HPTN 046: Efficacy of Extended Daily Infant Nevirapine through Age 6 Months Compared to 6 Weeks for Prevention of Mother-to-Child Transmission of HIV through Breastfeeding

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Previously shown: Daily infant nevirapine (NVP) given for 6, 14 or 28 weeks to breastfeeding, HIV-exposed infants reduces breastfeeding mother-to-child (MTCT) compared to single-dose (sd) NVP administered at birth

- SWEN
- PEPI - Malawi
- BAN

However, the incremental benefit of extending prophylaxis to 6 months compared to shorter courses has not been directly evaluated

Need for infant NVP safety and efficacy data from 6 weeks through 6 months of age during breastfeeding
HPTN 046

Study Design

Phase III, randomized, double-blind, placebo-controlled study in breastfeeding infants born to HIV-1 infected mothers

Birth  |  6 weeks  |  6 months  |  18 months

- NVP x 6 wks
- Randomize
- Extended NVP through 6 mos
- Placebo through 6 mos
- Follow-up
- Follow-up

Breastfeeding
Primary objectives: To determine the safety and efficacy of NVP administered through 6 months of age compared to 6 weeks of age in prevention of HIV (among breastfeeding infants determined to be HIV un-infected at 6 weeks of age)

Secondary objectives: To compare overall infant mortality at 6 months of age and rates of HIV infection and overall infant mortality through 18 months of age between the two study arms
Study Sites

- Durban, South Africa: Prince Mshiyeni Hospital
- Dar es Salaam, Tanzania: Muhimbili Hospital
- Kampala, Uganda: MUJHU Clinic/Mulago Hospital
- Chitungwiza, Zimbabwe: Chitungwiza Clinics
Methods

- Eligible mother-infant pairs enrolled at birth (within 7 days)
- All enrolled infants provided 6 weeks of daily open-label NVP beginning at enrollment
- Eligible infants randomized at 6 weeks of age (after completion of the open-label NVP regimen) to one of two study arms: NVP or placebo through 6 months of age or cessation of breastfeeding, whichever was earliest
- Randomization stratified by maternal antiretroviral use
- Women were advised to exclusively breastfeed through 6 months
HIV infection defined as confirmed positive DNA PCR; time of infection defined as midpoint between last negative and first positive test

- Kaplan-Meier curves used to estimate HIV transmission and overall survival rates through 6 months of age

- Infant clinical and laboratory evaluations:

<table>
<thead>
<tr>
<th></th>
<th>Birth</th>
<th>2 wk</th>
<th>5 wk</th>
<th>6 wk</th>
<th>8 wk</th>
<th>3 mo</th>
<th>4 mo</th>
<th>5 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
<th>18 mo</th>
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<tbody>
<tr>
<td>Hx/PE</td>
<td>X</td>
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</table>
| DNA PCR  | X     | X    | X    |      | X    | X    | X    | X    | X    | X    | X     | X     | HIV Ab
Randomized Infants and Maternal Characteristics

- 1,522 breastfed, uninfected infants born to 1,505 HIV-infected mothers randomized at age 6 weeks
  - N=759 extended nevirapine
  - N=763 placebo

- Mothers on ART for own health:
  - at randomization: 29% in each study arm
  - at 6 months: 31% in extended NVP arm; 32% in placebo arm

- Median maternal CD4+ count at randomization (6 weeks postpartum):
  - Extended NVP arm: 560 cells/mm³
  - Placebo arm: 528 cells/mm³
Breastfeeding status:
- At 3 months, 95% of infants in each arm were reported to be exclusively breastfed

Adherence to infant study drug:
- 88-96% through 6 months of age
- Balanced between arms

Retention:
- 97% at 6 months, 94% at 12 months
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Time to Breastfeeding Cessation
(Kaplan Meier Plot)

<table>
<thead>
<tr>
<th>% of Infants Not Breastfeeding by Study Arm</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended NVP</td>
<td>14.8%</td>
<td>51.5%</td>
<td>95.4%</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.9%</td>
<td>49.3%</td>
<td>95.5%</td>
</tr>
</tbody>
</table>

Log-rank test $p = 0.929$

Target age for 6 month visit (182 days)
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Time to Infant HIV Infection
(Infants Uninfected at 6 Wks: Kaplan Meier Plot)

### Postnatal Transmission (%, 95% CI) After Age 6 Weeks in Infants by Study Arm

<table>
<thead>
<tr>
<th></th>
<th>Age 6 mo</th>
<th>Age 9 mo</th>
<th>Age 12 mo</th>
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<tbody>
<tr>
<td>Extended NVP</td>
<td>1.1% (0.3-1.8)</td>
<td>1.5% (0.6-2.4)</td>
<td>2.1% (1.0-3.1)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.4% (1.3-3.6)</td>
<td>2.9% (1.7-4.1)</td>
<td>3.0% (1.8-4.2)</td>
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### P Value

<p>| | | | |</p>
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<td>0.049</td>
<td>0.078</td>
<td>0.265</td>
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**Cumulative Probability of HIV**

- Extended NVP
- Placebo

**Age in Days**

- Day 195
- Day 285
- Day 379
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Infant HIV Infection Stratified by Maternal HAART Status at Randomization
(Infants Uninfected at 6 Wks: Kaplan Meier Plot)

- Infants Born to Mothers on HAART
  - Extended NVP
  - Placebo
  - 6 mo: 0.5% Extended NVP, 3.3% Placebo
  - 9 mo: 0.5% Extended NVP, 0.5% Placebo
  - 12 mo: 0.5% Extended NVP, 0.5% Placebo
  - P Value: 0.968

- Infants Born to Mothers Not on HAART
  - Extended NVP
  - Placebo
  - 6 mo: 1.4% Extended NVP, 3.3% Placebo
  - 9 mo: 2.0% Extended NVP, 3.8% Placebo
  - 12 mo: 2.6% Extended NVP, 4.1% Placebo
  - P Value: 0.027, 0.071, 0.263
### HPTN 046

**HIV Infection in Infants of Mothers Not on ART by CD4 count and Study Arm**

<table>
<thead>
<tr>
<th></th>
<th>Age 6 mos</th>
<th></th>
<th>Age 9 mos</th>
<th></th>
<th>Age 12 mos</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD4 &lt;350</td>
<td>CD4 &gt;350</td>
<td>CD4 &lt;350</td>
<td>CD4 &gt;350</td>
<td>CD4 &lt;350</td>
<td>CD4 &gt;350</td>
</tr>
<tr>
<td><strong>Extended NVP</strong></td>
<td>4.8% (0.2-9.4)</td>
<td><strong>0.7%</strong> (0-1.5)</td>
<td>7.5% (1.7-13.3)</td>
<td><strong>0.9%</strong> (0-1.8)</td>
<td>8.9% (2.5-15.1)</td>
<td><strong>1.7%</strong> (0.4-2.9)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>7.9% (1.3-14.6)</td>
<td>2.8% (1.3-4.4)</td>
<td>7.9% (1.3-14.6)</td>
<td>3.3% (1.6-4.9)</td>
<td>9.6% (2.3-17.0)</td>
<td>3.3% (1.6-4.9)</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>0.451</td>
<td><strong>0.014</strong></td>
<td>0.923</td>
<td><strong>0.014</strong></td>
<td>0.874</td>
<td><strong>0.118</strong></td>
</tr>
</tbody>
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**WHO Guidelines:**
- **CD4 <350:** ART-Eligible for Own Health (ARV for treatment)
- **CD4 >350:** ART-Ineligible (ARV use for prophylaxis only)
### Infant Mortality After Age 6 Weeks

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Age 6 mos (%)</th>
<th>Age 9 mos (%)</th>
<th>Age 12 mos (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended NVP</td>
<td>1.2% (0.4-2.0)</td>
<td>2.2% (1.1-3.3)</td>
<td>3.1% (1.7-4.5)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.1% (0.3-1.8)</td>
<td>2.6% (1.5-3.8)</td>
<td>3.7% (2.3-5.2)</td>
</tr>
</tbody>
</table>

P Value:
- Age 6 mos: 0.81
- Age 9 mos: 0.59
- Age 12 mos: 0.54

Most Infant Mortality Occurred After Age 6 Months (post-weaning)
### HPTN 046 Safety

<table>
<thead>
<tr>
<th></th>
<th>Extended NVP N=758</th>
<th>Placebo N=761</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Adverse Events (AE)</td>
<td>83%</td>
<td>83%</td>
</tr>
<tr>
<td>AE probably or definitely related to study drug</td>
<td>12 infants</td>
<td>8 infants</td>
</tr>
<tr>
<td>Serious Adverse Events (SAE)*</td>
<td>19%</td>
<td>17%</td>
</tr>
</tbody>
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**SAE:**
- Neutropenia: 1 infant (12 infants), 2 infants (Placebo)
- Increased ALT: 1 infant (12 infants), 1 infant (Placebo)
- Skin rash: 0 infants (12 infants), 0 infants (Placebo)

*Most common SAEs: gastroenteritis (6%), malaria (5%), pneumonia (3%), sepsis (1%), with no difference between study arms*
Conclusions: Safety

- Extended NVP was safe and well tolerated by infants through 6 months of age
- There was no significant difference in AEs or SAEs between arms
Extending daily infant NVP from 6 weeks to 6 months lowered the risk of breastfeeding MTCT at age 6 months.

After prophylaxis was stopped at age 6 months, breastfeeding MTCT between 6 & 12 months was similar between study arms.

Overall mortality risk was similar between study arms.

- ~2/3 of deaths occurred after age 6 months when most infants stopped breastfeeding.
Extended NVP administered through 6 months compared to 6 weeks of age was associated with a 55% reduction in breastfeeding HIV infection at 6 months of age.

Reduction in postpartum infection with extended infant NVP primarily among infants of mothers NOT on ART AND with CD4 counts >350 cells/mm³:
- e.g., not meeting current WHO guidelines for treatment
- 76% reduction

These data support the benefits and safety of extended NVP for infants of mothers who do not yet require HAART for their own health.
Acknowledgements

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