Randomized Trial Of Raltegravir-ART vs. Efavirenz-ART When Initiated During Pregnancy (NICHD P1081)

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Background

• Pregnant women living with HIV require effective antiretroviral therapy (ART) for their own health and to prevent HIV infection of their infants

• Integrase inhibitors are potent and well tolerated, but randomized trials comparing their efficacy and safety to efavirenz containing ART initiated during pregnancy are lacking
Methods

• NICHD P1081 is a Phase IV multicenter, randomized, open-label trial comparing raltegravir (RAL) vs. efavirenz (EFV) in combination with ZDV and 3TC in ART-naïve pregnant women

• Outcomes: HIV virologic response, tolerability, and safety

• Study timeline:
  • Opened in September 2013 for women 28 to <37 weeks gestation
  • Entry gestational age limit reduced to 20 weeks in August 2016 after 22% of sample enrolled
  • Enrollment completed in February 2018
Methods (1)

• Enrollment sites in Brazil, Tanzania, South Africa, Thailand, Argentina and US

• Eligibility criteria: Pregnant women living with HIV who were between 20 to <37 weeks gestation and were naïve to ART

• Randomized to receive RAL or EFV with ZDV/3TC
  • A change to different nucleoside analogs was allowed if clinically indicated

• Samples were collected at entry for HIV RNA PCR, viral resistance testing, history/physical exam and hematology/chemistry testing
Methods (2)

• Participants followed until 24 weeks postpartum

• Primary outcome measures:
  • Efficacy: Plasma HIV-1 RNA PCR (VL) <200 copies/mL at delivery
  • Tolerability: Remaining on EFV or RAL (whichever was assigned) through delivery
  • Maternal and Infant Safety: Adverse events ≥grade 3

• Secondary Outcome Measures:
  • Efficacy/Tolerance: Rapid, sustained viral load reduction while staying on study drug until delivery
  • Adverse pregnancy outcome: Stillbirth, preterm birth
  • Infant HIV infection
Methods (3)

• The randomization and primary statistical comparisons were stratified by gestational age at entry

• Sample size target: 334 evaluable women
  • Primary efficacy population (n=307):
    • Screening/entry VL ≥200 copies, AND
    • No HIV genotypic resistance to any study ARV at screening/entry, AND
    • Valid VL result at delivery (or ≤ 21 days prior)

• Sensitivity analyses:
  a) Added the women with HIV genotypic resistance to any study ARV at screening/entry or no genotype test result (n=362)
  b) Also added the women with screening/entry VL < 200 copies/mL (n=387)
### Study Population

<table>
<thead>
<tr>
<th>Mean (SD) or N (%)</th>
<th>EFV (N=202)</th>
<th>RAL (N=206)</th>
<th>Total (N=408)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>26.7 (6.2)</td>
<td>27.6 (6.2)</td>
<td>27.2 (6.2)</td>
</tr>
<tr>
<td><strong>Race (Asian/Black/Hispanic/White)</strong></td>
<td>12%/37%/51%/1%</td>
<td>11%/35%/53%/1%</td>
<td>12%/36%/52%/1%</td>
</tr>
<tr>
<td><strong>Entry HIV RNA (log 10 copies/mL)</strong></td>
<td>3.9 (0.9)</td>
<td>3.9 (0.9)</td>
<td>3.9 (0.9)</td>
</tr>
<tr>
<td><strong>Entry HIV RNA &lt;200 copies/mL</strong></td>
<td>14 (7%)</td>
<td>9 (4%)</td>
<td>23 (6%)</td>
</tr>
<tr>
<td><strong>Absolute CD4 count (cells/mm3)</strong></td>
<td>460.1 (262.7)</td>
<td>411.3 (214.5)</td>
<td>435.3 (240.3)</td>
</tr>
<tr>
<td><strong>NRTI background regimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZDV/3TC</td>
<td>170 (84%)</td>
<td>171 (83%)</td>
<td>341 (84%)</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>31 (15%)</td>
<td>33 (16%)</td>
<td>64 (16%)</td>
</tr>
<tr>
<td><strong>Gestational age (wks) at entry</strong></td>
<td>26.9 (4.8)</td>
<td>26.8 (4.8)</td>
<td>26.9 (4.8)</td>
</tr>
<tr>
<td><strong>Gestational age strata at entry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-&lt;28 wks</td>
<td>102 (50%)</td>
<td>103 (50%)</td>
<td>205 (50%)</td>
</tr>
<tr>
<td>28-&lt;37 wks</td>
<td>100 (50%)</td>
<td>103 (50%)</td>
<td>203 (50%)</td>
</tr>
<tr>
<td><strong>Viral resistance at entry (RTI/INSTI)</strong></td>
<td>14 (7%)/0(0%)</td>
<td>21 (11%)/0(0%)</td>
<td>35 (9%)/0(0%)</td>
</tr>
</tbody>
</table>
Results – Primary Outcomes
Efficacy: Proportion with Delivery VL <200 copies/mL Overall and by Gestational Age at Entry (n=307 women*)

*Women with entry VL > 200 copies/ml and no HIV genotypic resistance to any study ART at entry
Tolerability: Proportion of Women who Remained on Assigned ARV (RAL or EFV) through Delivery (n=394 women*)

*Women who received at least one dose of study ARV and delivered on-study
Maternal and Infant Safety: Proportion with an Adverse Event > Grade 3

Women (n=403*)

- EFV: 30%
- RAL: 30%

Infants (n=393^a)

- EFV: 25%
- RAL: 25%

*p=.91

*Women who received at least one dose of study ARV

^aLive-born infants whose mother received at least one dose of study ARV and delivered on-study
# Secondary Efficacy/Tolerance Outcome Measure

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EFV arm</th>
<th>RAL arm</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid and sustained virologic response while remaining on study drug through delivery&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84/131 (64%)</td>
<td>121/132 (92%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Viral load ≥2.0 log decline or &lt;200 copies/mL by wk 2</td>
<td>91/131 (69%)</td>
<td>123/132 (93%)</td>
<td></td>
</tr>
<tr>
<td>Viral load &lt;1,000 copies/mL all time points after wk 4</td>
<td>117/123 (95%)</td>
<td>115/120 (96%)</td>
<td></td>
</tr>
<tr>
<td>Remained on study drug through delivery</td>
<td>129/131 (98%)</td>
<td>131/132 (99%)</td>
<td></td>
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</tbody>
</table>

<sup>a</sup>Cochran-Mantel-Haenszel test stratified by gestational age at entry (20-<28, 28-<31, 31-<34, or 34-<37 wks)

<sup>a</sup>Secondary composite outcome for all women in the primary virologic response and tolerability analyses with a VL result at study week 2 (day 11-17) and at least one subsequent VL result after study week 4.
Estimated Proportion with VL <200 copies/mL by Number of Days since Randomization

Median Time to VL <200 copies/mL:
RAL: 8 days
EFV: 15 days
Adverse Pregnancy Outcomes and Infant HIV Infection

<table>
<thead>
<tr>
<th>Adverse Outcomes</th>
<th>EFV arm</th>
<th>RAL arm</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>1/194 (1%)</td>
<td>3/200 (2%)</td>
<td>.62</td>
</tr>
<tr>
<td>Preterm delivery (&lt;37 wks gestation)</td>
<td>20/190 (11%)</td>
<td>24/195 (12%)</td>
<td>.63</td>
</tr>
<tr>
<td>Infant HIV infection</td>
<td>6/184 (3%)</td>
<td>1/190 (1%)</td>
<td>.06</td>
</tr>
</tbody>
</table>

* Fisher exact test
Conclusions

• Both RAL and EFV were safe and well tolerated in women initiating ART during pregnancy

• Women receiving RAL had:
  • Faster viral load reduction
  • Greater proportion with viral load <200 copies/mL at delivery, mainly among those who enrolled later in gestation

• These data support the use of RAL-ART during pregnancy, especially for women starting ART after 28 weeks gestation
Acknowledgements

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