Maternal Triple Antiretrovirals (mART) and Infant Nevirapine (iNVP) Prophylaxis for the Prevention of Mother-to-Child Transmission (MTCT) of HIV during Breastfeeding (BF)

Taha E. Taha, Patricia Flynn, Mae Cababasay, Mary Glenn Fowler, Lynne Mofenson, Maxensia Owor, David Shapiro, Susan Fiscus, Lynda Stranix-Chibanda, Anna Coutsoudis, Devasena Gnanashanmugam, Nahida Chakhtoura, Katie McCarthy, Cornelius Mukuzunga, Rachel Kawalazira, Daya Moodley, and the PROMISE Study Team
Statement

Dr. Taha has no relevant conflicts.
Background

• Breastfeeding (BF) is crucial to reducing infant morbidity and mortality in developing countries but may result in HIV transmission if the mother is HIV-infected.

• Prior clinical trials showed that both mART and iNVP are effective in PMTCT of HIV. PROMISE is the first randomized trial designed to directly compare the efficacy and safety of these two strategies during extended BF into the second year of life.
Overall Design of the PROMISE 1077BF Trial: Antepartum, POSTPARTUM and Maternal Health Components

Legend Figure 1A: The 1077BF antepartum component had 3 study arms: in version 2.0, HBV negative women were only randomized to ZDV-ART or ZDV-alone; in version 3.0 antepartum component, all women, regardless of HBV status were randomized to the 3 study arms in a 1:1:1 ratio.
Among HIV-infected women who do not meet criteria for initiation of HAART for their own health, what is the optimal intervention to prevent transmission of HIV to infants during breastfeeding?

2,431 mother-infant pairs

Maternal prophylaxis during breastfeeding

Infant prophylaxis during breastfeeding

n=1,220

n=1,211
Methods

• The Postpartum Component of PROMISE was conducted in sub-Saharan Africa (13 sites) and India (1 site)
• HIV-infected women with CD4+ ≥ 350 cells/mm$^3$ (or greater than country-specific guidelines) and their HIV-uninfected newborns were randomized
• Mother-infant pairs were enrolled between June 2011 and October 2014
Methods

• The regimens were continued through 18 months postpartum, through complete cessation of breastfeeding, infant HIV infection, or development of toxicity.

• Kaplan-Meier (K-M) probabilities and incidence rates per 100 person-years were used in primary analyses of efficacy and safety.
Results

• Overall, women enrolled into the Postpartum Component were asymptomatic
  – Median CD4+ count: 686 cells/mm$^3$
  – 97% WHO Clinical Stage I
  – Median age of mothers: 26 years old

• Infant’s median gestational age and birthweight were 39 weeks and 2.9 kg, respectively and did not differ by study arm.
Results

• Maternal and infant baseline characteristics were comparable by study arm.
• Median duration of BF was 15 months and not significantly different by study arm (p=0.85).
• There was no statistically significant difference in probability of MTCT of HIV by study arm (primary and sensitivity analyses) – see Figures.
Results: MTCT of HIV (Primary Analysis)

At 6 months of age, estimate 0.3% (95% CI, 0.1-0.6)

At 9 months of age, estimate 0.5% (95% CI, 0.2-0.8)

At 12 months of age, estimate 0.6% (95% CI, 0.4-1.1)
Results: MTCT of HIV (Sensitivity Analysis)
Results: Time to Infant Death (Primary Analysis)

Infant 12-month survival rate was extremely high (98.9%) and did not differ significantly by study arm.
Results: Time to Infant Death (Sensitivity Analysis)
Results

• The incidence rates (per 100 person-years) of maternal and infant safety endpoints did not differ significantly by study arm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>mARV (N=1220) Rate (95% CI)</th>
<th>iNVP (N=1211) Rate (95% CI)</th>
<th>p-value, K-M log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite maternal safety endpoint</td>
<td>14.8 (12.7-17.3)</td>
<td>14.6 (12.5-16.9)</td>
<td>0.99</td>
</tr>
<tr>
<td>(Grade 3/4 signs/symptoms; Grade 2-4 lab events; or maternal death)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite severe maternal safety endpoint</td>
<td>5.1 (4.3-6.1)</td>
<td>5.6 (4.8-6.6)</td>
<td>0.61</td>
</tr>
<tr>
<td>(i.e. excludes Grade 2 Lab events)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite infant safety endpoint</td>
<td>44.1 (39.2-49.5)</td>
<td>43.5 (38.7-48.8)</td>
<td>0.95</td>
</tr>
<tr>
<td>(Grade 3/4 signs/symptoms; Grade 3/4 lab event; or infant death)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• Both maternal ART and infant NVP were safe, associated with very low postnatal perinatal transmission rates during extended breastfeeding, and high infant survival rates.

• For mothers who either do not adhere to or tolerate ART, daily infant NVP throughout breastfeeding offers a safe and effective PMTCT alternative during breastfeeding.
Acknowledgements

The PROMISE Protocol Team gratefully acknowledges the dedication and commitment of the more than 3,500 mother-infant pairs without whom this study would not have been possible.

Sponsors:
US National Institutes of Health (D Gnanashanmugam, K Klingman, R Browning, L Purdue, N Chakhtoura, G Siberry, LM Mofenson)
Abbott, Gilead Sciences, Boehringer Ingelheim, GlaxoSmithKline

Protocol Chair and Vice Chairs:
MG Fowler, J McIntyre, T Chipato, P Flynn, J. Currier

Operations Center:
M Allen, A Coletti, K George, M Valentine, K McCarthy, V Hardy

Statistical and Data Management Center:
D Shapiro, T Fenton, K Butler, M Qin, C Marr, C Tierney, S Brummel, K Angelidou, M Basar, L Marillo, A Manzella, A Zadzilka

Laboratory Center: CMC: J McIntyre, L Stranix
S Fiscus, A Loftis
D Bhattacharya, R Hoffman, A Gupta, G Theron, B Chi, P Flynn, M Owor, JS Currier

Site PROMISE Principal Investigators:

India:
BJMC, Pune: R Bhosale, P Sambarey

Malawi:
Blantyre: B Makanani, M Mallewa, T Taha
UNC-Lilongwe, : F Martinson

South Africa:
CAPRISA Umlazi, Durban: D Moodley
Durban Paeds, Durban: R Bobat, S Pillay
FAM-CRU, Stellenbosch: G Theron
PHRU, Soweto: A Violari
Shandukani, Johannesburg: L Fairlie, A Coovadia

Tanzania:
KCMC, Moshi: P Mlay

Uganda:
MUJHU, Kampala: M Owor

Zambia:
George Clinic, Lusaka: M Mbewe, B Chi

Zimbabwe:
St. Mary’s, Seke North, and Parirenyatwa: T Chipato
Acknowledgements

PROMISE 1077BF/1077FF is funded by the US National Institutes of Health (NIH).

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The study products were provided free of charge by Abbott, Gilead Sciences, Boehringer Ingelheim, and GlaxoSmithKline.