

ViiV Healthcare Medicines: zidovudine, lamivudine, zidovudine/lamivudine, abacavir, zidovudine/lamivudine/abacavir, abacavir/lamivudine, amprenavir, fosamprenavir, maraviroc, delavirdine
Study No.: WWE112885/WE066 (EPIP095)/EPI40018
Title: The Antiretroviral Pregnancy Registry (APR, Registry)
Rationale: The purpose of the Antiretroviral Pregnancy Registry is to detect any major teratogenic effects involving any of the Registry drugs when administered to pregnant women. Given the increasing number of medications and more aggressive approach to HIV therapy, more HIV-infected women may be treated during pregnancy or become pregnant while under treatment. The paucity of data on antiretroviral therapy use during pregnancy and infant outcomes makes this Registry an essential component of the ongoing program of epidemiologic studies of the safety of these therapies. The intent of the Registry is to collect data on prenatal exposures to drugs monitored through the Registry, potential confounding factors (such as maternal age, disease status during pregnancy), and information about 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.
Objectives: The Registry is intended to provide an early signal of teratogenicity associated with prenatal use of the drugs monitored through the Registry.
Indication: HIV/AIDS
Study Investigators/Centers: The Registry is managed by Kendle International Inc. The scientific conduct and analysis of the Registry data 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 academic sector. Registry data are obtained from participating providers who encompass physicians in private practice as well as hospitals and community clinics. The registry is co-sponsored and co-funded by 16 pharmaceutical companies that manufacture drugs used in ART.
Research Methods: The Registry conforms to the FDA Guidance for Industry: Establishing Pregnancy Exposure Registries, the Guidelines for Good Pharmacoepidemiology Practices, and the FDA Guidance on Pharmacovigilance. The Antiretroviral Pregnancy Registry collects data on use of the following ViiV/GSK drugs: abacavir, amprenavir, fosamprenavir, lamivudine, zidovudine, maraviroc, delavirdine, and their combinations during pregnancy. The Registry requests information from medical providers about antiretroviral therapy, though there may be other drug exposures, which are not systematically collected. Registration is voluntary. Health professionals are strongly encouraged to enroll their antiretroviral-exposed pregnant patients into the Registry as early in the pregnancy as possible, preferably before prenatal testing is done. This is to maximize the data validity by minimizing potential biases introduced when a woman is enrolled after prenatal testing. Patients are followed through health care providers who provide information on maternal risk factors, pregnancy outcome, and neonatal health. In the month of expected delivery, a short follow-up form is sent to the health care provider to ascertain the pregnancy outcome and completion of the antiviral therapy information. Additional follow-up is not sought from health care providers. In an attempt to limit the bias in the analysis, the Registry assembled a group of providers who committed in writing to report every women who receives antiretroviral therapy during pregnancy, but before the pregnancy outcome is known, that comes to their site. This allows 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 those cases separately. Providers are encouraged to participate in this group.
Data Source: The main data source is prospective reports (i.e. those reports made to the Registry prior to the outcome of pregnancy being known) of prenatal exposures to abacavir, amprenavir, fosamprenavir calcium, lamivudine, zidovudine, maraviroc, delavirdine and their combinations. 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 also collected and the outcomes evaluated; however, due to the greater potential for bias, these reports are evaluated separately. Additionally, the Registry receives information on women enrolled in antiretroviral clinical studies in pregnancy. These reports may be received sporadically through the voluntary reporting process or systematically on every case in a clinical trial from a single source. The differences in the sources of information from clinical trial reports and, in some cases, the country where the study was conducted may make pooling these data with those reports from routine clinical practice for analysis inappropriate. So, data from clinical trials is presented separately.

Study Design: Prospective registry of voluntary reports. This is an observational, exposure-registration and follow-up study.

Study Population: The Antiretroviral Pregnancy Registry is an international registry, and as of 31st January, 2010 received reports from 66 countries. Each year the Registry enrolls approximately 1300 pregnant women in the USA, exposed to antiretroviral drugs. This number represents approximately 15% of the 8,680-8,900 HIV positive women who give birth to live infants annually in the US. Reports are predominantly from the US and its territories (84.9%). Non-US reports are most frequently from the United Kingdom (3.3%), France (1.2%), South Africa (1.9%), Germany (0.6%), Brazil (0.3%), Australia (0.3%) and Sweden (0.2%).

Study Exposures, Outcomes: 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 (minor errors of morphogenesis as well as anomalies that are considered to be normal in premature infants) occurring in infancy up to six years of age or in fetuses of at least 20 weeks gestational age. This definition is consistent with, but not restricted to the CDC population-based surveillance system definition. The CDC system includes conditional defects only in the presence of a major defect. To facilitate the recognition of a potential signal, the Registry developed an organ system classification, which removes some of the granularity in looking at individual defects by grouping similar defects or defects of similar etiology together. In addition, any structural or chromosomal defect detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, fetus, or deceased infant is evaluated. All birth defects are reviewed and classified by the consultant geneticist using the CDC MACDP system.

Exposures to individual drugs during the first and second/third trimester 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. 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) or protease inhibitors (PI). If there is more than one drug within the classification, only one occurrence is counted.

Data Analysis Methods: 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), and documentation on whether the patient was enrolled in a study conducted in pregnancy, during the reported period. Also, enough information needs to be collected to search for duplicate reporting of a case (e.g., last menstrual period, maternal age).

As women participating in a clinical study involving use of antiretrovirals in pregnancy must meet certain selection criteria and may be followed more closely than women not participating in such studies, such clinical 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. 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 ± 1 week for the first trimester, outside ± 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.

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. 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 not included in rate calculations. As the behaviour 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.

Given the inherent difficulties in identifying a comparison group for this Registry, three different methods are used to review the data for any signals of teratogenicity. First, the prevalence of birth defects in the Registry is compared to the prevalence observed in the MACDP, a population-based birth defects surveillance system administered by the CDC. The total prevalence of birth defects identified among births from 1968 through 2003 was 2.67% and the prevalence of birth defects identified among births in the years that most closely mirror the year the APR has been in operation (1989-2003) was 2.72% (95% CI 2.68, 2.76). Because population-based surveillance does not involve sampling, MACDP does not publish confidence intervals and the CI reported here is calculated by the Registry. As a second method of analysis, the risk of birth defects among women with first trimester exposures to antiretroviral medications are compared with the risk of birth defects among women with second or third trimester exposures to antiretroviral medications. Prevalence ratios and 95% CI are calculated to assess the presence or absence of any excess risk associated with timing of the exposure. A third is a qualitative analysis of cases for the emergence of any unique defects or patterns of defects. The CDC and other population-based registries ascertain defect cases by active review of medical records. This Registry's methods differ by using voluntary registration with active solicitation of outcome data.

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. To date the population exposed and monitored in the Registry is not sufficient to detect an increase in the risk of relatively rare defects.

Since reports of exposure are voluntary, they are subject to potential selection bias. These 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). Another limitation of an exposure-registration study is that the rates of drug associated adverse events cannot be extrapolated to reflect the true rates in the potential target population. Despite these limitations, such studies 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. 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 through the Registry.

Study Results: From 1st January 1989 through 31st January 2010, there were 13575 prospective cases reported to the Registry. There were 491 cases pending the outcome of pregnancy and 1217 lost to follow-up. Thus, there were 11867 evaluable prospective reports included in the primary analysis. Of the 11867 evaluable prospective reports, 5582 were first trimester exposures to one or more of the antiretroviral drugs followed in the Registry. There were 12098 outcomes of pregnancy, including 229 multiple births: 11261 live births, 299 spontaneous abortions, 161 stillbirths, and 377 induced abortions. Of the 11261 live births, 4954 had a maternal exposure to antiretroviral therapy during the first trimester. It should be noted that there were 1283 live births involving a maternal exposure to any single class of antiretroviral therapy (as opposed to exposure to more than one class of therapy) during the first trimester. There may have been an exposure to more than one therapy within the class in the first trimester or to other therapies in other classes in other trimesters. Of the 5689 birth outcomes with a 1st trimester exposure to an antiretroviral drug, there were 138 reports of defects (129/4825 defects in live births, 3/88 in stillbirths, and 6/363 in induced abortions occurring \geq 20 weeks gestation).

Of the 12098 live birth outcomes, 6408 are in the combined second and/or third trimester exposure group, with 160 reported birth defects. This includes 2136 live births with a second and/or third trimester exposure in the NRTI(s) only exposure group, with 59 defect reports. The live birth outcomes in the other therapy exposure classifications were as follows: for the PI + NRTI group there were 71 defects of 2914 live births; for the NRTI + NNRTI group, 17 defects of 805 births; for the PI + NRTI + NNRTI group, 3 defects of 75 births and in the other combination groups of 344 live births there were 10 defects reported. There were zero defects for the 24 births exposed to combinations including EI.

Defects among the exposures to individual GSK drugs during the first trimester are as follows: any NRTI, 136 defects among 4792 exposures; any abacavir regimens, 19 of 670; any lamivudine regimen, 99 of 3481; any zidovudine regimen 100 of 3289; any PI, 72 of 2528; any amprenavir regimen, 1 of 28; any fosamprenavir regimen, 1 of 72; any NNRTI, 32 of 1326, any delavirdine regimen, 0 of 11; any entry inhibitor, 0 of 19. There were no exposures to maraviroc reported in the first trimester. Defects among exposures to GSK drugs in the second/third trimester are as follows: any NRTI, 162 defects among 6362 exposures; any abacavir, 28 of 962; any lamivudine, 130 of 5194; any zidovudine, 173 of 6789; any PI, 97 of 3766; any amprenavir, 0 of 10; any fosamprenavir, 1 of 29; any NNRTI, 28 of 1197; any delavirdine, 0 of 3; any entry inhibitor, 0 of 14, any maraviroc, 0 of 2.

To date, no increases in risk of birth defects overall or in specific classes of drugs have been detected. For lamivudine and zidovudine, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date with the exception of hypospadias following first trimester exposure to zidovudine from the addition of WITS data. With the additional accrual of first trimester exposures, this finding has not persisted. For abacavir, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in the risk of overall birth defects. No such increases have been detected to date.

There were 138 of outcomes with birth defects seen among 4954 live births among women with exposures in the first trimester to any antiretroviral drug. By organ system, these were: 7 CNS defects, 14 face and neck, 6 cleft lip/palate, 6 conotruncal heart defects, 5 obstructive heart defects on the right side, 2 obstructive heart defects on the left side, 19 other heart defects, 10 other circulatory system defects, 1 respiratory defect, 3 upper gastrointestinal defect, 6 lower gastrointestinal defect, 2 female genitalia, 16 male genitalia defects, 16 renal and urinary system, 17 limb reduction/addition defects, 33 other musculoskeletal defects, 4 skin and skin derivatives, 11 chromosome anomalies, 9 other organs or organ systems, and 12 specified syndromes/sequences/associations.

There were 160 defects seen among 6306 women with any antiretroviral exposure beginning in the second/third trimester of pregnancy. By organ system, these were: 15 CNS defects, 24 face and neck, 13

cleft lip/palate, 6 conotruncal heart defects, 9 obstructive heart defects on the right side, 2 obstructive heart defects on the left side, 35 other heart defects, 9 other circulatory system defects, 1 respiratory defect, 2 upper gastrointestinal defect, 5 lower gastrointestinal defects, 8 male genitalia defects, 11 renal and urinary system, 25 limb reduction/addition defects, 33 other musculoskeletal defects, 5 skin and skin derivative, 16 chromosome anomalies, 7 other organs or organ systems, and 7 specified syndromes/sequences/associations.

No pattern of defects has been found in the overall evaluation of retrospective reports and Registry cases of birth defects.

In the analysis of reports from clinical studies in pregnancy, 13 infants with defects were identified among 255 evaluable (with sufficient data) birth outcomes (include live births, still births, spontaneous and induced abortions of ≥ 20 weeks of gestation) with reported first trimester exposures to an antiretroviral therapy. The prevalence of birth defects per 100 birth outcomes among women with first trimester exposures to an antiretroviral is 5.1 (95% CI: 2.7-8.6). The number of defects identified with a first exposure in the second or third trimester is 22/969 with a prevalence of 2.3 (95% CI: 1.4-3.4).

The prevalence 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 enrolment in clinical studies and rigorous infant follow-up and evaluation (e.g. echocardiography). In addition, women with first trimester exposures appeared to have more advanced disease. The primary anomaly accounting for the observed difference between the clinical studies and the primary prospective analysis is minor and self-limiting cardiovascular defects detected on echocardiogram.

Conclusion: In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds that the defects reported show no apparent increases in frequency 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. Health care providers are encouraged to report eligible patients to the Registry at www.APRegistry.com.