PROMISE UPDATE: Efficacy and Safety of Two Strategies to Prevent Perinatal HIV Transmission

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Three PROMISE Randomizations

**Antepartum** (14 wks-term) **Labor/ Delivery** **Postpartum** (for duration of BF) **Maternal Health** (after BF cessation)

Maternal CD4 >350

infant uninfected at birth

(Version 2.0)

<table>
<thead>
<tr>
<th>Randomize</th>
<th>Triple ARV Prophylaxis</th>
<th>Triple ARV Prophylaxis</th>
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<tbody>
<tr>
<td>ZDV</td>
<td>ZDV + sdNVP+ TRV</td>
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</table>

- **Mother**
  - Continue Triple ARV Regimen
  - Stop All ARVs

Late Presenters

infant uninfected at birth
PROMISE Research Questions Among Asymptomatic Women with High CD4 counts

- During Pregnancy, what is the relative safety and effectiveness of maternal triple ARV prophylaxis compared to zidovudine for reducing the risk of transmission?
- During Breastfeeding, what is the relative safety and effectiveness of maternal ARV prophylaxis compared to infant ARV prophylaxis for reducing the risk of transmission?
- After the risk of transmission to the infant has ceased, are maternal survival and other health outcomes ie disease progression vs complications of therapy, improved by stopping or continuing ART?
Includes NIH IMPAACT Clinical Research Sites in resource-limited international settings where the usual method of infant feeding is breastfeeding; and some sites (South Africa*, India*) where the option of formula feeding was also safe and available.

Sites in:

• **India*** (1)
• Malawi (2)
• **South Africa*** (5)
• Tanzania (1)
• Uganda (1)
• Zambia (1)
• Zimbabwe (3)
1077BA and 1077FA
Final Accrual by Country

South Africa (5) 31%
Zimbabwe (3) 16%
Uganda (1) 14%
Tanzania (1) 2%
Zambia (1) 2%
India (1) 3%
Malawi (2) 32%

n = 3543 mother-infant pairs
<table>
<thead>
<tr>
<th>Component or Substudy</th>
<th>WHO Clinical Stage</th>
<th>Screening median CD4 (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum Component V 2.0</td>
<td>97% stage 1</td>
<td>530 (436-668)</td>
</tr>
<tr>
<td>Antepartum Component V 3.0</td>
<td>97% stage 1</td>
<td>536 (436-680)</td>
</tr>
<tr>
<td>Postpartum Component</td>
<td>97% stage 1</td>
<td>686 (553-869)</td>
</tr>
<tr>
<td>Maternal Health Component</td>
<td>95% stage 1</td>
<td>820 (656-1019)</td>
</tr>
</tbody>
</table>
PROMISE Antepartum Component Study Eligibility

- HIV-infected pregnant women in 7 countries at 14 sites
- Eligibility based on:
  - Currently pregnant, gestational age \( \geq \) 14 weeks, documented HIV infection
  - No receipt of triple ARVs in current pregnancy
  - Did not meet country guidelines for ART
  - CD4 \( \geq \) 350 cells/uL or \( \geq \) country-specific threshold for ART (if 350 cells/uL—most sites now >500 cells/uL)
  - Laboratory:
    - Hematology and ALT screening values < grade 3
    - Cr Cl > 60 mL/min (Cockroft-Gault equation)
  - Age of legal majority
  - No active TB or other serious health conditions
  - No social circumstances that would prevent follow up
Antepartum Component
Maternal Randomization (Version 3)

Pregnant Women
(both HBV+ and HBV-)

Arm A
ZDV + sdNVP + FTC-TDF tail

Arm B
3TC-ZDV + LPV-RTV

Arm C
FTC-TDF + LPV-RTV

Version 3.0 ALL women randomized to A, B or C

Data Analysis Plan: Comparisons based on concurrent randomization

• Comparisons of Arms A and B include all women (all Versions, N=3,084)
• Comparisons of Arm C with Arm A or B restricted to Version 3 enrollees (N=1,229)
## Maternal Baseline Characteristics:
Young Pregnant African Women with High CD4 Counts

<table>
<thead>
<tr>
<th>Entry Characteristics (N=3,523)</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (median)</td>
<td>26 years</td>
</tr>
<tr>
<td>Race – Black African</td>
<td>97%</td>
</tr>
<tr>
<td>Gestational age (median)</td>
<td>26 weeks</td>
</tr>
<tr>
<td>CD4 cell count (median)</td>
<td>530 cells/uL</td>
</tr>
<tr>
<td>WHO Clinical Stage 1</td>
<td>97%</td>
</tr>
<tr>
<td>Hepatitis B Surface Antigen +</td>
<td>4%</td>
</tr>
<tr>
<td>No ARV for prior PMTCT or no prior pregnancy</td>
<td>94%</td>
</tr>
</tbody>
</table>
Antepartum Efficacy and Safety Outcomes Through 14 Days Post-Delivery

- Mother to Child HIV Transmission (primary efficacy outcome)
- Maternal Adverse Events and Mortality
- Adverse Pregnancy Outcomes
- Infant Adverse Events and Mortality
MTCT Through Age 14 Days
Significantly Lower in Triple ARV Arms

Difference in MTCT Risk (Repeated Confidence Interval):
-1.28% (95% CI -2.11%, -0.44%)
Viral Load of Transmitters and Non Transmitters at Baseline and Delivery Visits

Plasma HIV-1 RNA

At Baseline

At Delivery
PROMISE: Description of Early Transmission by Day 14 of Age

- There were 34 early transmissions by 14 days
- Median screening CD4 was **467 vs. 531** for transmitters vs. non-transmitters ($p=0.14$)
- VL at delivery was significantly higher for transmitters than non-transmitters and for ZDV vs. the triple ARV arms
- ZDV Arm-- 3/25 transmissions occurred where delivery maternal VL was < 400 copies or less
- Triple Arms – 3/7 transmissions occurred where delivery maternal VL was < 400 copies
- After adjusting for RNA, there was still a significant treatment effect favoring triple ARVs over ZDV
Maternal Grade 2-4 Adverse Events (Mostly LFTs) Significantly Higher in Both Triple ARV Arms (No Maternal Deaths)

All Versions (Arm A vs B)

Any Grade 2+ AE: Arm A 17%, Arm B 1%
Any Grade 2+ Chemistry: Arm A 15%, Arm B 6%

Version 3 only (Arm A vs C, B vs C)

Any Grade 2+ AE: Arm A vs C P=0.03
Arm A 21%, C 16%
Arm B 15%, C 16%

Any Grade 2+ Chemistry: Arm A vs C P<0.008
Arm A 5%, C 3%
Arm B 1%, C 1%
Triple ARV Regimens Associated with Moderate Adverse Pregnancy Outcomes, But Severe Outcomes Less in 3TC-ZDV than FTC-TDF Triple ARV (Version 3 Only, Arm A vs C, B vs C)
1077BF/FF Antepartum Component Infant Safety Results

- There were no significant differences in infant signs/symptoms and lab AEs by study arm for all infants and for version 3.0 only infants.

- There were 60 early infant deaths in all versions by 14 days; including 28 deaths in version 3.0.

- In V 3.0, there was a significantly lower risk of infant death for LPV-RTV + ZDV/3TC vs TDF/FTC:
  - 0.6%(2/346) vs. 4.4% (15/341), p=0.001
  - The difference was primarily seen in deaths among infants less than <34 weeks gestation.
START Results: May 2015 DSMB

- Study Design Entry Criteria  ART naïve, CD4 counts >500
- 4685 adults were enrolled at 215 sites in 35 countries; 27% were women, 21% were African, median age 36 yrs
- At the May 2015, the DSMB concluded that the primary question of START has been answered
- They found a highly significant difference between early ART compared to delayed ART in risk of AIDS events, Non AIDS events or death:
  - 41 events (early) vs 86 events (delayed start)
  - Hazard Ratio 0.47 [95% CI 0.32-0.68], p<.001
  - 53% less risk serious events with early ART
PROMISE Plans in Light of START

- Offer ART to all women in PROMISE who are not currently on ART
  - Offer SOC when possible or Study ARVs
- With Sponsors and DSMB, re-evaluate Postpartum and MH research questions in light of START
  - Review gender and age adjusted findings from START when available
  - Ascertain how many women in PROMISE will uptake offer of ART
- Follow up safety questions from the antepartum component including
  - impact of LBW and preterm delivery on 2 year HIV free survival
  - assess maternal ARV levels re early infant deaths
Conclusions

- The PROMISE results support the 2013 WHO recommendations for use of triple maternal ARVs in pregnancy to achieve the lowest risk of transmission.

- Safety wise, the Antepartum triple ARV regimens were associated with higher risk of
  - Adverse maternal and pregnancy outcomes including preterm birth and low birth weight,
  - Decreased risk of early infant death in ZDV/3TC arm

- The PROMISE team is carefully considering the START results and will be offering ART to all PROMISE women not currently on ART.
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.

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Higher Infant HIV Free-Survival up to 14 Days of Age in ZDV-3TC Triple Arm (Version 3 only, Arm A vs C, B vs C)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>341</td>
<td>15</td>
<td>0.84 (A vs. C)</td>
</tr>
<tr>
<td>B</td>
<td>346</td>
<td>3</td>
<td>0.002 (B vs. C)</td>
</tr>
<tr>
<td>C</td>
<td>335</td>
<td>16</td>
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Arm A: ZDV + sdNVP + FTC-TDF tail
Arm B: 3TC-ZDV + LPV-RTV
Arm C: FTC-TDF + LPV-RTV
Viral Load of Transmitters and Non Transmitters at Baseline and Delivery Visits

Plasma HIV-1 RNA

At Baseline

At Delivery
Moderate But Not Severe Adverse Pregnancy Outcomes Higher with Triple ARV (All Versions, Arm A vs B)

Arm A vs B
P<0.001

% with Event

Arm A vs B
P<0.001

ZDV (Arm A) 3TC-ZDV+LPV-RTV (Arm B)

No Significant Differences by Study Arm A vs B

Birth weight
Birth weight

Gest. Age
Gest. Age

Moderate Adverse Pregnancy Outcome

Severe Adverse Pregnancy Outcome