Post-Exposure Prophylaxis of Breastfeeding HIV-Exposed Infants with Antiretroviral Drugs to Age 14 Weeks: Updated Efficacy Results of the PEPI-Malawi Trial

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In 2008 we reported that Post-Exposure Prophylaxis of Infants (PEPI)-Malaw trial, data through August 2007, demonstrated extending daily infant antiretroviral prophylaxis to age 14 weeks reduced postnatal HIV-1 transmission by i) >65% during the period of prophylaxis ii) ~50% at age 9 months.

This analysis updates and extends efficacy estimates through age 24 months in all infants at study completion Sept. 2009.

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PEPI-Malawi Study Design

- Randomized, open-label, phase III trial of antiretroviral prophylaxis in Blantyre, Malawi, 2004-2009.

- Compares control arm of single-dose NVP+1 week ZDV to two 14 week extended prophylaxis arms in infants born to HIV-1 infected mothers.

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### Study Design

<table>
<thead>
<tr>
<th>Intra-partum*</th>
<th>Birth</th>
<th>Post-partum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aug 2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVP x1*</td>
<td>Infant NVP x1</td>
<td>Infant ZDV x1 wk</td>
</tr>
<tr>
<td><strong>Extended NVP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVP x1*</td>
<td>Infant NVP x1</td>
<td>Infant ZDV x1 wk</td>
</tr>
<tr>
<td><strong>Extended NVP + AZT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVP x1*</td>
<td>Infant NVP x1</td>
<td>Infant ZDV x1 wk</td>
</tr>
</tbody>
</table>

*If mothers diagnosed in time for intra-partum prophylaxis

**Mothers counseled to exclusively breastfeed and wean by 6 months**

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Primary Objectives

- Compare 14 week extended arms to control arm for probability of HIV-1 infection and death among infants not infected at birth.
  - Kaplan-Meier analysis of time to 1st positive HIV-1 test; death; & earliest of death or 1st positive HIV-1 test by arm
  - Primary outcome is HIV-1 infection by 9 months

- Evaluate safety of 14 week extended oral NVP and NVP+ZDV regimen in infants born to HIV-1 infected women.

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PEPI-Malawi Study

- Study visits at 1, 3, 6, 9 & 14 weeks and 6, 9, 12, 15, 18 & 24 months.

- Infant HIV-1 infection based on HIV-1 DNA PCR testing at each visit (or HIV-1 antibody ≥ 15 months).

- Safety based on clinical, hematology and chemistry assessments.

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Study Profile

Antenatal:
Consented and screened 36,835 women: 7,490 HIV-infected (20%)

2,135 HIV-infected women enrolled

Enrolled in study:
3,334 women
3,397 infants

Infants randomized at birth

Control:
1,090 infants
69 HIV-infected at birth
17 undetermined HIV result

Extended NVP:
1,160 infants
79 HIV-infected at birth
10 undetermined HIV result

Extended NVP+ZDV:
1,147 infants
83 HIV-infected at birth
13 undetermined HIV result

Primary Analysis Dataset:
1,004 infants
215 Lost to follow-up:
Uninfected at last visit
116 parental refusal
56 relocation/lost contact
43 no further interest
85 Died: Uninfected at last visit
Reached HIV infection endpoint, or HIV uninfected and completed study
704 infants

Primary Analysis Dataset:
1,071 infants
253 Lost to follow-up:
Uninfected at last visit
112 parental refusal
67 relocation/lost contact
74 no further interest
91 Died: Uninfected at last visit
Reached HIV infection endpoint, or HIV uninfected and completed study
727 infants

Primary Analysis Dataset:
1051 infants
237 Lost to follow-up:
Uninfected at last visit
103 parental refusal
71 relocation/lost contact
63 no further interest
86 Died: Uninfected at last visit
Reached HIV infection endpoint, or HIV uninfected and completed study
728 infants

Intrapartum/Postpartum:
Consented and screened 9,351 women: 2,328 HIV-infected (25%)

1,081 HIV-infected women enrolled

Reached HIV infection endpoint, or HIV uninfected and completed study:
704 infants
85 Died: Uninfected at last visit

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## Baseline Characteristics by Treatment Arm

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Extended NVP</th>
<th>Extended NVP+ZDV</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Value (SE)</td>
<td>N</td>
<td>Value (SE)</td>
</tr>
<tr>
<td><strong>Maternal factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>989</td>
<td>26.1 (4.92)</td>
<td>1047</td>
<td>26.2 (4.64)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>957</td>
<td>11.6 (1.83)</td>
<td>1017</td>
<td>11.6 (1.98)</td>
</tr>
<tr>
<td>CD4 (cells/μL) Median (IQR)</td>
<td>401.0</td>
<td>942 (259.0-583.0)</td>
<td>378.0</td>
<td>1001 (248.0-570.0)</td>
</tr>
<tr>
<td>Late presenters %</td>
<td>312/989 (31.6)</td>
<td>327/1047 (31.2)</td>
<td>309/1033 (29.9)</td>
<td>.70</td>
</tr>
<tr>
<td><strong>Infant factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>539/1004 (53.7)</td>
<td>526/1071 (49.1)</td>
<td>523/1051 (49.8)</td>
<td>.08</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1002</td>
<td>3034.1 (453.21)</td>
<td>1070</td>
<td>3009.2 (450.6)</td>
</tr>
</tbody>
</table>

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Visit-specific Breastfeeding Frequencies Among HIV Uninfected Infants at Prior Visits

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Probability of HIV-1 Infection in Infants Uninfected at Birth by Treatment Arm with 95% CIs

<table>
<thead>
<tr>
<th>Age</th>
<th>1wk</th>
<th>6wk</th>
<th>9wk</th>
<th>14wk</th>
<th>9mos</th>
<th>12mos</th>
<th>15mos</th>
<th>18mos</th>
<th>24mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.2</td>
<td>5.2</td>
<td>7.6</td>
<td>8.5</td>
<td>10.5</td>
<td>11.1</td>
<td>11.9</td>
<td>13.4</td>
<td>15.0</td>
</tr>
<tr>
<td>Extended NVP</td>
<td>0.1</td>
<td>1.6</td>
<td>2.4</td>
<td>2.6</td>
<td>4.0</td>
<td>5.0</td>
<td>6.3</td>
<td>7.4</td>
<td>9.5</td>
</tr>
<tr>
<td>Extended NVP+ZDV</td>
<td>0.1</td>
<td>1.4</td>
<td>2.0</td>
<td>2.5</td>
<td>4.9</td>
<td>6.0</td>
<td>7.3</td>
<td>8.1</td>
<td>9.8</td>
</tr>
</tbody>
</table>

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Probability of Death in Infants Uninfected at Birth by Treatment Arm

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Probability of HIV-1 Infection or Death in Infants Uninfected at Birth by Treatment Arm

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<table>
<thead>
<tr>
<th>Age</th>
<th>Control</th>
<th>Extended NVP</th>
<th>Extended NVP+ZDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 wk</td>
<td>0.5</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>6 wks</td>
<td>6.8</td>
<td>3.1</td>
<td>2.6</td>
</tr>
<tr>
<td>9 wks</td>
<td>9.6</td>
<td>4.1</td>
<td>3.7</td>
</tr>
<tr>
<td>14 wks</td>
<td>10.8</td>
<td>4.5</td>
<td>4.6</td>
</tr>
<tr>
<td>6 mos</td>
<td>13.6</td>
<td>6.6</td>
<td>7.8</td>
</tr>
<tr>
<td>9 mos</td>
<td>16.9</td>
<td>10.1</td>
<td>10.6</td>
</tr>
<tr>
<td>12 mos</td>
<td>18.4</td>
<td>12.9</td>
<td>13.9</td>
</tr>
<tr>
<td>15 mos</td>
<td>21.3</td>
<td>15.3</td>
<td>15.8</td>
</tr>
<tr>
<td>18 mos</td>
<td>23.3</td>
<td>17.9</td>
<td>17.7</td>
</tr>
<tr>
<td>24 mos</td>
<td>24.7</td>
<td>19.8</td>
<td>19.9</td>
</tr>
</tbody>
</table>
Protective Efficacy: Extended Treatment Arms vs. Control Arm

Extended Prophylaxis Stopped

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# Risk Factors for HIV-1 Infection

## Proportional Hazards Model

### Risk factors for HIV infection

<table>
<thead>
<tr>
<th>Risk factors for HIV infection</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arms:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended NVP vs. Control</td>
<td>0.60 (0.46, 0.78)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Extended NVP+ZDV vs. Control</td>
<td>0.65 (0.50, 0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Maternal CD4 counts</td>
<td>1.22 (1.16, 1.29)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>(Decrease of 100 units)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal Presentation</td>
<td>1.27 (1.00, 1.60)</td>
<td>0.05</td>
</tr>
<tr>
<td>(late vs. early)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant's gender</td>
<td>0.90 (0.72, 1.13)</td>
<td>0.37</td>
</tr>
<tr>
<td>(female vs. male)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant's birth weight (Kg)</td>
<td>0.82 (0.64, 1.05)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

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### Risk Factors for HIV-1 Infection or Mortality Proportional Hazards Model

<table>
<thead>
<tr>
<th>Risk factors for HIV infection or mortality</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment arms:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended NVP vs. Control</td>
<td>0.71 (0.58, 0.87)</td>
<td>0.001</td>
</tr>
<tr>
<td>Extended NVP+ZDV vs. Control</td>
<td>0.73 (0.60, 0.90)</td>
<td>0.003</td>
</tr>
<tr>
<td>Maternal CD4 counts (Decrease of 100 units)</td>
<td>1.14 (1.10, 1.18)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Maternal Presentation (late vs. early)</td>
<td>1.09 (0.91, 1.30)</td>
<td>0.35</td>
</tr>
<tr>
<td>Infant's gender (female vs. male)</td>
<td>1.01 (0.85, 1.19)</td>
<td>0.94</td>
</tr>
<tr>
<td>Infant's birth weight (Kg)</td>
<td>0.63 (0.52, 0.76)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

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### Serious Adverse Events by Treatment Arm

<table>
<thead>
<tr>
<th>Relatedness to Study Treatment</th>
<th>Control N(^1) (n(^2))</th>
<th>Extended NVP N(^1) (n(^2))</th>
<th>Extended NVP+ZDV N(^1) (n(^2))</th>
<th>P-value (^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not related</td>
<td>374 (555)</td>
<td>402 (571)</td>
<td>379 (573)</td>
<td>.68</td>
</tr>
<tr>
<td>Possibly related</td>
<td>42 (44)</td>
<td>46 (47)</td>
<td>73 (78)</td>
<td>.01</td>
</tr>
<tr>
<td>Probably related</td>
<td>3 (3)</td>
<td>6 (6)</td>
<td>8 (8)</td>
<td>.38</td>
</tr>
<tr>
<td>Total</td>
<td>395 (602)</td>
<td>435 (624)</td>
<td>429 (659)</td>
<td>.80</td>
</tr>
</tbody>
</table>

1. Number of infants with at least one event in category.
2. Total number of events in category.
3. P-value based on Exact Test.

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Conclusions

- Extended prophylaxis with NVP or NVP+ZDV is safe compared to control arm.

- Extended infant prophylaxis for 14 weeks reduces HIV-1 transmission and improves HIV-1-free survival in breastfed infants.

- Previously reported efficacy of the extended regimens is maintained.

- The protective efficacy of NVP is >70% during the intervention (during the period of prophylaxis up to 14 wks), 55% at 9 mos, 47% at 12 mos and decreases to 31% at 24 mos; longer prophylaxis therefore needed for HIV exposed infants who continue breastfeeding.

- No difference between extended NVP and NVP+ZDV.

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Acknowledgments

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