The Antiretroviral Pregnancy Registry: 25 Years of Monitoring for Birth Defects

WEPEB115

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Abstract

Background: Antiretrovirals (ARVs) have been effective in reducing vertical transmission of HIV. The Antiretroviral Pregnancy Registry (APR) has monitored prenatal ARV use for an early signal of teratogenicity for 25 years.

Methods: APR is an ongoing international, voluntary, prospective exposure–registration cohort study, overseen by an independent Advisory Committee. Birth defect prevalence and risk for major birth defects are estimated and compared to internal and external comparator groups. Statistical inference is based on exact methods for binomial proportions. Sufficient numbers of 1st trimester exposures have been monitored to allow detection of at least 1.5-fold increase in risk of overall birth defects for nine ARVs and a two-fold increase for six.

Results: Of the 17,618 evaluable prospectively enrolled pregnancies through July 2015, there were 16,699 live births (LB) with prenatal ARV exposure at any time during pregnancy and 473 birth defects for overall prevalence of 2.8 defects/100 live births (95% confidence interval [CI]: 2.6, 3.1). Among 7738 1st trimester exposures to ARVs, 221 birth defects were reported, with a prevalence of 2.9% (95% CI: 2.5, 3.3). Among 8959 2nd/3rd trimester exposures to ARVs, there were 250 birth defects, with a prevalence of 2.8% (95% CI: 2.4, 3.2). Prevalence ratio comparing 1st vs 2nd/3rd trimester exposures was 1.02 (95% CI: 0.86, 1.22).

Conclusions: To date, the overall birth defect prevalence in APR has not been significantly different from two population-based surveillance systems: 2.72/100 live births reported in the Metropolitan Atlanta Congenital Defects Program (MACDP, Centers for Disease Control and Prevention); and 4.17/100 LB from the Texas Birth Defects Registry (TBDR, Texas Department of State Health Services); or the APR internal comparator of 2nd/3rd trimester exposures. For didanosine and nelfinavir, a modest, statistically significant increase in prevalence is noted when compared to MACDP but not TBDR.

Introduction

- The APR is an international registry jointly sponsored by manufacturers of all FDA-approved and marketed antiretroviral drugs (ARVs) that began in 1989
  - Currently 25 sponsors
  - Monitors 97 drugs
    - 47 brand-named single-entity drugs or fixed-dose combinations (FDCs)
    - 50 generic versions

Objectives

- To provide early warning signal of major teratogenic effects of ARVs
- To estimate prevalence of and risk for major birth defects and compare to that of general population
- To supplement data from animal toxicology, clinical, and epidemiological studies

Methods

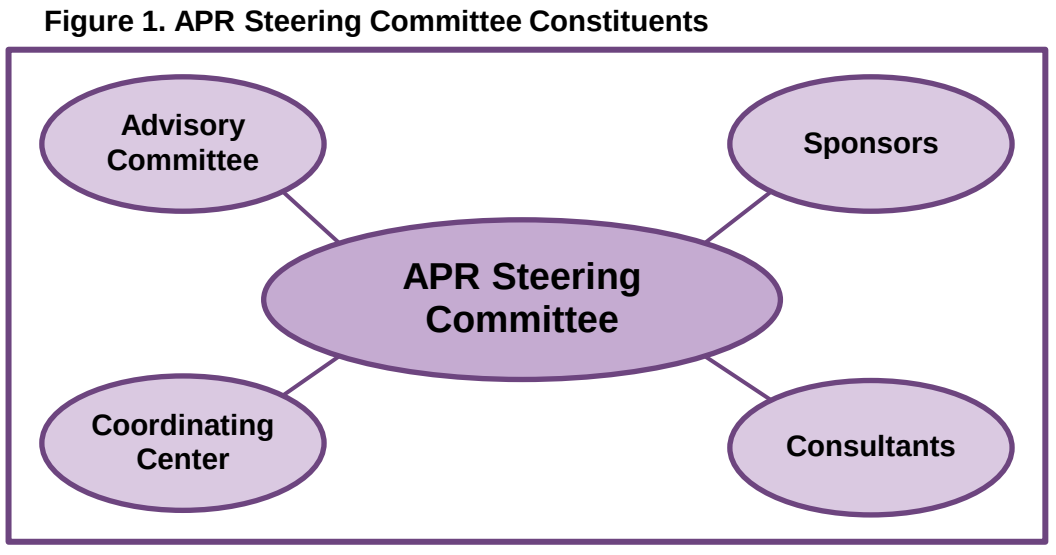
Study Design

- Prospective exposure–registration cohort
- Health care providers voluntarily:
  - Register pregnant women exposed to ARVs
  - Report data on ARV exposure throughout pregnancy
  - Provide fetal/neonatal outcome data

Registry Oversight

- APR is overseen by a committee of experts in obstetrics, pediatrics, teratology, infectious diseases, epidemiology, biostatistics, and patient advocacy from academia, government, and the pharmaceutical industry
- Birth defects are assessed by a geneticist with special focus on
  - The timing of exposure and relevance to the specific defect
  - Other potential causes
- All individual cases and aggregate data are reviewed semi-annually and an interim report is prepared

Figure 1. APR Steering Committee Constituents



Statistical Considerations

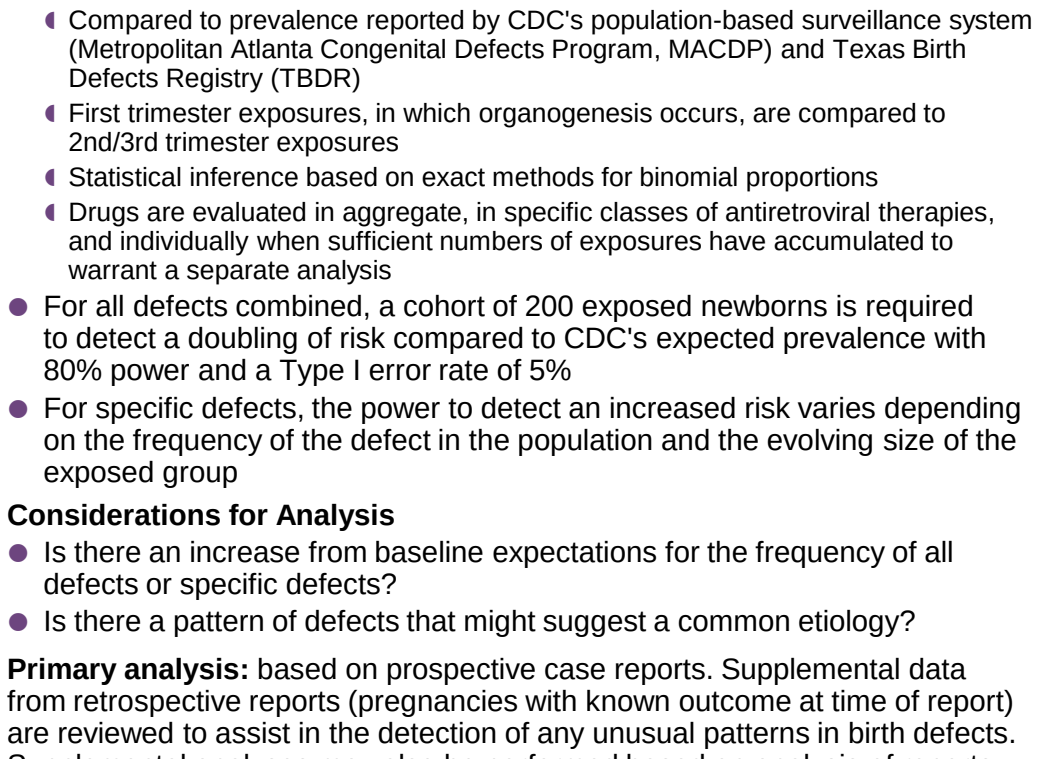
- Prevalence: number of birth defects in outcomes >20 weeks/total number of live births
  - Compared to prevalence reported by CDC's population-based surveillance system (Metropolitan Atlanta Congenital Defects Program, MACDP) and Texas Birth Defects Registry (TBDR)
  - First trimester exposures, in which organogenesis occurs, are compared to 2nd/3rd trimester exposures
  - Statistical inference based on exact methods for binomial proportions
  - Drugs are evaluated in aggregate, in specific classes of antiretroviral therapies, and individually when sufficient numbers of exposures have accumulated to warrant a separate analysis
- For all defects combined, a cohort of 200 exposed newborns is required to detect a doubling of risk compared to CDC's expected prevalence with 80% power and a Type I error rate of 5%
- For specific defects, the power to detect an increased risk varies depending on the frequency of the defect in the population and the evolving size of the exposed group

Considerations for Analysis

- Is there an increase from baseline expectations for the frequency of all defects or specific defects?
- Is there a pattern of defects that might suggest a common etiology?

Primary analysis: based on prospective case reports. Supplemental data from retrospective reports (pregnancies with known outcome at time of report) are reviewed to assist in the detection of any unusual patterns in birth defects. Supplemental analyses may also be performed based on analysis of reports from clinical trials/studies in pregnancy; these data are examined separately from the primary Registry analysis due to the potential for selection or ascertainment bias.

Figure 2. Birth Defect Analysis Flowchart



Results

Prospective Data Received From 1998 Through 31 Jan 2016

Table 1. Maternal Demographics at Registration

	Primary analysis	Lost to follow-up
Pregnancies enrolled	17,899	2105
Age (years)		
N	17,672	1770
Median (interquartile range)	28.0 (9.0)	28.0 (8.0)
Min - max	13-55	15-47
Missing	227	335
Indication for ARV at start of pregnancy		
HIV infected[a]	16,410 (91.7%)	1116 (53.0%)
HIV uninfected[b]	287 (1.6%)	98 (4.7%)
Post-exposure prophylaxis (PEP)	0 (0.0%)	2 (0.1%)
Pre-exposure prophylaxis (PrEP)	32 (0.2%)	10 (0.5%)
Hepatitis B mono-infected	269 (1.5%)	190 (9.0%)
Unknown	447 (2.5%)	338 (16.1%)
Missing	479 (2.7%)	363 (17.2%)
Clinical indicators		
CD4+ T-cell categories at start of pregnancy		
≥500 cells/µL	5472 (30.6%)	428 (20.3%)
200-499 cells/µL	7342 (41.0%)	516 (24.5%)
<200 cells/µL	2647 (14.8%)	170 (8.1%)
Unknown	429 (2.4%)	198 (9.4%)
Not applicable	556 (3.1%)	419 (19.9%)
Missing	1453 (8.1%)	374 (17.8%)
Worst disease severity by history		
HIV		
A. Asymptomatic, acute (primary) HIV or PGL	12,740 (71.2%)	852 (40.5%)
B. Symptomatic, not (A) or (C) conditions	1280 (7.2%)	73 (3.5%)
C. Other AIDS-indicator conditions	2191 (12.2%)	149 (7.1%)
D. CD4 <200 cells/µL	153 (0.9%)	10 (0.5%)
Not applicable	52 (0.3%)	33 (1.6%)
Unknown	501 (2.8%)	382 (18.1%)
Missing	727 (4.1%)	520 (24.7%)
Hepatitis B		
Compensated liver disease (Pugh score <7)	384 (2.1%)	70 (3.3%)
Compensated liver disease (Pugh score ≥7)	6 (0.0%)	3 (0.1%)
Unknown	8465 (47.3%)	653 (31.0%)
Not applicable	558 (3.1%)	374 (17.8%)
Missing	8486 (47.4%)	1005 (47.7%)

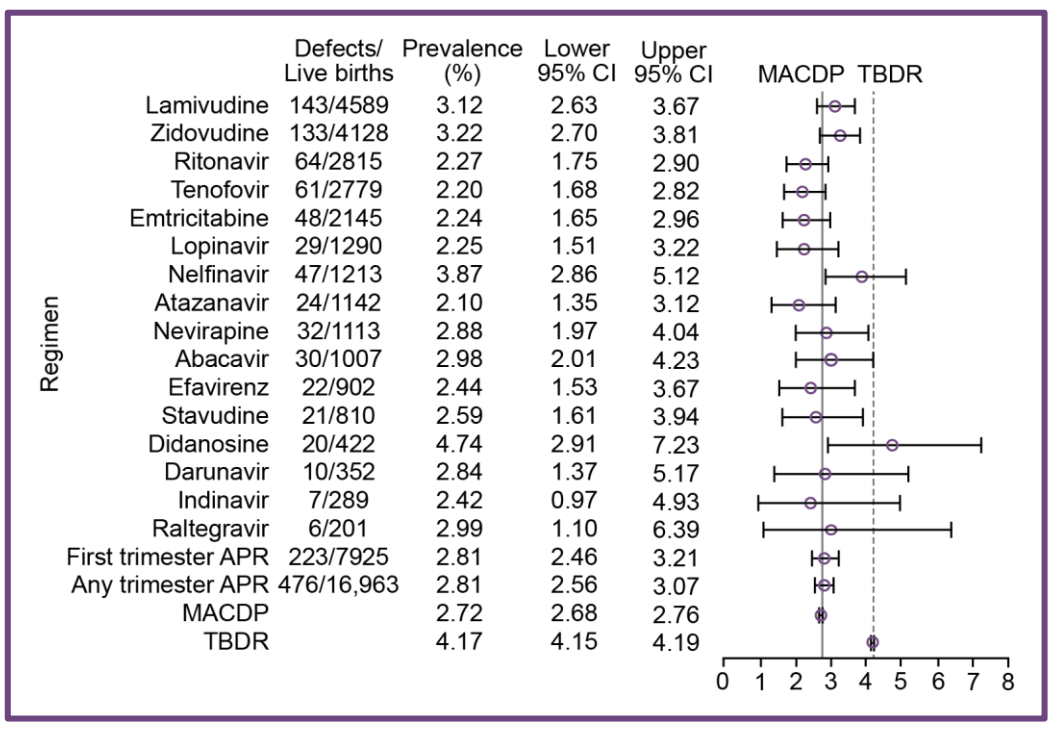
[a]Includes 184 patients co-infected with HIV and hepatitis B. Includes 231 patients co-infected with HIV and hepatitis C. [b]Where antiretroviral drugs have been used for prophylaxis.

Table 2. Prevalence of Birth Defects (95% CI) Relative to Timing of First ARV Exposure[a]

	1st Trimester (n=7925)	2nd/3rd Trimester (n=9036)	Total (N=16,963)
Births with at least 1 defect, (%)	223 (2.8%)	251 (2.8%)	476 (2.8%)
95% CI	2.5%-3.2%	2.4%-3.1%	2.6%-3.1%
Relative risk vs 2nd/3rd trimester	1.01	—	—
95% CI	0.85-1.21	—	—

[a]Prevalence rates for birth defects according to the Metropolitan Atlanta Congenital Defects Program and the Texas Birth Defects Registry are 3% and 4% of live births, respectively.
ARV, antiretroviral; CI, confidence interval.

Figure 3. Birth Defects Among First Trimester Exposures for Specific Drugs



Conclusions

- No increases in risk of overall birth defects or specific defects have been detected when compared with observed MACDP or TBDR rates or with rates among those with earliest exposure in the second or third trimester
- Our analysis of individual drugs with sufficient data to warrant a separate analysis, with the exception of didanosine and nelfinavir, shows no significant increases in risk of birth defects
- We found a modest but statistically significant increase in overall rates of defects following first trimester exposure to didanosine (1.7-fold) and nelfinavir (1.7-fold), when compared with the MACDP, but not the TBDR. No specific pattern of birth defects was detected following either didanosine or nelfinavir exposure
- For abacavir, atazanavir, emtricitabine, lamivudine, lopinavir, 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 two-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 darunavir, efavirenz, indinavir, raltegravir, 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

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 apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause. The Registry notes modest but statistically significant elevations of overall defect rates with didanosine and nelfinavir compared with its population-based comparators, the MACDP and TBDR. 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. Given the emergence of new therapies about which data are still insufficient, health care providers are strongly encouraged to report eligible patients to the Registry at www.APRegistry.com.

Acknowledgments

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Reference

Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2016. Wilmington, NC: Registry Coordinating Center; 2016. Available from URL: www.APRegistry.com.