Infectious Morbidity, Mortality and Growth of HIV-exposed, Uninfected, Formula Fed Infants in Brazil and South Africa Enrolled in NICHD HPTN 040/ PACTG 1043

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040 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.
Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy

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

HIV Infection Status
6 mo f/up

Target:
1731 Formula-Fed Infants

6 wk
3 mo

Birth <48h 2-4d 5-7d 2wk
In Utero and Intrapartum HIV Transmission

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

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Background

- Infants enrolled into 040 were followed for 6 months and formula fed exclusively. This was an entry criterion for the study and standard of care in settings were 040 was conducted.

- Formula feeding is associated with significant infectious morbidity, mortality and poor growth in resource limited settings.

- Diarrheal and respiratory illnesses are traditionally higher in populations of formula fed infants from these settings.
Rationale

- A critical endpoint in HIV PMTCT studies is HIV-free survival. Prevention of perinatal HIV-infection is suboptimal if infants succumb to complications unassociated to HIV but related to PMTCT (formula feeding).

- The population of formula fed HIV-exposed unaected infants enrolled into 040 was evaluated for morbidities and mortality potentially associated with formula feeding/absence of breastfeeding.
Breastfeeding Rates

<table>
<thead>
<tr>
<th>Visit</th>
<th>BF by Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>146 (9.2%)</td>
</tr>
<tr>
<td>4-7 days</td>
<td>23 (1.5%)</td>
</tr>
<tr>
<td>10-14 days</td>
<td>13 (0.8%)</td>
</tr>
<tr>
<td>4-6 weeks</td>
<td>10 (0.7%)</td>
</tr>
<tr>
<td>3 months</td>
<td>8 (0.5%)</td>
</tr>
<tr>
<td>6 months</td>
<td>4 (0.3%)</td>
</tr>
</tbody>
</table>

Breastfeeding rates similar between arms.

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Study Objectives

- **Primary Objective:** To evaluate the frequency of severe morbidity and mortality in a representative sub-cohort of 1000 HIV-uninfected formula fed-infants from Brazil and South Africa enrolled in the 040 study.

- Sub-cohort selected using a proportionately allocated stratified random sample. 1000 was approximately 58% of the original cohort.
Secondary Objectives

1. To determine the frequency of infectious morbidities.

2. To determine the frequency of failure to thrive, median Z-scores at specific time points, and proportion of patients below a Z-score threshold (WAZ and HAZ).

3. To compare six month mortality data of formula fed infants in our study with country specific mortality data.

4. To evaluate potential associations between maternal demographic and clinical/obstetric baseline parameters and adverse infant outcomes.
Inclusion:

1. All live HIV-1 exposed infants who completed 6 months of study follow-up who were determined to be HIV-uninfected at their 3 month study visit were included in the selection pool.

2. All HIV exposed infants who died before the 6 month follow-up study visit completion and not determined to be HIV-infected until the time of death were included in the selection pool.

Exclusion:

1. All HIV-infected infants

2. All live infants with less than 6 months of follow-up (Loss to F/up rate in study 3.3%)

3. Any evidence of breastfeeding during the study.
## Baseline Parameters

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Black</th>
<th>Native Brazilian</th>
<th>Mulatto/Mixed</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Race</td>
<td>208 (21%)</td>
<td>480 (48.6%)</td>
<td>9 (0.9%)</td>
<td>283 (28.6%)</td>
<td>8 (0.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age</td>
<td>26</td>
<td>13 - 47</td>
</tr>
<tr>
<td>Maternal CD4</td>
<td>466</td>
<td>12-2556</td>
</tr>
<tr>
<td>Maternal Virus Load</td>
<td>13580</td>
<td>200-1526786</td>
</tr>
<tr>
<td>Infant Birth Weight</td>
<td>3012.5</td>
<td>1510-4850</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>32-36 weeks</th>
<th>≥37 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>105 (10.5%)</td>
<td>895 (89.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prenatal Care</th>
<th>Yes</th>
<th>0 visits</th>
<th>1-2 visits</th>
<th>3+ visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>660 (67%)</td>
<td>324 (33%)</td>
<td>161 (16%)</td>
<td>492 (50%)</td>
</tr>
</tbody>
</table>

1000 infants selected from 988 mothers. Same proportion as in parent study: 766 from Brazil, 234 from S. Africa.
Infectious SAEs: Birth – 6 mo.

- All Infectious SAEs ≥ grades 3 to 5:
  - Respiratory
  - Gastro-intestinal (also Grade 2 SAEs)
  - Systemic/ CNS
  - Congenital
  - Other

- Grade 2 SAEs at the 10-14 day time point were excluded from analysis (events related to vomiting of study drug)
Infectious SAEs Rate per 100 Infant-Years

Number of ISAEs per 100 Infant-Years

Overall, Brazil, South Africa

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Proportion of subjects with at least 1 SAE

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Weight-for-Age and Height-for-Age Z-scores by study visit n= 1000 Infants

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Weight-for-Age Z-scores by study visit n= 1000 Infants

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
WAZ in 1000 HIV-exposed infants

Malnutrition

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### Six Month Mortality

<table>
<thead>
<tr>
<th>Mortality</th>
<th>No. deaths</th>
<th>Mean Age/Range</th>
<th>6 mo IMR/1000</th>
<th>Country 12 mo IMR*</th>
<th>Infant-years</th>
<th>IMR/1000 IY**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>7/766 (0.9%)</td>
<td>114 d. (12-150)</td>
<td>9.1 (±1.8)</td>
<td>19</td>
<td>380.9</td>
<td>18.4</td>
</tr>
<tr>
<td>S. Africa</td>
<td>15/234 (6.4%)</td>
<td>35 d. (1 – 196)</td>
<td>64.1 (±3.0)</td>
<td>56</td>
<td>111.7</td>
<td>134.3</td>
</tr>
</tbody>
</table>

- 2006 WHO 12 month mortality data
- ** IMR/ 1000 IY in HIV-exposed infants in Zimbabwe reported at 124.5 *Marinda PIDJ 07*

- **Cause of death:** Brazil: 4 pneumonias/ 3 sepsis  
  S. Africa: 4 pneumonias / 2 sepsis/ 3 gastroenteritis/ 5 SIDS/ 1 cong. syphilis
### Infant Mortality by Multivariate logistic regression

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CL)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>South African birth</td>
<td>6.22 (2.46 – 15.75)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Maternal virus load at delivery</td>
<td>1.71 (1.01 – 2.91)</td>
<td>0.0476</td>
</tr>
<tr>
<td>WAZ at birth ≤ -2 SD to &gt; - 3 SD</td>
<td>5.16 (1.80-14.77)</td>
<td>0.0022</td>
</tr>
<tr>
<td>WAZ at birth ≤ -3 SD</td>
<td>6.18 (1.80-21.31)</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

### Infant ISAE by Multivariate logistic regression

<table>
<thead>
<tr>
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<th>OR (95% CL)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal education, of 8 years</td>
<td>3.47 (1.49-8.09)</td>
<td>0.0040</td>
</tr>
<tr>
<td>Maternal education, &lt; 8 years</td>
<td>3.65 (1.71-7.80)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Maternal virus load at delivery &gt; 1,000,000 copies/ ml</td>
<td>9.92 (1.56-63.08)</td>
<td>0.0151</td>
</tr>
</tbody>
</table>
Summary

• Mortality of HIV-1 exposed uninfected formula fed infants was lower than country specific rates for the general population in Brazil but slightly higher in South Africa.

• Mortality of HIV-exposed infants in S. Africa was similar to that reported for HIV-exposed, uninfected infants in Zimbabwe.

• Infectious SAEs were observed in 23% of infants, 24% in Brazil, 19% in S. Africa. Gastrointestinal events were more common in S. Africa (24.1 p/100 IY) than in Brazil (4.7p/100 IY). Malnutrition was slightly more common in S. Africa.
Summary/ Conclusion

- Infant mortality was associated with South African birth, a high maternal virus load, and low weight-for-age birth Z-scores. Infectious significant adverse events were associated with maternal education and very high maternal virus load at delivery.

- Formula fed, HIV-exposed, uninfected infants born in S. Africa to mothers with a high virus burden and/or a low birth weight are at higher risk of death.
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 Iguaçu, Rio de Janeiro: Jose Henrique Pilotto, Ivete Martins Gomes
  - Hospital Nossa Senhora da Conceicao, Porto Alegre: Bruno 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
  - Fed 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: Moeen 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: Midnела Flores