Similar Clinical Outcomes Between Formula and Breastfeeding Women in PROMISE

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Background: PROMISE

• Study of antiretroviral strategies in pregnant and postpartum women with high CD4 cell counts
  ➢ Implemented in 2010, prior to results of studies of ART in men and non-pregnant women with high CD4 cell counts
  ➢ 1077HS: Performed in locations where standard of care was ART in pregnancy & postpartum formula feeding (single randomization postpartum to continue or discontinue ART)
  ➢ 1077BF/FF: Performed in locations where standard of care included short course antiretrovirals in pregnancy & postpartum breastfeeding. Randomizations antepartum, postpartum, and at cessation of breastfeeding to examine a range of infant and maternal outcomes

• Focus today: Maternal health outcomes of postpartum breastfeeding women (1077BF/FF)
  • Presentation of results from PROMISE 1077BF/FF (“predominately breastfeeding”)
  • Review the study design of PROMISE 1077HS (“formula feeding”)
  • Cross study comparison: breastfeeding (1077BF/FF) versus formula feeding women (1077HS)
Antepartum women, CD4 $350 \text{ cells/mm}^3$ or higher

**PROMISE 1077BF/FF Study Design**

Cessation of breastfeeding

Cessation of breastfeeding

Cessation of breastfeeding

Antepartum ART

Three-drug ART

Continue ART

Discontinue ART

R = randomization

Postpartum

Continue ART

Discontinue ART

Continue ART

Discontinue ART

Three-drug ART

Continue ART

Discontinue ART

R

R

R

Short course (ZDV+sdNVP)

Formula feeding women were eligible, enrolled and randomized postpartum to continue versus discontinue with no additional randomization; however, 95% of participants were breastfeeding → “Breastfeeding PROMISE study”

*R* Fowler MG et al; NEJM Nov 2016;
Flynn M et al, JAIDS Apr 2018
Study Design PROMISE BF/FF (“Breastfeeding”): Randomized Trial

• Key Eligibility for this Analysis
  • HIV-infected postpartum women
  • No clinical indication for ART based on local guidelines
  • CD4 cell count 350 cells/mm³ or higher (prior to ART and at delivery)
  • ART naïve except for PMTCT
  • Randomized to receive ART for PMTCT during current pregnancy in the PROMISE antepartum component

• Study Follow-up
  • Participants were randomized within 42 days after delivery to continue or discontinue ART; those who stopped were restarted when CD4 dropped below 350 cells/mm³ or when clinically indicated (per protocol)
  • Participants were seen 4 weeks after enrollment and every 12 weeks thereafter
  • ART was provided by the study (Lopinavir/r +TDF/FTC preferred regimen)
Study Design: Endpoints

**Primary Composite Endpoint:**
- Time to AIDS event (WHO Clinical Stage 4 Condition) or death

**Key Secondary Endpoints:**
- Time to composite endpoint of HIV/AIDS-related event* or WHO Clinical Stage 2 or 3 Condition
- Time to WHO Clinical Stage 2 or 3 events (post-hoc)
- Safety Endpoint: Time to first targeted Grade 2, Grade 3 or 4 event**

* WHO Clinical Stage 4 illnesses, pulmonary tuberculosis (TB) and other serious bacterial infections
**Selected Grade 2 lab abnormalities (renal, hepatic and hematologic) and all Grade 3 or higher lab values and signs and symptoms
Study Design: Sample Size and Monitoring

- Sample size determined by enrollment to PROMISE antepartum component; power calculations assumed an annualized primary event rate of 3.33%
- Intent-to-treat analysis included all women randomized in the postpartum component
- Comparisons between treatment groups based on log rank tests and Cox regression models for estimation of treatment effect sizes
- Enrollment from June 2011-October 2014
- Analyses reflect follow-up until July 7, 2015
  - Participants were informed about the START results and all were offered ART
Study Sites

15 clinical research sites in 7 countries

- India
- Malawi
- South Africa
- Tanzania
- Uganda
- Zambia
- Zimbabwe
Results

1,994 received antepartum ART

1,612 eligible

n=801
n=811

CONTINUE ART
(median = 1.38 years)
23 (3%) premature d/c from study follow-up
14% discontinued ART

DISCONTINUE ART
(median = 2.04 years)
34 (4%) premature d/c from study follow-up
6% restarted ART prior to study threshold

328 not enrolled
-32% missed timeline
-13% clinical indication for ART
-10% infant ineligible
-4% lab out of range
-55% other/no reason given

Study Sites

- India 33%
- Malawi 33%
- South Africa 26%
- Tanzania 2%
- Uganda 15%
- Zimbabwe 18%
- Zambia 3%

328 not enrolled
-32% missed timeline
-13% clinical indication for ART
-10% infant ineligible
-4% lab out of range
-55% other/no reason given
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CONTINUE ART n=801</th>
<th>DISCONTINUE ART n=811</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (IQR)</strong></td>
<td>27 years (23-31)</td>
<td>27 years (24-31)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Black African</td>
<td>781 (98%)</td>
<td>787 (97%)</td>
</tr>
<tr>
<td>Indian</td>
<td>20 (2%)</td>
<td>22 (3%)</td>
</tr>
<tr>
<td><strong>Median Screening CD4 count (IQR)</strong></td>
<td>726 cells/mm³ (593-911)</td>
<td>730 cells/mm³ (586-902)</td>
</tr>
<tr>
<td><strong>WHO Stage 1</strong></td>
<td>96%</td>
<td>98%</td>
</tr>
<tr>
<td><strong>HIV-1 RNA &lt;1,000 copies/ml</strong></td>
<td>93.6%</td>
<td>94.0%</td>
</tr>
<tr>
<td><strong>On Study ART regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPV/r based</td>
<td>98%</td>
<td>N/A</td>
</tr>
<tr>
<td>NNRTI</td>
<td>&lt;1%</td>
<td></td>
</tr>
</tbody>
</table>
During F/U 11% of women in the discontinue arm started ART for CD4 <350 cells/mm³ (median 316 cells/mm³)
Primary Efficacy Outcome

AIDS-defining event or death
Shading: 95% CIs

p=0.37

Clinical Endpoints

Continue
  3 deaths: disseminated/miliary TB (1), suicide (1), ruptured ectopic pregnancy (1)

Discontinue
  1 extrapulmonary TB
  7 deaths: bacterial pneumonia (1), bacterial sepsis (2), pulmonary hypertension (1), pulmonary TB (1), diabetic ketoacidosis (1), hepatitis (unknown etiology) with fulminant liver failure (1)

Outcome*  | Continue ART | Discontinue ART | Hazard Ratio (95% CI)
--- | --- | --- | ---
Primary Efficacy Composite Endpoint  | 3 | 0.24 | 8 | 0.49 | 0.55 (0.14, 2.08)
AIDS Defining Event  | 1 | 0.08 | 4 | 0.25 | 0.36 (0.04, 3.30)
Death  | 3 | 0.24 | 7 | 0.43 | 0.65 (0.17, 2.53)

*Sensitivity analysis excluding formula feeding women (n=85) did not change results
Time to WHO Clinical Stage 2 or 3 Condition

**Key WHO 2/3 conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Continue (33)</th>
<th>Stop (72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate weight loss</td>
<td>17</td>
<td>36</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Fungal nail infections</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Severe weight loss</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Continue ART</th>
<th>Discontinue ART</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of HIV/AIDS Related Event or WHO Stage 2 or 3 Event</td>
<td>42 3.47</td>
<td>86 5.61</td>
<td>0.63 (0.43, 0.91)</td>
</tr>
<tr>
<td>WHO Stage 2 or 3 Event</td>
<td>33 2.70</td>
<td>72 4.66</td>
<td>0.60 (0.39, 0.90)</td>
</tr>
</tbody>
</table>

*Sensitivity analysis excluding formula feeding women (n=85) did not change results*
Primary Safety Endpoint

Composite of the time to the first grade 3 or 4 sign or symptom, or grade 2, 3, or 4 hematology or chemistry event, whichever comes first.

<table>
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<tr>
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<th>Continue ART</th>
<th>Discontinue ART</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2, 3, and 4 Toxicity</td>
<td>160 (15.3)</td>
<td>189 (13.9)</td>
<td>0.95 (0.76, 1.17)</td>
</tr>
<tr>
<td>Grade 3 and 4 Toxicity</td>
<td>70 (6.0)</td>
<td>93 (6.2)</td>
<td>1.01 (0.74, 1.38)</td>
</tr>
</tbody>
</table>

p=0.61

Continue ART
Discontinue ART
Formula Feeding Study: PROMISE 1077HS

- Women on ART during pregnancy enrolled 0-42 days postpartum (N=1653)
- Continue ART (N=827)
  - Median follow-up 2.31 years
- Discontinue ART (N=825)
  - Median follow-up 2.35 years

- Sites where three drug ART was standard in pregnancy, along with formula feeding postpartum
- Enrolled Jan 2010-Nov 2014 in Argentina, Botswana, Brazil, China, Haiti, Peru, Thailand, and the United States
- Similar pre-specified outcomes as PROMISE breastfeeding women
- Provides contemporary comparison cohort (breastfeeding versus formula feeding women)
Hazard ratios and 95% confidence intervals for PROMISE outcomes: breastfeeding compared to formula feeding women

*Hazard ratio is for the continue ART compared to the discontinue ART within each study.

# Events cART v dART (HR):
Breastfeeding: 3 v 8 (0.55)
Formula Feeding: 4 v 6 (0.68)

# Events cART v dART (HR):
Breastfeeding: 33 v 72 (0.60)
Formula Feeding: 39 v 80 (0.48)
Limitations and Conclusions

- Limitations include lower than expected number of events, use of LPV/r, and relatively short follow-up
- ART was safe and well-tolerated among postpartum women with CD4 cell counts \( \geq 350 \) cells/mm\(^3\)
- Rates of AIDS defining events were low, more common in women who discontinued, but not statistically significant by randomized arm
  - Rates of WHO Stage 2 and 3 events were approximately halved with continued ART
- Comparable outcomes between breastfeeding and formula feeding women (>3,000 women from 15 countries)
- Studies that provide longer follow-up and newer regimens are needed to further inform strategies for optimizing health outcomes in reproductive-age women
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