The
Antiretroviral Pregnancy Registry

Developing Registries for Post-Marketing Risk Assessment: Lessons Learned

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On behalf of the APR Steering Committee

Forum for Collaborative HIV Research
Global Surveillance of Antiretroviral Drug Safety
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The Antiretroviral Pregnancy Registry

For:

Abacavir (ZIAGEN®, ABC)
Abacavir+lamivudine (EPZICOM®, EPZ)
Abacavir+lamivudine+zidovudine (TRIZIVIR®, TZV)
Adefovir dipivoxil (HEPSERA®, ADV)
Amprenavir (AGENERASE®, APV)
Atazanavir sulfate (REYATAZ®, ATV)
Darunavir (PREZISTA™, DRV)
Delavirdine mesylate (RESCRIPTOR®, DLV)
Didanosine (VIDEX®,VIDEX® EC, ddI)
Didanosine generic – Barr Labs
Didanosine generic – Aurobindo
Didanosine (unknown manufacturer)
Efavirenz+tenofovir disoproxil fumarate+emtricitabine (ATRIPLA®, ATR)
Efavirenz (SUSTIVA®, STOCRIN®, EFV)
Efavirenz (unknown manufacturer)
Emtricitabine (EMTRIVA®, FTC)
Enfuvirtide (FUZEON®, T-20)
Entecavir (BARACLUDE®, ETV)
Etravirine (INTELENCE™, ETR)
Fosamprenavir calcium (LEXIVA®, FOS)
Indinavir (CRIXIVAN®, IDV)
Lamivudine (EPIVIR®, 3TC)
Lamivudine (unknown manufacturer)
Lamivudine+zidovudine (COMBIVIR®, ZDV+3TC)
Lamivudine+zidovudine (unknown manufacturer)
Lopinavir+ritonavir (KALETRA®, ALUVIA®, LPV/r)
Maraviroc (SELZENTRY ®, CELSENTRI ®, MVC)
Nelfinavir (VIRACEPT®, NFV)
Nevirapine (VIRAMUNE®, NVP)
Nevirapine (unknown manufacturer)
Raltegravir (ISENTRESS™, RAL)
Ritonavir (NORVIR®, RTV)
Saquinavir (FORTOVASE®, SQV-SGC) *(Fortovase no longer manufactured as of 6July06)*
Saquinavir mesylate (INVIRASE®, SQV-HGC)
Stavudine (ZERIT®, d4T)
Stavudine generic - Aurobindo
Stavudine generic – Mylan
Stavudine generic – Cipla
Stavudine (unknown manufacturer)
Telbivudine (SEBIVO®, TYZEKA®, LdT)
Tenofovir disoproxil fumarate (VIREAD®, TDF)
Tenofovir disoproxil fumarate+emtricitabine (TRUVADA®, TVD)
Tipranavir (APTIVUS®, TPV)
Zalcitabine (HIVID®, ddC) *(HIVID no longer manufactured as of 12Dec06)*
Zidovudine (RETROVIR®, ZDV)
Zidovudine generic – Ranbaxy
Zidovudine generic – Teva/GSK
Zidovudine generic – Roxane/BI
Zidovudine generic – Aurobindo
Zidovudine generic - Cipla
Zidovudine generic – Mylan
Zidovudine generic – Hetero
Zidovudine (unknown manufacturer)

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Introduction

- Registries are valuable tools for identifying and characterizing safety signals as a means of risk management in marketed products.
- Disease registries can help collect data on drug exposure and other factors associated with a clinical condition.
- Registries require unique approaches in design, data collection, statistical analysis, and reporting and dissemination of data.
- Challenges in subject recruitment and retention, comparison groups, privacy issues (informed consent, HIPAA), and data integrity require nontraditional and often creative solutions.

Introduction

Utility of Pregnancy Registries

- Monitor for suspected risks raised by preclinical studies, premarketing clinical studies, or post-marketing case reports
- Identify factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or maternal characteristics
- Provide margins of reassurance regarding the lack of risk when a precise measure is impossible
- Serve as hypothesis-generating tools
- Look for potential adverse outcomes in a setting where routine clinical trials are impractical

Objectives

- To describe challenges and critical success factors in conducting registries for post-marketing risk assessment using the Antiretroviral Pregnancy Registry (APR) as an example
- To review APR data

Background

- APR is an international prospective registry designed to monitor congenital anomalies following prenatal exposure to antiretroviral drug therapy
- Provides post-marketing safety surveillance of 34 products from 16 pharmaceutical companies
- Study ongoing for 20 years (since January 1, 1989)
- Combines site-based with open enrollment from over 1700 sites; 13,000+ patients from over 40 countries
- Sponsors devote significant financial resources to this effort

Background

Purpose of APR

- Estimate the prevalence of major birth defects and compare to the general population
- Provide an early warning signal of major teratogenicity
- Supplement data from animal toxicology, retrospective spontaneous reports, clinical trials, and epidemiological studies

Significance of APR

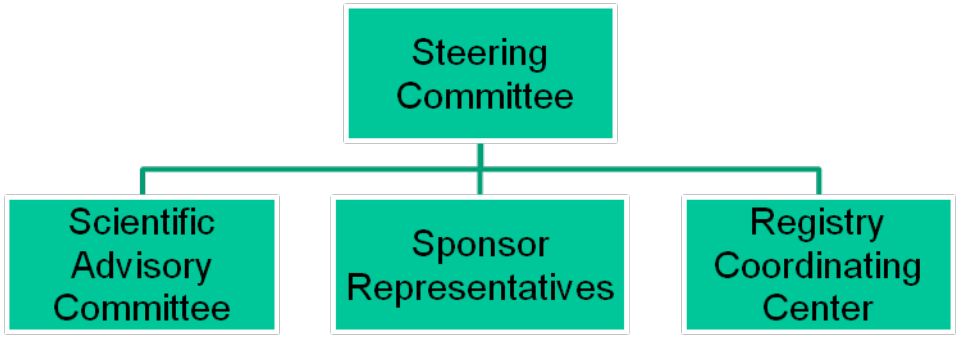
- Unique project expressly established to evaluate prospective and retrospective data related to prenatal exposure to marketed antiretroviral drug therapy
- Designed to assist clinicians and patients in weighing potential risks and benefits of treatment

Methods

Study Design

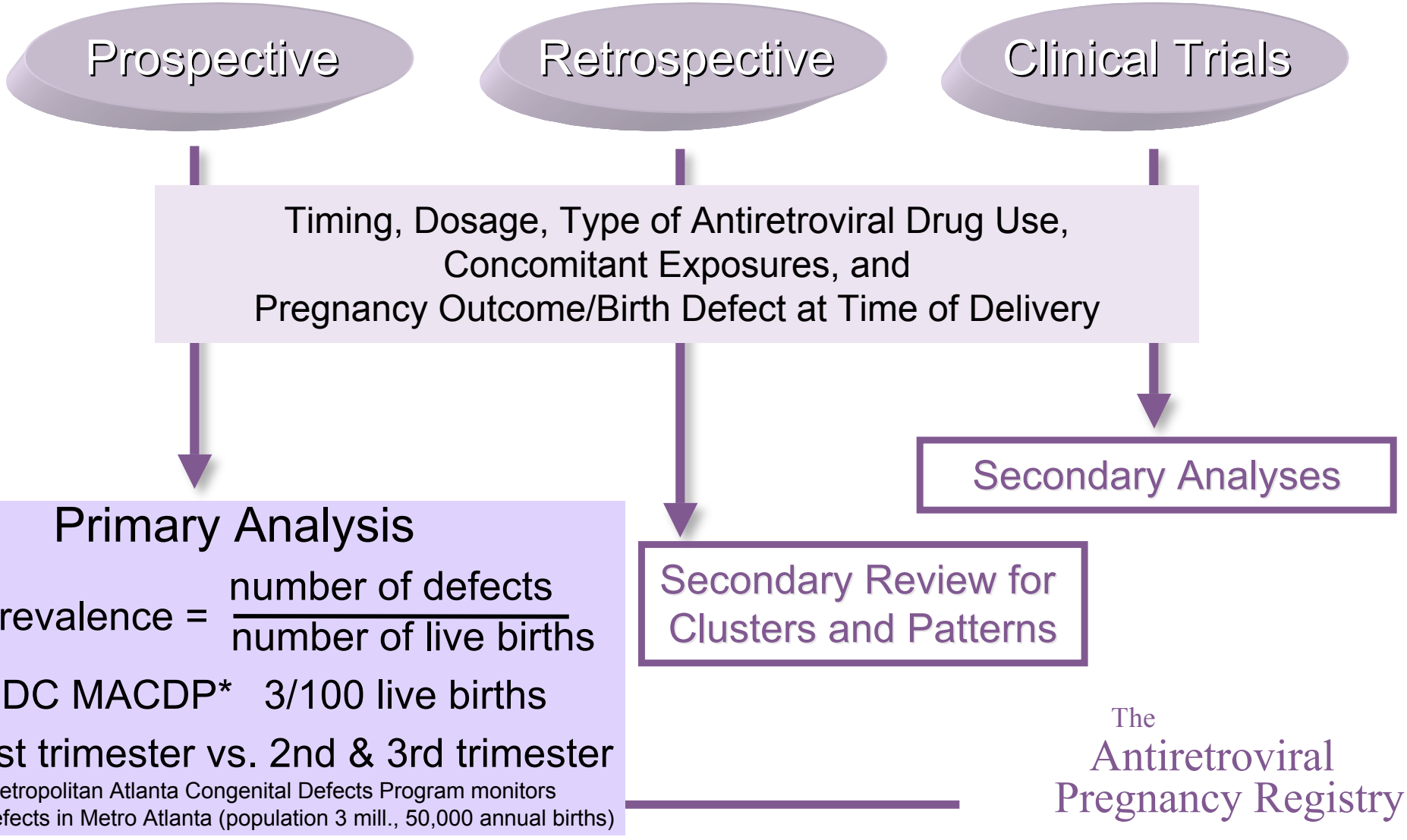
- Prospective exposure-registration cohort
- Healthcare providers voluntarily:
  - Register pregnant women exposed to antiretroviral therapy
  - Report data on antiretroviral therapy exposure throughout pregnancy
  - Provide fetal/neonatal outcome data

Governance Structure



- APR is overseen by a committee of experts in obstetrics, pediatrics, teratology, infectious disease, epidemiology, and biostatistics from academia, government, and the pharmaceutical industry

Methods



The Antiretroviral Pregnancy Registry

Challenges and APR Solutions

Challenge	APR Solution / Success Factors	Pro/Con to APR Solution
Study Design: Collecting adequate data with minimal burden on the reporter	Brief CRFs focusing on critical variables only Single reporter (HCP) Short duration: follow-up ends at the time of pregnancy outcome	Pro: Simple registration and follow-up process facilitates enrollment and reduces losses to follow-up Con: Ascertainment bias (birth defects after the delivery hospitalization may not be reported)
Comparison Group(s): Enrolling controls is costly and logistically difficult. Existing Databases often lack critical variables	APR uses 2 control groups: External: CDC's published rates from population based birth defect surveillance study (MACDP) Internal: 1st Trimester exposures compared with 2nd and 3rd trimester exposures	Pro: Comparison data readily available. No burden of recruiting controls. Con: Exposed group could differ in characteristics other than exposure. Regional bias to cohort may be present

Primary Analysis

Prevalence of Birth Defects and Confidence Intervals

Prospective Data Received 1998 through July 2009

Number of Live Births	10803	
Number of Live Births with at least one defect	288	(2.7%)

Earliest Exposure	Defects/Live births	% (95% CI)
First Trimester	134/4702	2.8% (2.4–3.4)
Second/Third Trimester	153/6100	2.5% (2.1–2.9)
Any Trimester	288/10803	2.7% (2.4–3.0)

Risk of defects for first trimester exposures relative to second/third trimester exposures

1.14 (95% CI: 0.90–1.43)

Comparator prevalence rate: 2.72/100 live births (95% CI = 2.7-2.8)

Birth Defects

Prevalence of Birth Defects (95% CI)
July 31, 2009

	First Trimester Exposure	
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)
Efavirenz	14/501	2.8% (1.5, 4.7)
Lopinavir	9/526	1.7% (0.8, 3.2)
Didanosine	17/370	4.6% (2.7, 7.3)
Emtricitabine	1/384	2.9% (1.4, 5.1)
Atazanavir sulfate	9/343	2.6% (1.2, 4.9)
Indinavir	6/276	2.2% (0.8, 4.7)

Results

- Among 4702 live births with 1st trimester exposure, there were 134 cases with birth defects, or 2.8 per 100 live births (95% CI: 2.4-3.4). Expected population prevalence is 2.7 per 100 live births.
- To date, 14 drugs have met the threshold of 200 live births with first trimester exposures needed to detect an increased risk (major defect). No increases in risk have been detected with the exception of didanosine during previous years. The Registry continues to monitor didanosine, however no pattern of birth defects has been detected.

Conclusions

Scientific Benefits

- Reduces competition for enrollment of eligible population
- Standardizes study methodology
- Optimizes evaluation of multi-drug regimen outcomes
- Enhances ability to engage advisors with greatest expertise
- Provides clinicians with comprehensive reporting

Operational Benefits

- Reduces competition for enrollment of eligible population
- Uses limited clinical research resources efficiently
- It is cost-effective
- Risk management plan, regulatory commitment
- Mediates data management issues

The Antiretroviral Pregnancy Registry

Conclusions

Key Lessons Learned

- Focus upon well-defined study objectives and collection of pertinent data obtaining targeted follow-up of outcomes of interest
- Engaged stakeholders to gain broad participation
- Maintain scientific rigor throughout all processes
- Because it is accessible to any company who wishes to participate, broad participation and recognition

Conclusions

Success of the Registry depends upon:

- Broad participation of health care providers who register patients and provide follow up information
- Commitment and contributions of 100% providers
- Ascertainment of data on
  - Pregnancy and prenatal events
  - Prenatal ART drug exposure
  - Birth outcomes and defects

Conclusions

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.

References

- Covington D, Roberts S, Tilson H, Watts H, Sacks S, Vannappagari V. Developing Registries for Post-Marketing Risk Assessment: The Antiretroviral Pregnancy Registry Experience. Poster presentation at the 43rd DIA Conference, Atlanta, GA, June 2007.
- Tilson HH, Doi PA, Covington DL, Parker A, Shields K, White W. The Antiretrovirals in Pregnancy Registry: A Fifteenth Anniversary Celebration. Obstetrical & Gynecological Survey 2007;62(2):137-48.
- Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 July 2009. Wilmington, NC: Registry Coordinating Center; 2009. Available at http://www.apregistry.com. Accessed May 2010.
- Food and Drug Administration (FDA). Guidance for Industry: Establishing pregnancy exposure registires. Rockville (MD): US Department of Health and Human Services, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research; 2002. Available from URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071639.pdf. Accessed May 2010.

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The
Antiretroviral
Pregnancy Registry

Scientific Advisory Committee

- Members
  - Experts in teratology, HIV, maternal fetal medicine, biostatistics
    - Agency representatives
      - FDA, NIH-NICHD, CDC
    - Academia
    - Private Practice
    - Patient advocacy representative
    - Birth Defect Evaluator

- Duties
  - Provides scientific guidance
  - Reviews and interprets data
  - Authors an executive summary and a consensus statement
  - Advises on data collection and Registry conduct
  - Disseminates Registry data
  - Encourages referral of cases

Sponsors

- Members
  - Representative from each pharmaceutical manufacturer
    - Epidemiologists,
    - Pharmacovigilance specialists
    - Specialists in infectious disease, HIV/AIDS, obstetrics and gynecology
- Duties
  - Oversee management of the Registry Coordinating Center
  - Approve annual operating budget
  - Share financial responsibilities
  - Meet regulatory reporting requirements

Registry Coordinating Center

- Members
  - Epidemiologist
  - Statistician
  - Birth Defect Evaluator
  - Project leader
  - In-house Clinical Research Associates
  - Data management personnel
- Duties
  - Enrolls cases and obtains follow-up of outcomes
  - Manages data
  - Performs statistical analysis of data and drafts interim report
  - Manages IRB submissions
  - Facilitates adverse event reporting to the sponsors
  - Performs general administrative duties