Preterm Birth, low birth weight and fetal antiretroviral exposure:
Estimated gestational age and birth weight data from singleton live births, 1989 through 31 January 2009


for
The APR Steering Committee
Background

- Reports from several cohorts of ARV-exposed newborns suggest increased prevalence of PTB and LBW associated with protease inhibitor (PI) exposure, while others do not.

- Recent summary: K Patel et al, JID Apr 2009:1035, P1025
The Antiretroviral Pregnancy Registry

Presented at the 2nd International Workshop on HIV Pediatrics
16-17 July 2010, Vienna Austria
- Preterm birth and low birth weight are poorly understood.
- Differences in prevalence between populations is not understood.
- Reports have appeared of groups from markedly different background rates.
- P1025 established no significant difference between “no previous” & other exposures.
The Antiretroviral Pregnancy Registry

Collaborative Project Sponsored by:

Abbott Laboratories
AurobindoPharma Ltd
BoehringerIngleheim Pharmaceuticals, Inc
Bristol-Myers Squibb Company
Cipla Ltd
Gilead Sciences Inc
Hetero USA
Merck & Company Inc

Mylan Laboratories
Novartis Pharmaceuticals
Pfizer Inc
Ranbaxy Inc
Roche
Teva Pharmaceuticals
Tibotec BVBA
Viiv Healthcare (represented by GlaxoSmithKline)

Advisory Committee:
Independent representatives from CDC, NIH, FDA, Academic Medicine, Obstetric& Pediatric Clinical Specialists and Community Peer Advocates

Presented at the 2nd International Workshop on HIV Pediatrics
16-17 July 2010, Vienna Austria
Significance

- Unique project established in 1989 to evaluate prenatal exposure to ARTs
- Designed to assist clinicians and patients in weighing potential risks and benefits of treatment
- Prospective, voluntary registration of pregnant women taking ARV.
- Registration must occur prior to outcome of pregnancy.
The Antiretroviral Pregnancy Registry

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24 different agents in 64 formulations
## Demographics

Median Age = 28 years, range = 13-55

Reports from 66 countries, including:

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>84.9%</td>
</tr>
<tr>
<td>UK</td>
<td>3.3%</td>
</tr>
<tr>
<td>France</td>
<td>1.2%</td>
</tr>
<tr>
<td>South Africa</td>
<td>1.9%</td>
</tr>
<tr>
<td>Germany</td>
<td>0.6%</td>
</tr>
<tr>
<td>Brazil</td>
<td>0.3%</td>
</tr>
<tr>
<td>Australia</td>
<td>0.3%</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.2%</td>
</tr>
<tr>
<td>Other</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

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### Study Population for gestational age & birth weight analysis

Prospective data - 1989 through 31 January 2009

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies enrolled</td>
<td>12451</td>
</tr>
<tr>
<td>Outcome pending</td>
<td>426 (3.4%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1082 (8.7%)</td>
</tr>
<tr>
<td>All pregnancies closed</td>
<td>10942 (87.9%)</td>
</tr>
<tr>
<td>Reports of Live Births with evaluable data</td>
<td>10022 (80.5%)</td>
</tr>
</tbody>
</table>
ART Drug Exposure

ARV by Trimester of earliest exposure

Class of ART exposure

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>3421</td>
</tr>
<tr>
<td>NtRTI</td>
<td>63</td>
</tr>
<tr>
<td>NNRTI</td>
<td>42</td>
</tr>
<tr>
<td>PI</td>
<td>103</td>
</tr>
<tr>
<td>NRTI/NNRTI</td>
<td>1837</td>
</tr>
<tr>
<td>NRTI/NtRTI</td>
<td>296</td>
</tr>
<tr>
<td>NRTI/NtRTI/NNRTI</td>
<td>181</td>
</tr>
<tr>
<td>NRTI/PI</td>
<td>4714</td>
</tr>
<tr>
<td>NtRTI/PI</td>
<td>9</td>
</tr>
<tr>
<td>NNRTI/PI</td>
<td>17</td>
</tr>
<tr>
<td>NRTI/NNRTI/PI</td>
<td>269</td>
</tr>
<tr>
<td>NRTI/NtRTI/PI</td>
<td>765</td>
</tr>
<tr>
<td>NRTI/NtRTI/NNRTI/PI</td>
<td>91</td>
</tr>
<tr>
<td>NRTI/PI/EI</td>
<td>6</td>
</tr>
<tr>
<td>NRTI/NtRTI/PI/EI</td>
<td>10</td>
</tr>
<tr>
<td>NRTI/NtRTI/PI/InSTI</td>
<td>9</td>
</tr>
<tr>
<td>Other combination</td>
<td>34</td>
</tr>
</tbody>
</table>

Due to unknown trimester of exposure data for 1 case, the specific counts may not sum to the overall total.

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The Antiretroviral Pregnancy Registry

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* P=0.001

% Birth Weight<2500g (+/- 95%CI)

Bronx 2002-3

Cotter No Rx

Any Rx

NYS (all)
The Antiretroviral Pregnancy Registry

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* P=0.001
Caution when interpreting data – individual treatment groups (esp BW<1500g) are generally small; differences may not be meaningful. Number of del <1500g:

- Cotter et al: 10
- Patel et al: 26
- APR (2009) 53

Unfortunately, studies are so different that they may not lead to meaningful meta-analysis.
We still do not know the effect of maternal disease stage and activity on complications of pregnancy.

“Preterm delivery syndrome” is thought to be due to multiple etiologies with infection and immunologic causes being most common.
Further research into immunologic and infectious interactions with maintenance of pregnancy is likely to give us important insight into both HIV pathogenesis and the preterm delivery syndrome.
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.
Success

Success of the Registry depends upon:

- Broad participation of health care providers who register patients and provide follow up information
- Complete ascertainment of data on
  - Pregnancy and prenatal events
  - Prenatal ART drug exposure
  - Birth outcomes and defects
Contacts

www.APRegistry.com (website)
registries@kendle.com (e-mail)

The Antiretroviral Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405

US, Canada (toll-free)
Phone: 800-258-4263
Fax: 800-800-1052

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Phone: 00800-5913-1359
Fax: 00800-5812-1658

Brazil (toll-free)
Fax: 888-259-5618

International
Phone: 910-256-0238
Fax: 910-256-0637

Europe
Phone: +32-2-714-5028
Fax: +32-2-714-5024
Pregnancy Outcomes

Evaluable Pregnancies (11867) → 229 multiple births → Pregnancy Outcomes (12098)

- Live Birth, 11261, 93%
- stillbirth, 161, 1%
- spontaneous abortion, 377, 3%
- induced abortion, 299, 3%
# Birth Defects

## Prevalence of Birth Defects (95% CI)

**January 31, 2010**  
First Trimester Exposure

<table>
<thead>
<tr>
<th>Drug</th>
<th>N (Dose)</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>99/3481</td>
<td>2.8% (2.3%, 3.5%)</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>100/3289</td>
<td>3.0% (2.5%, 3.7%)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>37/1080</td>
<td>3.4% (2.4%, 4.7%)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>24/1122</td>
<td>2.1% (1.4%, 3.2%)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>19/882</td>
<td>2.2% (1.3%, 3.3%)</td>
</tr>
<tr>
<td>Stavudine</td>
<td>19/795</td>
<td>2.4% (1.4%, 3.7%)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>19/879</td>
<td>2.2% (1.3%, 3.4%)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>19/670</td>
<td>2.8% (1.7%, 4.4%)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>14/546</td>
<td>2.6% (1.4%, 4.3%)</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>10/590</td>
<td>1.7% (0.8%, 3.1%)</td>
</tr>
<tr>
<td>Didanosine</td>
<td>17/380</td>
<td>4.5% (2.6%, 7.1%)</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>12/456</td>
<td>2.6% (1.4%, 4.6%)</td>
</tr>
<tr>
<td>Atazanavir sulfate</td>
<td>9/393</td>
<td>2.3% (1.0%, 4.3%)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>6/276</td>
<td>2.2% (0.8%, 4.7%)</td>
</tr>
</tbody>
</table>
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CD4 T-Cell

- <= 200 cells/µL: 17.7%
- Unknown/Missing: 5.8%
- 200-499 cells/µL: 46.2%
- >= 500 cells/µL: 30.3%

71.40% Asymptomatic, acute (primary) HIV or *PGL

*PGL-persistent generalized lymphadenopathy

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Methods

- Prospective
- Retrospective
- Clinical Trials

Timing, Dosage, Type of Antiretroviral Drug Use, Concomitant Exposures, and Pregnancy Outcome/Birth Defect at Time of Delivery

Primary Analysis
- Prevalence = number of defects / number of live births
- CDC MACDP* 3/100 live births
- 1st trimester vs 2nd & 3rd trimester

Secondary Analyses
- Secondary Review for Clusters and Patterns

Secondary Review for Clusters and Patterns

*Metropolitan Atlanta Congenital Defects Program monitors defects in Metro Atlanta (population 3 mill., 50,000 annual births)

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# Birth Defects

Confidence Intervals for Birth Defects – All Prospective Registry Cases with Follow-up Data Closed Through 31 January 2010

<table>
<thead>
<tr>
<th></th>
<th>Number of Live Births</th>
<th>Number of Live Births with at least one defect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11261</td>
<td>299 (2.7%)</td>
</tr>
</tbody>
</table>

95% Confidence Intervals for % of Birth Defects for exposures in:

<table>
<thead>
<tr>
<th>Exposition Details</th>
<th>Number of Events</th>
<th>Percentage (% with Defects)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Trimester</td>
<td>138/4954</td>
<td>(2.8%)</td>
<td>(95% CI: 2.3–3.3)</td>
</tr>
<tr>
<td>Second/Third Trimester</td>
<td>160/6306</td>
<td>(2.5%)</td>
<td>(95% CI: 2.2–3.0)</td>
</tr>
<tr>
<td>Any Trimester</td>
<td>299/11261</td>
<td>(2.7%)</td>
<td>(95% CI: 2.4–3.0)</td>
</tr>
</tbody>
</table>

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

1.10 (95% CI: 0.88–1.37)

Due to unknown trimester of exposure data for 1 case with birth defects, the specific counts may not sum to the overall total.