®], STOCRIN[®], EFV), efavirenz/emtricitabine/tenofovir disoproxil (ATRIPLA[®] ATR), efavirenz/lamivudine/tenofovir disoproxil fumarate (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 (CRIVAN[®], IDV), lamivudine (EPIVIR[®], 3TC), lamivudine/raltegravir (DUTREBIS[™], DUT), lamivudine/tenofovir disoproxil fumarate (CIMDUO[™], 3TC/TDF), lamivudine/zidovudine (COMBIVIR[®], CBV), 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).

† Nesheim SR, FitzHarris LF, Lampe MA, Gray KM. Reconsidering the number of women with HIV infection who give birth annually in the United States. Public Health Reports 2018. DOI: 10.1177/0033354918800466. Available from URL: <http://journals.sagepub.com/doi/10.1177/0033354918800466>.

Data Summary

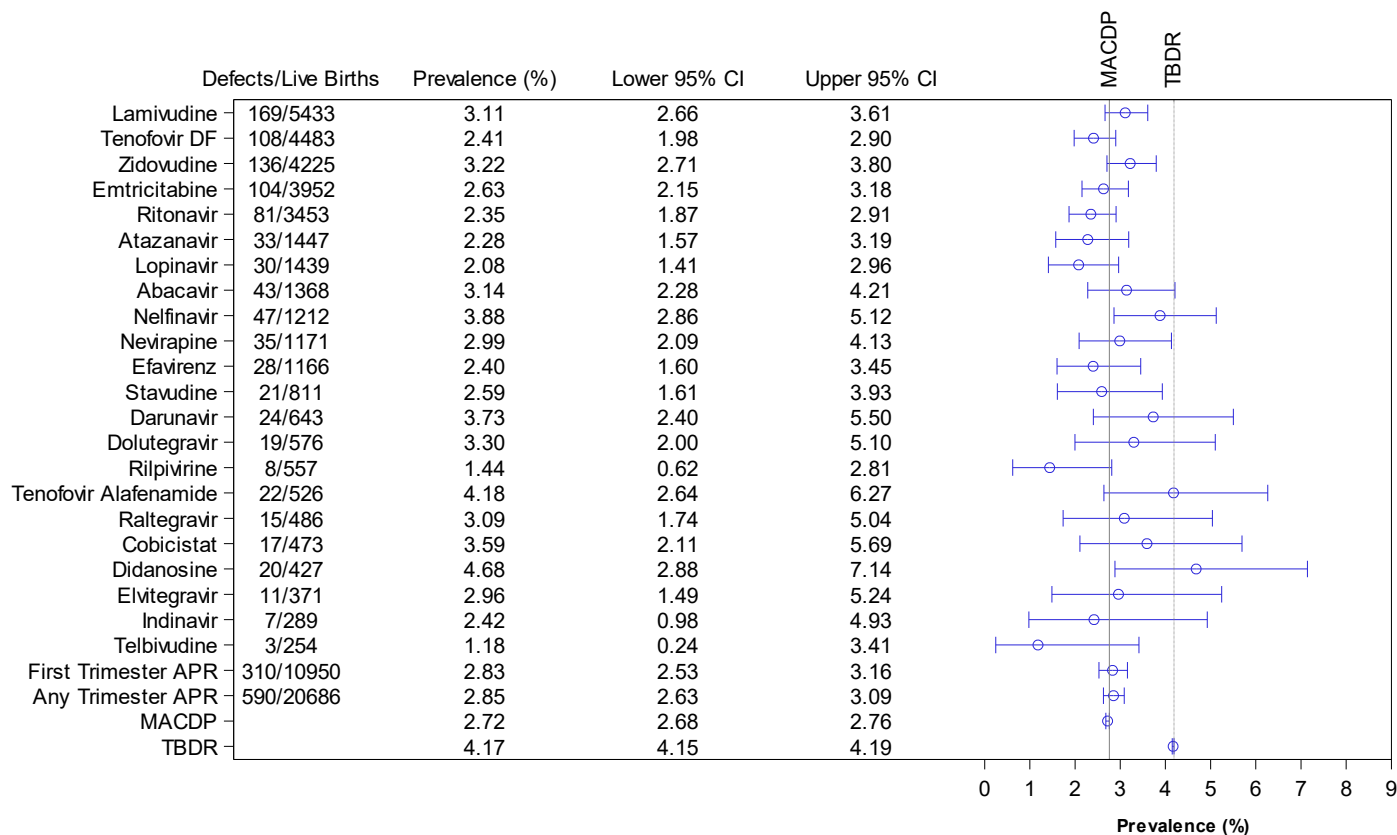
During the last report period, 266 new prospective enrollments were received bringing the total number of enrolled women to 24,876.

Primary Registry Analysis (Prospective Reports): In review of the data through 31 January 2021, among the 21,861 prospective Registry reports with outcomes, the prevalence of birth defects per 100 live births among women with a first trimester exposure to any of the antiretroviral therapies included in the Registry is 2.8 (95% confidence interval (CI): 2.5 - 3.2, i.e., 310 outcomes with defects of 10,950 live births (Table 7). The prevalence of defects is not significantly different from the prevalence of defects among women with an initial exposure during the second and/or third trimester (2.9 per 100 live births) (prevalence ratio: 0.99, 95% CI: 0.84, 1.16).

Measured against 20,686 live births with exposure at any time during pregnancy, there were 590 outcomes with birth defects identified, a prevalence of 2.9 birth defects per 100 live births (95% CI: 2.6 - 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) (3, 4, 5, 6) (2.72 per 100 live births) and the Texas Birth Defects Registry (TBDR) (7) (4.17 per 100 live births). No increases in risk of specific defects have been detected to date when compared with observed MACDP or TBDR rates or with rates among those with earliest exposure in the second or third trimester. In analyzing individual drugs with sufficient data to warrant a separate analysis, with the exception of didanosine and nelfinavir, no increases of concern in risk have been detected. For didanosine and nelfinavir, there is a modest but statistically significant increase in overall rates of defects when compared with the MACDP though not the TBDR. The clinical relevance of these statistical findings is unclear. These defects are listed in Appendix C. Having reached the threshold of 200 first trimester exposed cases, the prevalence of birth defects for tenofovir alafenamide (TAF) was initially statistically significantly higher than the MACDP. However, as the number of cases with TAF exposure increased, the prevalence 4.18% (95% CI: 2.64 - 6.27) is no longer statistically significantly different from either MACDP (2.72%; 95% CI: 2.68 - 2.76) or TBDR (4.17%; 95% CI: 4.15 - 4.19). A detailed review of cases did not identify a pattern of birth defects for didanosine, nelfinavir, or TAF. The Registry will continue to monitor these drugs for any signal or pattern of birth defects.

For cobicistat, darunavir, didanosine, dolutegravir, elvitegravir, indinavir, raltegravir, rilpivirine, stavudine, telbivudine, and tenofovir alafenamide, 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, efavirenz, emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, tenofovir disoproxil fumarate, and zidovudine sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date. (See table below for number of defects and prevalence per 100 live births for first trimester exposures to all drugs with sufficient data to warrant separate analysis. See Appendix A for additional data.) There are insufficient data to make similar comparisons for other drugs or specific subgroups of defects. 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 January 2021



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.

Supplemental Analyses

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

Clinical Studies: In the analysis of reports from clinical studies in pregnancy, 24 infants with defects were identified among 613 live births with first trimester exposures to an antiretroviral therapy. The prevalence of birth defects per 100 live births among women with first trimester exposures to an antiretroviral (primarily nucleoside reverse transcriptase inhibitors) is 3.9 (95% CI: 2.5 - 5.8) (Table 12). The number of defects identified with an initial exposure in the second or third trimester is 70 among 2773 live births, and the prevalence of birth defects per 100 live births is 2.5 (95% CI: 2.0 - 3.2). It is not surprising that the rate of detection of birth defects was relatively high among infants born to women enrolled in clinical studies conducted in pregnant women, as this group is often very different compared with either the CDC population-based surveillance system or the Registry. Differences include severity of disease at the time of maternal enrollment in clinical studies and rigorous infant follow-up and evaluation (e.g., echocardiography). In addition, in past reports, women with first trimester exposures appeared to have more advanced disease. This may change as antiretroviral treatment is now recommended for all HIV infected individuals regardless of clinical

and immunologic or virologic status. The higher rates of defects observed in clinical studies compared to the primary analysis are principally minor, spontaneously resolving cardiovascular defects that were detected on echocardiogram. To date, we have received 63 prospective cases of VSD, distributed across trimesters and drug exposures. Thus, the overall rate remains low and there is no apparent excess of cases among zidovudine or any drug exposure group or relevant trimester of exposure.

Reports from the Published Literature: There is a growing body of literature on the potential association between prenatal antiretroviral exposure and birth defects. The Registry attempts to identify these studies through a systematic literature search conducted annually. The Registry has not identified a signal in any of the published studies reviewed to date.

Data Limitations

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

ADVISORY COMMITTEE CONSENSUS*

In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no significant increases in frequency of birth defects with first trimester exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Because of the data from an observational study in Botswana, the Registry continues to closely monitor cases of neural tube defects with periconception exposures to dolutegravir and other integrase inhibitors (see page 13). Given the use of new therapies about which data are still insufficient, healthcare providers are strongly encouraged to report eligible patients 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 defects with first trimester exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause; however, potential limitations of registries should be recognized. Providers are strongly encouraged to report eligible patients to 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 January 2021. Wilmington, NC: Registry Coordinating Center; 2021. Available from URL: www.APRegistry.com.