Phase III Randomized Trial of the Safety and Efficacy of Three Neonatal Antiretroviral Regimens for the Prevention of Intrapartum HIV-1 Transmission

NICHD HPTN 040/ PACTG 1043

Karin Nielsen-Saines*, D. Heather Watts, Valdilea G. Veloso, Yvonne J. Bryson, Esau C. Joao, Jose Henrique Pilotto, Glenda Gray, Gerhard Theron, James Bethel, Lynne Mofenson for the NICHD/HPTN 040 Study Group

NICHD HPTN 040

IMPAACT-HPTN
Washington, D.C.
June 8, 2011
Background

- Women with undiagnosed HIV during pregnancy are at high risk of HIV-mother-to-child transmission.

- Observational data show HIV transmission of 9.3% with infant ZDV started within 48 hours of birth compared to 26.6% with no ZDV in infants born to women without ARV in pregnancy. *NEJM 1998:339*

- Identification of HIV-exposed infants at delivery allows starting infant ARV prophylaxis, formula feeding or ARV prophylaxis during breastfeeding.

- Strategies such as HIV rapid testing during labor identify women for their own medical care.
How common is HIV-infection diagnosis at delivery?

Estimated coverage of women using IV ZDV during labor per Brazilian region, 2002

Brasil: ~ 35.5%

Source: Brazilian MOH 2002
Hypothesis

- Multidrug antiretroviral regimens given to the HIV-exposed neonate within 48 hours of birth, in the absence of maternal ARV before labor, will be more effective in preventing intrapartum MTCT than ZDV alone.
Study Design and Objectives

- **Study Design:** Phase III, 3-arm, randomized open-label.

- **Primary objectives:** To compare the **efficacy** at 3 months of age, **safety** and **tolerance** of 3 infant ARV regimens for the prevention of vertical HIV transmission to infants born to HIV-infected women with no ARV during pregnancy.

- **Secondary objectives:** evaluate risk factors for transmission, rates of ARV resistance and disease progression between arms in infected infants, and NVP, NFV, and 3TC pk.
Study Design

No Maternal AP ARV

Arm 1
n=577
ZDV x 6 wk

Arm 2
n=577
ZDV x 6 wk
NVP
NVP
NVP

Arm 3
n=577
ZDV x 6 wk
3TC + Nelfinavir x 2 wk

Target: 1731 Formula-Fed Infants

6 mo f/up

6 wk
3 mo

NICHHD HPTN 040

HIV Infection Status

Birth <48h 2-4d 5-7d 2wk 6 wk
### NICHD/HPTN 040: Study Regimens and Dosing

*Nielsen-Saines K et al. 18th CROI, Boston, 2011 Abs 124LB*

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Study Drug Regimen Started Within 48 Hrs of Birth</th>
</tr>
</thead>
</table>
| 1 (ZDV control) | 557 | - ZDV x 6 weeks  
- 12 mg po BID if BW >2 kg  
- 8 mg po BID if BW ≤2 kg |
| 2 (ZDV/NVP)   | 557 | - ZDV as above  
- NVP:  1st dose within 48 hr of birth (birth-48 hrs)  
- 2nd dose 48 hrs after 1st  
- 3rd dose 96 hrs after 2nd  
- NVP dose: 12 mg po if BW >2 kg  
- 8 mg po if BW ≤2 kg |
| 3 (ZDV/3TC/NFV) | 557 | - ZDV as above  
- 3TC + NFV daily for 2 weeks  
- 3TC dose:  6 mg po BID if BW >2 kg  
- 4 mg po BID if BW ≤2 kg  
- NFV dose:  200 mg po BID if BW >3 kg  
- 150 mg po BID if BW >2 and <3 kg  
- 100 mg po BID if BW ≤2 kg |
Randomization at Study Sites n = 1745
4/2004 to 7/2010

- **Brazil:**
  - Rio de Janeiro:
    - Hospital dos Servidores do Estado = 426
    - Hospital Geral de Nova Iguacu = 418
  - Belo Horizonte:
    - Univ Fed Minas Gerais = 43
  - Porto Alegre:
    - Hospital Conceição = 102
    - Hospital Femina = 98
    - Sta Casa da Misericordia = 83
  - Sao Paulo:
    - Universidade Federal de Sao Paulo, Sao Paulo = 11
    - Universidade de Sao Paulo, Ribeirao Preto = 43

- **Argentina:**
  - Hospital Dr. Diego Paroissien Buenos Aires = 28

- **U.S. sites:**
  - UMD, NJ = 5
  - Miller Children’s Hosp, LB, CA = 1
  - San Juan City Hosp, PR = 2
  - Gainesville, Univ FL = 2
  - Jacksonville, Univ FL = 3
  - Johns Hopkins Univ, MD = 1

- **South Africa:**
  - Chris Hani Baragwanath Hosp Johannesburg = 326
  - Tygerberg Hospital Cape Town = 153
Inclusion Criteria:

1. No maternal ARV in current pregnancy except ZDV in labor.
2. Single + HIV rapid test (pending confirmatory testing) of mother or infant or + HIV serology per country algorithm
3. Maternal informed consent
4. No life-threatening conditions; ability to take PO meds
5. Birth weight > 1.5 kg
6. No extreme prematurity (< 32 weeks gestation)

<table>
<thead>
<tr>
<th>Maternal Lab Evaluations</th>
<th>Entry Labor + Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>X</td>
</tr>
<tr>
<td>Syphilis testing (VDRL)</td>
<td>X</td>
</tr>
<tr>
<td>HIV-1 RNA</td>
<td>X</td>
</tr>
<tr>
<td>T-cell subsets (CD4/CD8)</td>
<td>X</td>
</tr>
<tr>
<td>Urine for storage</td>
<td>X</td>
</tr>
</tbody>
</table>
Study Procedures

- Infants with + HIV DNA PCR at birth and + results on repeat testing were diagnosed with *in utero* infection and excluded from transmission analysis.

<table>
<thead>
<tr>
<th>Infant Lab Evaluations</th>
<th>Birth</th>
<th>4 – 7 days</th>
<th>10 – 14 days</th>
<th>4– 6 wks</th>
<th>3 mo.</th>
<th>6 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 DNA PCR (Roche 1.5)</td>
<td>X</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CBC w/ differential</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Serum transaminases</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>HIV-1 RNA (inf)</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>T cell subsets (inf)</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>PK studies (subset)</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Maternal Characteristics

- **Median age**: 26 (13-47 years)
- **Race**: 49% Black, 27% Mulatto, 21% White, 3% Other
- **Median CD4s**: 463 (12-2678)
  - 44% > 500, 43% 200-500, 11% < 200, Missing 2%
- **Median log RNA**: 4.17 (1.65-6.78)
- **Some prenatal care**: 63% (48% at least 3 visits)
- **ZDV during labor**: 41%
- **C-sections (n=599)**: Elective: 23% / Non-elective: 12%
  - 89% of C-sections in Brazil (n= 535)/ 7.8% in S. Africa (n= 47)
- **Vaginal deliveries**: 65%
- All parameters evenly distributed btn study arms.
Infant Parameters

- Median birth weight: 3.0 kg.
- Term (> 36 wk gestation): 90%
- Apgar scores between 7-10: 88%
- Infants formula fed (formula provided by study)
  - Postpartum BF: 9.3% (before maternal HIV diagnosis)
  - 4-7 days BF: 1.5% → 3 mo BF rate: 0.5%
- Treatment adherence: > 96% all arms
- Retention at 3 mo.: 96.2%
- Loss to follow-up: 3.5%
- No difference in infant parameters by study arms
Mortality

- Death of study participants: 43 (2.6%):
  - Per study arm: ZDV: 11 (1.9%)
    ZDV + NVP: 15 (2.7%)
    ZDV + NFV + 3TC: 17 (3.1%)
  - Per country:
    - Brazil: 17 (1.4%) IMR 14 (country IMR 19)
    - S. A.: 26 (5.5%) IMR 54 (country IMR 56)
  - Per HIV status:
    - HIV-infected: 16 (37%)
    - HIV- uninfected: 6 (14%)
    - HIV-status unknown: 21 (49%)

\[ p = 0.49 \]
HIV-Infection Status at 3 Mos

Kaplan-Meier survival curves used for estimates of HIV transmission

- Randomized: n=1745
  - No study drug: -11 infants (0.6%)
- Enrolled: n=1735
  - Mother HIV-infected: -51 infants (2.9%)
- Evaluable: n=1684
  - Uninfected: n=1447 (83.4%)
  - Infected: n=140 (8.3%)
    - In utero: n=93 (5.4%)
    - Intrapartum: n=47 (2.7%)
  - Unknown: n=97 (5.6%)*

* 95/97 DNA neg before 3 mo 2+ at birth, no confirmation
## HIV-Infection Status by Study Arm

<table>
<thead>
<tr>
<th>HIV Status</th>
<th>ZDV</th>
<th>ZDV + NVP</th>
<th>ZDV + 3TC/ NFV</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected - in Utero</td>
<td>37</td>
<td>28</td>
<td>28</td>
<td>93</td>
</tr>
<tr>
<td>Infected - Intrapartum</td>
<td>24</td>
<td>11</td>
<td>12</td>
<td>47</td>
</tr>
<tr>
<td>Uninfected</td>
<td>474</td>
<td>490</td>
<td>483</td>
<td>1447</td>
</tr>
<tr>
<td>Unknown</td>
<td>31</td>
<td>33</td>
<td>33</td>
<td>97</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>566</td>
<td>562</td>
<td>556</td>
<td>1684</td>
</tr>
</tbody>
</table>
In Utero and Intrapartum HIV Transmission

Statistical comparisons between single and multiple ARV arms:
Hochberg’s modified Bonferroni approach

% based on KM curves

ZDV (11.1%)
ZDV/NVP (7.1%)
ZDV/3TC/NFV (7.4%)

ZDV vs. ZDV/NVP: Intrapartum: p = 0.045; Overall transmission: p = 0.034
ZDV vs. ZDV/3TC/NFV: Intrapartum: p = 0.045; Overall transmission: p = 0.034
### 2 Pairwise Comparisons:

<table>
<thead>
<tr>
<th>HIV Status</th>
<th>ZDV n= 566</th>
<th>ZDV + NVP n= 562</th>
<th>ZDV + 3TC/ NFV n= 556</th>
<th>Total n= 1684</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected - in utero</td>
<td>n = 37</td>
<td>n = 28</td>
<td>n = 28</td>
<td>n = 93</td>
<td></td>
</tr>
<tr>
<td>KM Rate (IU)</td>
<td>6.8%</td>
<td>5.1%</td>
<td>5.2%</td>
<td>5.7%</td>
<td>0.2432</td>
</tr>
<tr>
<td>95% CL</td>
<td>5.0 - 9.3</td>
<td>3.5 - 7.3</td>
<td>3.6 - 7.4</td>
<td>4.7 - 7.0</td>
<td></td>
</tr>
<tr>
<td>Infected - Intrapartum</td>
<td>n = 24</td>
<td>n = 11</td>
<td>n = 12</td>
<td>n = 47</td>
<td></td>
</tr>
<tr>
<td>KM Rate (IP)</td>
<td>4.9%</td>
<td>2.2%</td>
<td>2.5%</td>
<td>3.2%</td>
<td>0.046</td>
</tr>
<tr>
<td>95% CL</td>
<td>3.3-7.2</td>
<td>1.2 – 4.0</td>
<td>1.4 - 4.3</td>
<td>2.4 - 4.2</td>
<td></td>
</tr>
<tr>
<td>All infected</td>
<td>n = 61</td>
<td>n = 39</td>
<td>n = 40</td>
<td>n = 140</td>
<td></td>
</tr>
<tr>
<td>KM Rate All</td>
<td>11.0%</td>
<td>7.1%</td>
<td>7.4%</td>
<td>8.5%</td>
<td>0.034</td>
</tr>
<tr>
<td>95% CL</td>
<td>8.7-14.0</td>
<td>5.2-9.6</td>
<td>5.5-9.9</td>
<td>7.3-10.0</td>
<td></td>
</tr>
</tbody>
</table>
## Risk Factors for Transmission

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>OR (95% CL)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV+3TC+NFV</td>
<td>0.50 (0.24 - 1.01)</td>
<td>0.0539</td>
</tr>
<tr>
<td>ZDV+NVP</td>
<td>0.39 (0.19 - 0.82)</td>
<td>0.0128</td>
</tr>
<tr>
<td>ZDV</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Log$_{10}$Viral Load</td>
<td>2.28 (1.56 - 3.35)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>(continuous variable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illegal substance use</td>
<td>2.51 (1.08-5.86)</td>
<td>0.0328</td>
</tr>
</tbody>
</table>

Adjusted multivariate logistic regression analysis

Not associated
- Age
- Race
- Prenatal care
- ZDV in labor
- Maternal Syphilis
- Region of birth
- Mode of delivery
- Gestational age
- CD4 cell count
- Alcohol use
- Tobacco use
- Duration ruptured membranes
## ARV-Related Toxicities
*(Lab SAEs grades >=2)*

<table>
<thead>
<tr>
<th>Subjects with abnormal results</th>
<th>ZDV</th>
<th>ZDV + NVP</th>
<th>ZDV + 3TC/ NFV</th>
<th>Total</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>153</td>
<td>132</td>
<td>147</td>
<td>432</td>
<td>0.35</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>93</td>
<td>84</td>
<td>153</td>
<td>330</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Transaminitis (AST)</td>
<td>18</td>
<td>11</td>
<td>14</td>
<td>43</td>
<td>0.43</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt; 75,000)</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>26</td>
<td>0.75</td>
</tr>
<tr>
<td>Total</td>
<td>286</td>
<td>246</td>
<td>864</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARV resistance mutations (Viroseq)</td>
<td>Overall n (%)</td>
<td>ZDV n (%)</td>
<td>ZDV+NVP n (%)</td>
<td>ZDV+3TC+NFV n (%)</td>
<td>p-value</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------</td>
<td>-----------</td>
<td>---------------</td>
<td>-------------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>NRTI mutations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In utero</td>
<td>2 ( 2.53)</td>
<td>0</td>
<td>0</td>
<td>2 ( 8.33)</td>
<td>0.1717</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>1 ( 2.44)</td>
<td>0</td>
<td>1 (10.00)</td>
<td>0</td>
<td>0.4878</td>
</tr>
<tr>
<td>All</td>
<td>3 ( 2.50)</td>
<td>0</td>
<td>1 ( 3.03)</td>
<td>2 ( 5.88)</td>
<td>0.1706</td>
</tr>
<tr>
<td><strong>PI mutations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In utero</td>
<td>2 ( 2.53)</td>
<td>0</td>
<td>0</td>
<td>2 ( 8.33)</td>
<td>0.1717</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Overall</td>
<td>2 ( 1.67)</td>
<td>0</td>
<td>0</td>
<td>2 ( 5.88)</td>
<td>0.1525</td>
</tr>
<tr>
<td><strong>NNRTI mutations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In utero</td>
<td>9 (11.39)</td>
<td>2 ( 6.25)</td>
<td>5 (21.74)</td>
<td>2 ( 8.33)</td>
<td>0.1871</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>3 ( 7.32)</td>
<td>1 ( 4.76)</td>
<td>1 (10.00)</td>
<td>1 (10.00)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Overall</td>
<td>12 (10.00)</td>
<td>3 ( 5.66)</td>
<td>6 (18.18)</td>
<td>3 ( 8.82)</td>
<td>0.1482</td>
</tr>
<tr>
<td><strong>Any combination:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In utero</td>
<td>10 (12.66)</td>
<td>2 ( 6.25)</td>
<td>5 (21.74)</td>
<td>3 (12.50)</td>
<td>0.2005</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>4 ( 9.76)</td>
<td>1 ( 4.76)</td>
<td>2 (20.00)</td>
<td>1 (10.00)</td>
<td>0.5300</td>
</tr>
<tr>
<td>Overall</td>
<td>14 (11.67)</td>
<td>3 ( 5.66)</td>
<td>7 (21.21)</td>
<td>4 (11.76)</td>
<td>0.0850</td>
</tr>
</tbody>
</table>
Summary

- The risk of *intrapartum* HIV transmission was significantly reduced in the 2 and 3-drug arms as compared to ZDV alone (2.2%, 2.5%, 4.9%, $p = 0.046$).

- The overall HIV transmission rate (*in utero* + *intrapartum*) was also significantly lower in the 2 and 3 drug arms as compared to ZDV alone (7.1%, 7.4%, 11.1%, $p = 0.034$).

- Parameters independently associated with transmission on multivariate analysis were treatment arm (NVP arm), maternal viral load and drug use.

- Adherence was 96% or higher in all treatment arms and retention was 96% at 3 months of age.
Summary/ Conclusions

- 43 infant deaths occurred in the study. None were related to study drug. 6 mo IMR were lower than 12 mo country-specific statistics. Majority of deaths were due to respiratory infections.

- Infants at high risk of HIV-infection, i.e., born to mothers who received no ARV during pregnancy should receive a 2 or 3-drug ARV regimen within 48 hours of life to reduce the risk of HIV infection.

- Although NVP resistance was slightly higher in the NVP arm, it was not significantly greater. Lower toxicity profile (< neutropenia) and ease of use suggests a 2 drug regimen w/ NVP may be preferable.
Acknowledgments…. 

• **Mothers and children who enrolled in the study.**
• **Pharmaceutical**: GlaxoSmithKline (Helen Watson); Boehringer-Ingelheim (Lauren Petrella)
• **Study Sponsor**: Eunice Kennedy Shriver National Institute of Child Health and Human Development: Lynne Mofenson; Jack Moye; George Siberry; Heather Watts
• **NIAID**: Elizabeth Smith and Sheryl Zwerski
• **Study Coordination**: Westat Inc: Margaret Camarca, Jiahong Xu, James Bethel
• **Institutions and Investigators**: UCLA: Karin Nielsen, Ruth Dickover, Yvonne Bryson
  • Fiocruz, Rio de Janeiro: Valdilea Veloso, Mariza Morgado, Francisco Bastos, Beatriz Grinstejn
  • Hospital dos Servidores, Rio de Janeiro: Esau C. Joao, M. Leticia Santos Cruz
  • Hospital Geral de Nova Iguacu, Rio de Janeiro: Jose Henrique Pilotto, Ivete Martins Gomes
  • Hospital Nossa Senhora da Conceicao, Porto Alegre: Breno Riegel Santos, Rita Lira
  • Hospital Femina, Porto Alegre: Rosana Fonseca, Carla Fraga
  • Irmandade Santa Casa de Misericordia, Porto Alegre: Regis Kreitchmann, Debora Coelho
• **Fed University of Minas Gerais, Belo Horizonte**: Jorge Pinto, Fabiana Kakehasi
• **Univ de Sao Paulo, Ribeirao Preto**: Marisa Mussi-Pinhata, Geraldo Duarte
• **Univ of Sao Paulo, Sao Paulo**: Daisy Machado, Regina Succi
• **Hospital Diego Paroissien, Buenos Aires**: Edgardo Szyld, Mariana Ceriotto
• **Univ of Witwatersrand, Johannesburg**: Glenda Gray, James McIntyre
• **Univ of Stellenbosch / Tygerberg Hospital, Cape Town**: Gerhard Theron, Elke Maritz
• **Boston University**: Mark Mirochnick
• **Johns Hopkins Univ, Baltimore**: Allison Agwu,
• **Univ Florida, Gainesville**: Robert Lawrence; **Univ Florida, Jacksonville**: Mobeen Rathore
• **Long Beach Miller Children’s, Long Beach**: Audra Deveikis
• **Univ Medical and Dental School of NJ, Newark**: James Oleske
• **San Juan City Hospital, San Juan**: Midnela Flores