

# Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 – 31 July 2009\*

## EXECUTIVE SUMMARY

### *Background*

The purpose of the Antiretroviral Pregnancy Registry (Registry) is to detect any major teratogenic effects involving any of the Registry drugs\* to which pregnant women are exposed (1). Registration is voluntary and confidential with information obtained from the health care provider. A Registry-assigned identifier allows for follow-up capability. Information on subjects is provided to the Registry prospectively (prior to the outcome of pregnancy being known) through their health care provider, with follow-up obtained from the health care provider after the outcome is determined. (For more details, see Appendix F: Methods 122.) 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.

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 women and the exposed fetus.

Each year the Registry enrolls approximately 1300 pregnant women in the US exposed to antiretroviral drugs. This number represents approximately 15% of the 8,650-8,900 HIV positive women who give birth to live infants annually in the US (2). Each year the Registry also enrolls approximately 200 pregnant women from other countries.

### *Data Summary*

**Primary Registry Analysis (Prospective Reports):** In review of the data through 31 July 2009, among the prospective Registry reports, the prevalence of birth defects per 100 live births among women with a first trimester exposure to any of the antiretroviral therapies included in the Registry is 2.8 (95% confidence interval (CI): 2.4 - 3.4, i.e., 134 outcomes with defects of 4702 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 (2.5 per 100 live births) (prevalence ratio: 1.14, 95% CI: 0.90, 1.43).

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\*Drugs included: abacavir (ZIAGEN<sup>®</sup>, ABC), abacavir/lamivudine (EPZICOM<sup>®</sup>, EPZ), abacavir/lamivudine/zidovudine combination (TRIZIVIR<sup>®</sup>, TZV), adefovir dipivoxil (HEPSERA<sup>®</sup>, ADV), amprenavir (AGENERASE<sup>®</sup>, APV), atazanavir sulfate (REYATAZ<sup>®</sup>, ATV), darunavir (PREZISTA<sup>™</sup>, DRV), delavirdine mesylate (RESCRIPTOR<sup>®</sup>, DLV), didanosine (VIDEX<sup>®</sup>, VIDEX<sup>®</sup> EC, ddl), efavirenz (SUSTIVA<sup>®</sup>, STOCRIN<sup>®</sup>, EFV), efavirenz/emtricitabine/tenofovir DF (ATRIPLA<sup>®</sup> ATR), emtricitabine (EMTRIVA<sup>®</sup>, FTC), enfuvirtide (FUZEON<sup>®</sup>, T-20), entecavir (BARACLUDE<sup>®</sup>, ETV), etravirine (INTELENCE<sup>™</sup>, ETR), fosamprenavir calcium (LEXIVA<sup>®</sup>, FOS), indinavir (CRIXIVAN<sup>®</sup>, IDV), lamivudine (EPIVIR<sup>®</sup>, 3TC), lamivudine/zidovudine (COMBIVIR<sup>®</sup>, ZDV+3TC), lopinavir/ritonavir (KALETRA<sup>®</sup>, ALUVIA<sup>®</sup>, LPV/r), maraviroc (SELZENTRY<sup>™</sup>, CELENTRI<sup>™</sup>, MVC), nelfinavir (VIRACEPT<sup>®</sup>, NFV), nevirapine (VIRAMUNE<sup>®</sup>, NVP), raltegravir (ISENTRESS<sup>™</sup>, RAL), ritonavir (NORVIR<sup>®</sup>, RTV), saquinavir (FORTOVASE<sup>®</sup>, SQV-SGC), saquinavir mesylate (INVIRASE<sup>®</sup>, SQV-HGC), stavudine (ZERIT<sup>®</sup>, d4T), telbivudine (SEBIVO<sup>®</sup>, TYZEKA<sup>®</sup>, LdT), tenofovir DF (VIREAD<sup>®</sup>, TDF), tenofovir DF/emtricitabine (TRUVADA<sup>®</sup>, TVD), tipranavir (APTIVUS<sup>®</sup>, TPV), zalcitabine (HIVID<sup>®</sup>, ddC), and zidovudine (RETROVIR<sup>®</sup>, ZDV).

Measured against 10803 live births with exposure at any time during pregnancy, there were 288 outcomes with birth defects identified, a prevalence of 2.7 birth defects per 100 live births (95% CI: 2.4 - 3.0). This proportion is not substantially different than the CDC's birth defects surveillance system (MACDP)<sup>†</sup> (3, 4, 5, 6) where total prevalence of birth defects identified among births from 1989 through 2003 was 2.72 per 100 live births (95% confidence interval: 2.68, 2.76), and the prevalence of birth defects per 100 live births diagnosed during the first seven days of life ("early diagnosis") was 2.09 (95% CI: 2.07, 2.12). Because population-based surveillance does not involve sampling, MACDP does not publish confidence intervals (CIs). The CIs reported around MACDP rates in this report were calculated by the Registry. Additionally, ascertainment from CDC's active surveillance system does not rely on voluntary reports.

For the overall population exposed to antiretroviral drugs in this Registry, no increases in risk of overall birth defects or specific defects have been detected to date when compared with observed rates for "early diagnoses" in population-based birth defects surveillance systems or with rates among those with earliest exposure in the second or third trimester. In analyzing individual drugs with sufficient data to warrant a separate analysis, no increases in risk of concern have been detected.<sup>ψ</sup>

For abacavir, atazanavir, efavirenz, emtricitabine, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, and tenofovir, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date. For lamivudine and zidovudine sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date. (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.

The Advisory Committee pays particular attention to findings from animal studies. Therefore, the Advisory Committee is closely monitoring first trimester exposures to efavirenz for anomalies including central nervous system defects. Defects have been reported in 14 among the 501 infants with first trimester exposure to efavirenz, including a single case of myelomeningocele and a single case of anophthalmia with severe oblique facial clefts and amniotic banding.

### First Trimester Exposure

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<sup>†</sup>MACDP, the Metropolitan Atlanta Congenital Defects Program actively searches for birth defects among all births in five counties of the metropolitan Atlanta area with approximately 50,000 annual births in a population of about 2.9 million. For more information, see references 3, 4, and 5. 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 (6).

<sup>ψ</sup> A noted exception was an unexplained excess of first trimester defects following exposure to didanosine, reported during previous years. Thorough analysis of all cases and subsequent experience has been performed. No pattern of birth defects has been detected with didanosine. An additional defect case has been received in this period. The Registry will continue to monitor didanosine for any signal or pattern of birth defects. The Committee concludes that this early increase does not represent a "true signal." The committee also notes the exception of hypospadias following first trimester exposure to zidovudine from the addition of the WITS data. With additional accrual of first trimester exposures without additional reports of hypospadias, this finding has not persisted.

Regimen	Defects/Live Births	Prevalence (95% Confidence Interval)
Lamivudine	96/3314	2.9% (2.3%, 3.5%)
Zidovudine	97/3167	3.1% (2.5%, 3.7%)
Nelfinavir	37/1075	3.4% (2.4%, 4.7%)
Ritonavir	22/1000	2.2% (1.4%, 3.3%)
Nevirapine	18/842	2.1% (1.3%, 3.4%)
Stavudine	19/771	2.5% (1.5%, 3.8%)
Tenofovir	18/756	2.4% (1.4%, 3.7%)
Abacavir	19/628	3.0% (1.8%, 4.7%)
Lopinavir	9/526	1.7% (0.8%, 3.2%)
Efavirenz	14/501	2.8% (1.5%, 4.7%)
Emtricitabine	11/384	2.9% (1.4%, 5.1%)
Didanosine	17/370	4.6% (2.7%, 7.3%)
Atazanavir sulfate	9/343	2.6% (1.2%, 4.9%)
Indinavir	6/276	2.2% (0.8%, 4.7%)

### **Supplemental Analyses**

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

**Clinical Studies:** In the analysis of reports from clinical studies in pregnancy, 13 infants with defects were identified among 249 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 5.2 (95% CI: 2.8 - 8.8) (Table 12). The number of defects identified with an initial exposure in the second or third trimester is 22/919, and the prevalence of birth defects per 100 live births is 2.4 (95% CI: 1.5 - 3.6). It is not surprising that the rate of detection of birth defects was relatively high among infants born to women enrolled in clinical studies conducted in pregnant women, as this group is often very different compared with either the CDC population-based surveillance system or the Registry. Differences include severity of disease at the time of maternal enrollment in clinical studies and rigorous infant follow-up and evaluation (e.g., echocardiography). In addition, women with first trimester exposures appeared to have more advanced disease. The primary anomaly accounting for the observed difference from the primary analysis is minor and self-limiting cardiovascular defects detected on echocardiogram.

**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 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](http://www.APRegistry.com).