SYSTEMATIC REVIEW OF CLINICAL OUTCOMES OF INFANTS BORN TO WOMEN RECEIVING LOPINAVIR/РИTONAVIR-BASED ANTIRETROVIRAL THERAPY (ART) DURING PREGNANCY

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01.14.14
Introduction

Lopinavir/ritonavir (LPV/r) plus 2 nucleoside reverse transcriptase inhibitors is recommended by the 2012 DHHS Perinatal Guidelines to treat HIV-1 infection in pregnant women and reduce risk of mother-to-child transmission (MTCT)

Increased risk of adverse infant outcomes, such as infant mortality, preterm birth, and low birth weight, have been reported for infants born to HIV-infected women and have been associated with class of ART intervention during pregnancy

Objective:

• To assess MTCT and adverse clinical outcomes in a systematic review of published data on infants born to HIV-infected pregnant women treated with LPV/r-based regimens
Search Strategy and Results

Publication search strategy:
• PubMed/EMBASE databases and HIV congresses were searched for studies published through January 2013 and March 2013, respectively
• Included publications of randomized trials, or prospective/retrospective cohort studies on outcomes of infants of HIV+ pregnant women on LPV/r-based therapy during pregnancy

Post-marketing safety data:
• The AbbVie Global Safety Database was searched for the infant outcome of prematurity, regardless of causality and seriousness

Search Results
• A total of 27 publications describing 17 studies were included in the qualitative synthesis
  • 12 full-length articles
  • 15 abstracts
• The included studies reported on 4331 women treated with LPV/r
# Results

<table>
<thead>
<tr>
<th></th>
<th>Studies reporting (N)</th>
<th>Rate reported in included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTCT</td>
<td>10</td>
<td>0-2.8%</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>13</td>
<td>8.7–25.0%</td>
</tr>
<tr>
<td>Very preterm birth</td>
<td>6</td>
<td>0.4-5.0%</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>6</td>
<td>0.4-5.0%</td>
</tr>
<tr>
<td>Very low birth weight</td>
<td>4</td>
<td>0.3-3.0%</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>5</td>
<td>1.0-4.8%</td>
</tr>
<tr>
<td>Infant mortality</td>
<td>4</td>
<td>0-5.8%</td>
</tr>
</tbody>
</table>

Post-marketing safety data estimated a prematurity reporting rate of 0.66/10 000 patient treatment years for LPV/r.

In one study, infants born to women who received LPV/r 800/200 mg/day vs. >800/200 mg/day had similar rates of preterm birth, low birth weight, and MTCT.¹

## Birth defects

- According to a 2010 manuscript reporting on the Antiretroviral Pregnancy Registry (APR), the overall prevalence of birth defects among infants prenatally exposed to LPV/r was 2.4% (23/955); comparable birth defect rates among infants prenatally exposed to LPV are reported in the APR 2013 interim report.
- Three other studies reported birth defect prevalence of 2% to 8.5%³,⁴,⁵

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Results- Infant Safety

Among live births, 2% of infants in the NRTI group (TZV), 3% in the PI group (LPV/r+CBV), and 4% in the observational group (NVP+3TC/ZDV) died by 6 months\(^1\)

- 14/21 infant deaths occurred among preterm infants (5 in the NRTI group, 6 in the PI group, and 3 in the observational group)\(^1\)

The rate of hospitalization was 2-fold higher and mortality was 5-fold higher in preterm vs. term infants regardless of ARV type\(^1\)

### Infant Morbidity and Mortality Through Six Months of Life\(^1\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Preterm, N (%)</th>
<th>Term, N (%)</th>
<th>P-value</th>
<th>TZV, N (%)</th>
<th>LPV/r+CBV, N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resp Tract Infect</td>
<td>8 (9.1)</td>
<td>9 (2.0)</td>
<td>0.003</td>
<td>10 (3.8)</td>
<td>7 (2.6)</td>
<td>0.47</td>
</tr>
<tr>
<td>Diarrheal Disease</td>
<td>0 (NA)</td>
<td>12 (2.7)</td>
<td>0.23</td>
<td>9 (3.4)</td>
<td>3 (1.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1 (1.1)</td>
<td>4 (0.9)</td>
<td>1.0</td>
<td>5 (1.9)</td>
<td>0 (NA)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4 (4.6)</td>
<td>11 (2.5)</td>
<td>0.29</td>
<td>10 (3.8)</td>
<td>5 (1.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>20 (22.7)</td>
<td>56 (12.7)</td>
<td>0.02</td>
<td>40 (15.2)</td>
<td>36 (13.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Death</td>
<td>6 (6.8)</td>
<td>6 (1.4)</td>
<td>0.002</td>
<td>5 (1.9)</td>
<td>7 (2.6)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

27% of infants had >1 serious adverse event (SAE) in 1 study
- Most common: infectious disease\(^2\)

16% of infants had a grade 3/4 adverse events in 1 study
- Most common: neonatal sepsis, aspiration\(^1\)

In 3 studies reporting grade 3/4 lab abnormalities, the most common abnormalities by study were decreased Hgb (15%)\(^2\), neutropenia (18%)\(^1\), and AST (1.9%, standard LPV/r dose; 1.6%, high dose)\(^3\)

1: Mma Bana, Shapiro et al., Botswana; 2: Kesho Bora, Kenya, South Africa; 3: Peixoto et al., Brazil.
Conclusions

In this systematic review on outcomes of infants exposed to LPV/r in utero, MTCT rates were less than 3% across studies.

Reported preterm birth rates and post-marketing safety data suggest that in utero exposure to LPV/r may not increase risk of preterm birth.

Studies reporting incidence of birth defects in infants exposed to LPV/r in utero ranged from 2-8.5%.

- Data from the Antiretroviral Pregnancy Registry indicates similar rates of birth defects in infants exposed to LPV/r in utero compared to the general population.

In one study, the incidence of mortality among preterm infants was comparable among infants treated with NRTI- and PI-based ARV therapy in utero.
Acknowledgements and Disclosures

All authors are AbbVie employees and may hold AbbVie stock or options.

AbbVie interpreted the data, and reviewed and approved of the presentation.

All authors had access to all relevant data.

Medical writing support was provided by Christine Ratajczak, Ph.D. (AbbVie).