Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 – 31 July 2005*

EXECUTIVE SUMMARY

Background

The purpose of the Antiretroviral Pregnancy Registry (Registry) is to detect any major teratogenic effect involving any of the Registry drugs* when administered to pregnant women (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 Methods section beginning on page 33.) 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.

Given the increasing number of medications and more aggressive approach to therapy, more HIV-infected women may be treated during pregnancy or become pregnant while under treatment. The paucity of data on use and infant outcomes of antiretroviral therapies during pregnancy makes this Registry an essential component of the ongoing program of epidemiologic studies of the safety of these therapies.

Each year the Registry enrolls approximately 1000 pregnant women exposed to antiretroviral drugs. This number represents approximately 15% of the 6000-7000 HIV positive women who give birth to live infants annually in the US (2).

Data Summary

Prospective Registry: In review of the data through 31 July 2005, 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 3.0 (95% confidence interval (CI): 2.3 - 3.8, i.e., 59 outcomes with defects of 1980 live births (Table 7). The prevalence of defects is not significantly different from the prevalence of defects among women with the first exposure during the second and/or third trimester (2.3 per 100 live births) (prevalence ratio: 1.30, 95% CI: 0.93, 1.83).

Measured against 5169 live births with exposure at any time during pregnancy, there were 132 outcomes with birth defects identified, a prevalence of 2.6 birth defects per 100 live births (95% CI: 2.1 - 3.0). This proportion is not significantly higher than the CDC's population-based birth defects surveillance system

*Drugs included: abacavir (ZIAGEN®, ABC), abacavir/lamivudine (EPZICOM™), abacavir/lamivudine/zidovudine combination (TRIZIVIR®, TZV), adefovir dipivoxil (HEPSERA®, ADV), amprenavir (AGENERASE®, APV), atazanavir sulfate (REYATAZ®, ATV), delavirdine mesylate (RESCRIPTOR®, DLV), didanosine (VIDEX®, VIDEX® EC, ddI), efavirenz (SUSTIVA®, STOCRIN®, EFV), emtricitabine (EMTRIVA®, FTC), enfuvirtide (FUZEON®, T-20), entecavir (BARACLUDE™, ENT), fosamprenavir calcium (LEXIVA®, FOS), indinavir (CRIXIVAN®, IDV), lamivudine (EPIVIR®, 3TC), lamivudine/zidovudine (COMBIVIR®, ZDV+3TC), lopinavir/ritonavir (KALETRA®, LPV/r), nelfinavir (VIRACEPT®, NFV), nevirapine (VIRAMUNE®, NVP), ritonavir (NORVIR®, RTV), saquinavir (FORTOVASE®, SQV-SGC), saquinavir mesylate (INVIRASE®, SQV-HGC), stavudine (ZERIT®, d4T), tenofovir DF (VIREAD®, TDF), tenofovir DF/emtricitabine (TRUVADA®, TVD), tipranavir (APTIVUS®, TPV), zalcitabine (HIVID®, ddC), and zidovudine (RETROVIR®, ZDV).

(MACDP)† (5, 6) where total prevalence of birth defects identified among births from 1991 through 1995 was 3.1 per 100 live births (95% confidence interval: 3.1, 3.2), and the prevalence of birth defects per 100 live births identified either prior to birth or during the first day of life ("early diagnosis") was 2.2 (95% CI: 2.1, 2.2). However, ascertainment from CDC's active surveillance system does not rely on voluntary reports.

No increases in risk of overall birth defects or specific defects 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. For abacavir, didanosine, efavirenz, nelfinavir, nevirapine, ritonavir, and stavudine, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. With the exception of didanosine, 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 any abacavir-, didanosine-, efavirenz-, lamivudine-, nelfinavir-, nevirapine-, ritonavir-, stavudine-, and zidovudine-containing regimen. The Registry notes the high frequency of birth defects after first trimester exposure to didanosine. All cases were thoroughly reviewed and no pattern was discovered. The Registry will continue to monitor didanosine exposures. There are insufficient data to make similar comparisons for other drugs or specific subgroups of defects. In reviewing all reported defects from the prospective Registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the defects reported show no pattern to suggest a common cause.

	First Trimester Exposure	
Regimen	***Defects/Live Births***	***Prevalence (95% confidence interval)***
Lamivudine	43/1555	2.8% (2.0%, 3.7%)
Zidovudine	41/1371	3.0% (2.2%, 4.0%)
Nelfinavir	20/534	3.7% (2.3%, 5.7%)
Nevirapine	9/449	2.0% (0.9%, 3.8%)
Stavudine	12/446	2.7% (1.4%, 4.7%)
Abacavir	11/322	3.4% (1.7%, 6.0%)
Ritonavir	7/243	2.9% (1.2%, 5.9%)
Efavirenz	5/228	2.2% (0.7%, 5.1%)
Didanosine	14/220	6.4% (3.5%, 10.5%)

Clinical Studies: In the analysis of reports from clinical studies in pregnancy, 16 infants with defects were identified among 233 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 6.9 (95% CI: 4.0 - 10.9) (Table 12). The number of defects identified with a first exposure in the second or third trimester is 21/897, and the prevalence of birth defects per 100 live births is 2.3 (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.

†MACDP, the Metropolitan Atlanta Congenital Defects Program monitors all major birth defects 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 5 and 6.

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. 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

Primary Registry Analysis (Prospective Reports)

The Registry's analytic approach is to evaluate drugs in specific classes of antiretroviral therapies (FIs [fusion inhibitor(s)], NRTIs [nucleoside analog reverse transcriptase inhibitor(s)], NNRTIs [non-nucleoside reverse transcriptase inhibitor(s)], NtRTIs [nucleotide reverse transcriptase inhibitors], and PIs [protease inhibitor(s)]). Currently there are nine specific drugs with large enough groups of exposed women to warrant a separate analysis. These drugs are abacavir, didanosine, efavirenz, lamivudine, nelfinavir, nevirapine, ritonavir, stavudine, and zidovudine.

No increases in risk of overall birth defects or specific defects 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. For abacavir, efavirenz, nelfinavir, nevirapine, ritonavir, and stavudine 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. Although no pattern of birth defects has been detected with didanosine, the Committee continues to monitor the apparent increased frequency of defects among infants exposed to didanosine in the first trimester of gestation.

To date, the Registry has not demonstrated an increased prevalence of birth defects overall, or in the specific classes studied, or among women exposed to abacavir, didanosine, efavirenz, lamivudine, nelfinavir, nevirapine, ritonavir, stavudine, or zidovudine individually or in combination during the first trimester when compared with observed rates for "early diagnoses" in population-based birth defects surveillance systems. While the Registry to date has not detected a major teratogenic signal overall or within classes of drugs or the nine individual drugs analyzed separately, the 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.

Supplemental Analyses

Retrospective Reports: Retrospective reports are those reported to the Registry after the outcome or perceived outcome of pregnancy is known. 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.

Reports from Clinical Studies in Pregnancy: 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. The Registry will continue to examine data as available from further studies.

Reports from the Published Literature: The registry has not identified a signal in any of the published studies reviewed to date.