Safety of Triple Drug Antiretroviral Prophylaxis in High Risk HIV-Exposed Neonates

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4. The Hospital for Sick Children, Toronto, Canada
Background: PMTCT in Canada

Vertical transmission in Canada 1997-2011
(Canadian Perinatal HIV Surveillance Database, n=2495 MIP)

- 2.7% vertical transmission overall
- 0.3% (5/1780) with >4 weeks of cART in pregnancy
- 10.7% (12/112) with <4 weeks of cART in pregnancy
- 0.5% with undetectable maternal VL close to delivery (<50 or <40 c/ml)
- 3.1% with maternal VL 40 - 1000 c/ml close to delivery
How should infants of mothers with suboptimal virologic control be managed?

Department of Health & Human Services recommendations for “high risk” infants:

• If no antepartum maternal treatment given
  ➢ **Zidovudine** for 6 weeks PLUS
  ➢ Three doses of **nevirapine** in first week of life (birth, 48 hours later, and 96 hours after second dose; AI)

• “...the decision to combine other drugs should be made in consultation with a pediatric HIV specialist, preferably before delivery, and should be accompanied by counseling of the mother on potential risks and benefits... (BIII)”

• Triple cART has been given to neonates born to mothers with sub-optimal viral control for over 10 years

• 2 most common regimens
  ZDV/3TC/Nelfinavir
  ZVD/3TC/Nevirapine

Dosing (term infants)

ZDV: 4mg/kg BID
3TC: 2mg/kg BID
Nelfinavir: 40-50mg/kg/BID
or
NVP: 150mg/m² daily, increased to BID dosing after two weeks of age
Objective:
To determine the safety of triple cART at treatment doses in HIV-exposed newborn infants

Specific outcomes:
- Incidence of anemia and neutropenia among cART vs ZDV treated infants
- Incidence of treatment discontinuation due to adverse events
- Growth parameters among cART vs ZDV treated infants at 1 and 6 months of age
Methods

• Retrospective review of all HIV exposed infants born at 4 Canadian Hospital Centers between 1997-2012

• Eligibility criteria for infants
  ➢ Born to HIV infected mother and initiated on cART at treatment doses within 72 hours of birth*
  ➢ Single or three dose nevirapine regimens excluded

• Controls
  ➢ All ZDV treated infants followed at the Hospital for Sick Children over three year period (2010-2012)

*Per institution protocol, majority started within 12 hours of birth
Results

• 148 infants received triple cART
  ➢ Rationale for cART
    • Documented detectable maternal viral load (78.4%)
    • Other overlapping factors: poor adherence (45%), late diagnosis (20%), no antenatal care (8%), refused treatment (8%)
  ➢ Regimens
    • 59 – Zidovudine, Lamivudine & Nevirapine
    • 82 – Zidovudine, Lamivudine & Nelfinavir
    • 7 – Zidovudine, Lamivudine & Lopinavir/r

• 145 zidovudine monotherapy recipients as comparison group
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>cART</th>
<th>Zidovudine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>29.3 ± 5.0</td>
<td>33.7 ± 5.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Maternal viral load (c/mL)</td>
<td>9806±34,539</td>
<td>&lt;50±137</td>
<td>0.003</td>
</tr>
<tr>
<td>Maternal CD4 count (cells/µL)</td>
<td>411 ±258</td>
<td>519 ±220</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### Timing of Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Prior to pregnancy</th>
<th>During pregnancy</th>
<th>At delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61.9%</td>
<td>34.7%</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td>88.3%</td>
<td>11.7</td>
<td>0</td>
</tr>
</tbody>
</table>

### Mode of Delivery

<table>
<thead>
<tr>
<th></th>
<th>Vaginal</th>
<th>C/section Elective</th>
<th>C/Section: Emergency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>37.8%</td>
<td>46.6%</td>
<td>15.4%</td>
</tr>
<tr>
<td></td>
<td>60.7%</td>
<td>26.9%</td>
<td>12.4%</td>
</tr>
</tbody>
</table>

| Infant sex (% female) | 48.9% | 54.5% | NS       |

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>37.7±2.53</th>
<th>38.4±1.94</th>
<th>0.02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (&lt; 37 weeks; %)</td>
<td>20%</td>
<td>11.8%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

§ Only one with a viral load > 1000 copies/mL
Vertical transmission

• cART Recipients
  ➢ Vertical transmission in **8.8%** (13/148)
  ➢ 46% likely infected *in utero*: DNA PCR positive within 48 hours of birth in 6 of 13
  ➢ 13 infected infants who had started cART at birth for prophylaxis:
    • Sustained virological suppression achieved in 4 cases (Oral Abstract #TUAB0206LB)
    • 9 never suppressed: Failure associated with poor adherence, treatment interruptions or intermittent viral load blips

• None of ZDV treated infants infected
Clinical adverse events

• Non-specific symptoms/signs in cART recipients: 15.5%
  ➢ “Related to cART”: Irritability (0.68%), jitteriness (1.35%), vomiting (3.38%), diarrhea (2.70%), rash (2.70%)

• Treatment discontinuation
  ➢ cART recipients (n=14) (9.5%)
    • Possible medication toxicity (n=10)
    • Stopped by parents; no toxicity (n=4)
  ➢ ZDV recipients (n=3) (2.1%)
    • Anemia in all 3; hemoglobin < 80 g/L in 2
# Treatment discontinuation due to possible adverse events in cART recipients

<table>
<thead>
<tr>
<th>Case</th>
<th>Regimen</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZDV/3TC/NVP</td>
<td>Rash, vomiting, diarrhea at 7 days §</td>
</tr>
<tr>
<td>2</td>
<td>ZDV/3TC/NVP</td>
<td>Rash at 10 days</td>
</tr>
<tr>
<td>3</td>
<td>ZDV/3TC/NVP</td>
<td>Hemogoblin 62 g/L at 2 weeks; transfused PRBC</td>
</tr>
<tr>
<td>4</td>
<td>ZDV/3TC/NLF</td>
<td>Hemogoblin 76 g/L at 4 weeks</td>
</tr>
<tr>
<td>5</td>
<td>ZDV/3TC/NLF</td>
<td>Neutropenia (0.4 cells/mm³) at 4 weeks</td>
</tr>
<tr>
<td>6</td>
<td>ZDV/3TC/NLF</td>
<td>Persistent vomiting at 3 weeks</td>
</tr>
<tr>
<td>7</td>
<td>ZDV/3TC/NLF</td>
<td>Possible pancreatitis (lipase 162 U/L) at 2 weeks</td>
</tr>
<tr>
<td>8</td>
<td>ZDV/3TC/NLF</td>
<td>Elevated GGT (494 U/L) on day 10</td>
</tr>
<tr>
<td>9</td>
<td>ZDV/3TC/NLF</td>
<td>CPK 1243 U/L at 4 weeks</td>
</tr>
<tr>
<td>10</td>
<td>ZDV/ABC/LPV</td>
<td>Hemogoblin 92 g/L at 4 weeks</td>
</tr>
</tbody>
</table>

§ Likely secondary to viral illness; brother with similar symptoms
Impact of treatment on hemoglobin

- Month 1: cART and ZDV
- Month 2: cART and ZDV
- Month 6: cART and ZDV

- p = 0.15
- p = 0.20
- p = 0.05
## Laboratory measures at 6 months of age

<table>
<thead>
<tr>
<th>Variable (mean ± SD)</th>
<th>cART</th>
<th>ZDV</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count (x10^9/L)</td>
<td>9.50±3.10</td>
<td>9.50±2.60</td>
<td>0.96</td>
</tr>
<tr>
<td>Neutrophil count (x10^9/L)</td>
<td>2.09±1.24</td>
<td>2.04±1.38</td>
<td>0.75</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>118±11</td>
<td>121±8</td>
<td>0.05</td>
</tr>
<tr>
<td>Platelet count (x10^9/L)</td>
<td>432±139</td>
<td>425±113</td>
<td>0.66</td>
</tr>
<tr>
<td>ALT (units/L)</td>
<td>24.7±15.9</td>
<td>22.4±9.30</td>
<td>0.89</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.94±0.90</td>
<td>1.76±0.73</td>
<td>0.18</td>
</tr>
</tbody>
</table>
# Impact of treatment on hemoglobin

<table>
<thead>
<tr>
<th></th>
<th>1 MONTH</th>
<th>2 MONTHS</th>
<th>6 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cART</td>
<td>ZDV</td>
<td>cART</td>
</tr>
<tr>
<td>Normal</td>
<td>49.3 %</td>
<td>60.7 %</td>
<td>46.3 %</td>
</tr>
<tr>
<td>Mild</td>
<td>25.7 %</td>
<td>17.9 %</td>
<td>35.8 %</td>
</tr>
<tr>
<td>Moderate</td>
<td>21.6 %</td>
<td>20.0 %</td>
<td>16.3 %</td>
</tr>
<tr>
<td>Severe</td>
<td>3.4 %</td>
<td>1.4 %</td>
<td>1.6 %</td>
</tr>
</tbody>
</table>

| p value §        | 0.03    | NS       | NS       |

## Grading of anemia:
- At 1 month: mild = 95-105 g/L; moderate = 80-94 g/L; severe < 80 g/L
- At 2 & 6 months: mild = 85-100 g/L; moderate = 75-84 g/L; severe < 75 g/L

§ Mantel-Haenszel $\chi^2$
Impact of treatment on neutrophil count

- p = 0.68
- p = 0.69
- p = 0.23
## Impact of treatment on neutrophil count

<table>
<thead>
<tr>
<th></th>
<th>1 MONTH</th>
<th></th>
<th>2 MONTHS</th>
<th></th>
<th>6 MONTHS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cART</td>
<td>ZDV</td>
<td>cART</td>
<td>ZDV</td>
<td>cART</td>
<td>ZDV</td>
</tr>
<tr>
<td>Normal</td>
<td>67.2 %</td>
<td>67.0 %</td>
<td>71.3 %</td>
<td>66.9 %</td>
<td>73.3 %</td>
<td>69.5 %</td>
</tr>
<tr>
<td>Mild</td>
<td>14.1 %</td>
<td>23.2 %</td>
<td>13.9 %</td>
<td>13.0 %</td>
<td>16.2 %</td>
<td>14.1 %</td>
</tr>
<tr>
<td>Moderate</td>
<td>10.2 %</td>
<td>7.9 %</td>
<td>8.1 %</td>
<td>12.9 %</td>
<td>6.7 %</td>
<td>10.9 %</td>
</tr>
<tr>
<td>Severe</td>
<td>8.6 %</td>
<td>2.9 %</td>
<td>6.5 %</td>
<td>7.2 %</td>
<td>3.8 %</td>
<td>5.5 %</td>
</tr>
<tr>
<td>p value §</td>
<td>0.04</td>
<td></td>
<td>NS</td>
<td></td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
## Impact of Treatment on Growth

<table>
<thead>
<tr>
<th></th>
<th>cART</th>
<th>ZDV</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (gm)</td>
<td>2920±580</td>
<td>3093±560</td>
<td>0.02</td>
</tr>
<tr>
<td>1 month measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (gm)</td>
<td>3920±610</td>
<td>4170±590</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>51.7±2.71</td>
<td>52.3±272</td>
<td>0.06</td>
</tr>
<tr>
<td>Head Circumference (cm)</td>
<td>36.7±1.50</td>
<td>37.2±1.30</td>
<td>0.002</td>
</tr>
<tr>
<td>6 month measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (gm)</td>
<td>8000±1120</td>
<td>8230±1140</td>
<td>NS</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>67.0±2.84</td>
<td>68.2±3.30</td>
<td>0.002</td>
</tr>
<tr>
<td>Head Circumference (cm)</td>
<td>43.6±1.86</td>
<td>44.2±1.76</td>
<td>0.009</td>
</tr>
<tr>
<td>∆ Weight 1-6 months</td>
<td>4090±922</td>
<td>4070±939</td>
<td>NS</td>
</tr>
<tr>
<td>∆ Height 1-6 months</td>
<td>15.5±2.68</td>
<td>15.9±2.81</td>
<td>NS</td>
</tr>
<tr>
<td>∆ HC 1-6months</td>
<td>7.07±1.32</td>
<td>7.00±1.44</td>
<td>NS</td>
</tr>
</tbody>
</table>
## WHO Z-Score Differences

<table>
<thead>
<tr>
<th></th>
<th>cART</th>
<th>ZDV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 month Z Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>-0.84 ± 1.19</td>
<td>0.31 ± 1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height</td>
<td>-1.29±1.36</td>
<td>-0.94±1.38</td>
<td>0.05</td>
</tr>
<tr>
<td>Weight &lt;-2 SD (n,%)</td>
<td>19 (15.4%)</td>
<td>8 (5.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>6 month Z Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>0.38±1.16</td>
<td>0.71±1.43</td>
<td>0.06</td>
</tr>
<tr>
<td>Height</td>
<td>0.16±0.19</td>
<td>0.76±1.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight&lt;-2SD (n,%)</td>
<td>1 (0.3%)</td>
<td>2 (0.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight&gt;2 SD</td>
<td></td>
<td>55 (20.2%)</td>
<td></td>
</tr>
</tbody>
</table>
Summary & Conclusions

• Despite triple cART PEP, the vertical transmission rate was 8.8% in these high risk situations

• Triple cART in neonates was generally well tolerated
  - No significant differences in absolute laboratory measures at 1, 2 and 6 months of age
  - Possible increase in severe symptoms (*sample size limitations*) at 1 month of age
  - No significant differences in grade II or higher anemia or neutropenia at 2 and 6 months of age
Summary & Conclusions

However...

• Higher incidence of early treatment discontinuation among cART treated infants (9.5% vs 2.2%)

• cART treated infants
  ➢ Lower birth weight, higher rate pre-term delivery
  ➢ Lower growth parameters at birth and 1 month of age, but “Catch up” at 6 month of age
Further Directions

- Close monitoring and long term follow-up of cART treated infants is necessary
- There remain practical & knowledge gaps regarding neonatal cART
  - Limited availability of newborn-friendly formulations
  - Options for PMTCT of drug resistant virus
  - Pharmacokinetic studies of antiretroviral medications in neonates & pre-term infants