Virologic efficacy of raltegravir vs. efavirenz based antiretroviral treatment in HIV1-infected adults with tuberculosis

W48 results of the ANRS 12300 Reflate TB2 trial

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for the ANRS 12300 Reflate TB2 study group

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Disclosures

- Grant research from Gilead not related to the present study (Voice program 2015)
Alternatives to efavirenz in HIV/TB co-infection

• Alternatives to Efavirenz (EFV)-based regimens are needed for patients co-infected with HIV and tuberculosis (HIV/TB): CNS tolerance and drug resistance to NNRTIs

• Integrase inhibitors (INSTIs) have been assessed as alternatives

• Dolutegravir (DTG) and raltegravir (RAL) PK show interaction with rifampin (RIF) is compensated when double dose of INSTI is used

• INSPIRING study: phase 3b non comparative, randomized, open-label trial evaluating DTG 50mg bid vs EFV 600mg qd

Dooley KE et al. CID 2019
What is the appropriate dose of raltegravir?

- **Phase II: ANRS 12180 REFLATE TB**
  Evaluate efficacy and safety of RAL 400 mg bid, RAL 800 mg bid, or EFV 600 mg qd in TB/HIV patients on RIF containing TB treatment

- **Choice of the RAL dose: 400mg bid vs. 800mg bid**
  - Similar proportion of patients with HIV RNA<50 copies/mL at W48
  - Drug-drug interaction (DDI) lower than that observed in healthy volunteers
  - Better tolerance profile: 2 patients experienced grade 3-4 hepatotoxicity in the RAL 800 mg bid
  - Pill burden and cost

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**% pts with HIV RNA<50 copies/mL at W48**

<table>
<thead>
<tr>
<th></th>
<th>EFV 600 mg qd</th>
<th>RAL 400 mg bid</th>
<th>RAL 800 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>51</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>67%</td>
<td>76%</td>
<td>63%</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Comparison of Plasma Raltegravir Pharmacokinetics Following Administration of Raltegravir 400 mg Twice Daily (Arm 1). With and Without Rifampicin**

![Graph and Table]

Grinsztejn et al. Lancet HIV 2014
Taburet et al. CID 2015

De Castro et al. 10th IAS conference. Mexico. Slides MOAB0101
Study design

Phase III open label randomized non-inferiority multicenter trial
Brazil, Côte d’Ivoire, France, Mozambique, Vietnam
230 patients/arm (80% power, non-inf. margin -12%, one-sided α=2.5%)

Inclusion criteria
- HIV1 infection
- ART naïve
- Confirmed or probable TB
- Standard TB Tx ≤8 weeks

Exclusion criteria
- HIV2 infection
- TB meningitis
- ALT >5ULN, Hb <6.5g/dL, Creat cl. <60mL/min
- Pregnancy/breastfeeding

Primary endpoint
FDA snapshot
HIV-1 RNA < 50 copies/mL

TB Treatment RHZE2/RH4

TDF/3TC qd + EFV 600 mg qd
TDF/3TC qd + RAL 400 mg bid

1:1*

Screening (W-2) W0 W24 W48

*Stratification by country

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**Study flow chart**

- **Screened**: 625
  - **Not eligible**: 162
    - **Eligible but not randomized**: 3
      - 1 Death before randomisation
      - 1 Withdrawal
      - 1 Creat. clear. <60 ml/min
- **Randomized**: 460
  - **EFV arm**: 230
    - **ITT set**: 227
      - Study completed: 203 (88%)
      - Early termination of study: 27 (12%)
        - Death: 14 (6%)
        - LFU: 10 (4%)
        - Withdrawal: 1 (0%)
        - Transfer out: 2 (1%)
  - **RAL arm**: 230
    - **ITT set**: 228
      - Study completed: 201 (87%)
      - Early termination of study: 29 (13%)
        - Death: 12 (5%)
        - LFU: 10 (4%)
        - Withdrawal: 1 (0%)
        - Transfer out: 6 (3%)
## Baseline characteristics (1)

<table>
<thead>
<tr>
<th></th>
<th>EFV arm (n=227)</th>
<th>RAL arm (n=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>37 (30 - 43)</td>
<td>34 (28 - 42)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>19.1 (17.5 - 20.8)</td>
<td>19.1 (17.6 - 21.2)</td>
</tr>
<tr>
<td>Gender female</td>
<td>90 (40%)</td>
<td>90 (39%)</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
<td>108 (35 - 238)</td>
<td>98 (39 - 242)</td>
</tr>
<tr>
<td>CD4 &lt; 50/mm³</td>
<td>77 (34%)</td>
<td>75 (33%)</td>
</tr>
<tr>
<td>HIV RNA (Log10 copies/mL)</td>
<td>5.5 (5.0 - 5.9)</td>
<td>5.5 (5.0 - 5.8)</td>
</tr>
<tr>
<td>HIV RNA ≥100,000 copies/mL</td>
<td>164 (72%)</td>
<td>172 (75%)</td>
</tr>
<tr>
<td>Time on TB treatment at enrolment</td>
<td>20 (15 - 27)</td>
<td>20 (15 - 28)</td>
</tr>
<tr>
<td>Cotrimoxazole prophylaxis</td>
<td>201 (89%)</td>
<td>199 (87%)</td>
</tr>
<tr>
<td>ALT (UI/L)</td>
<td>23 (15 - 37)</td>
<td>24 (15 - 39)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>98 (77 - 118)</td>
<td>103 (85 - 132)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.9 (8.2 - 11.4)</td>
<td>9.8 (8.7 - 11.2)</td>
</tr>
<tr>
<td>HBs Ag positive</td>
<td>21 (9%)</td>
<td>24 (11%)</td>
</tr>
<tr>
<td>HCV Ab positive</td>
<td>7 (3%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>
## Baseline characteristics (2)

Data are n(%) or median (IQR)

<table>
<thead>
<tr>
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<th>EFV arm (n=227)</th>
<th>RAL arm (n=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous tuberculosis disease treated</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Time on TB Tx at enrolment</td>
<td>20 (15 – 27)</td>
<td>20 (15 – 28)</td>
</tr>
<tr>
<td>Tuberculosis site of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>159 (70%)</td>
<td>152 (67%)</td>
</tr>
<tr>
<td>Extra-pulmonary</td>
<td>43 (19%)</td>
<td>44 (19%)</td>
</tr>
<tr>
<td>Pulmonary + extra-pulmonary</td>
<td>25 (11%)</td>
<td>32 (14%)</td>
</tr>
<tr>
<td>Bacteriological confirmation</td>
<td>159 (70%)</td>
<td>149 (65%)</td>
</tr>
<tr>
<td>Smear positive</td>
<td>113 (50%)</td>
<td>93 (41%)</td>
</tr>
<tr>
<td>Xpert MTB positive</td>
<td>132 (58%)</td>
<td>132 (58%)</td>
</tr>
<tr>
<td>MTB culture positive</td>
<td>114 (50%)</td>
<td>112 (49%)</td>
</tr>
<tr>
<td>Probable tuberculosis</td>
<td>66 (29%)</td>
<td>76 (33%)</td>
</tr>
<tr>
<td>LAM positive</td>
<td>18 (8%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Bacteriological confirmations or LAM+</td>
<td>177 (78%)</td>
<td>164 (72%)</td>
</tr>
<tr>
<td>No bacteriological data</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>
Efficacy outcome – W48

Primary endpoint ITT:
HIV RNA<50 copies/mL at W48 (FDA snapshot)

- Treatment Difference (95% CI): RAL - EFV
  - RAL arm
  - EFV arm

Virologic success (HIV-1 RNA<50 c/mL)
- EFV arm (n=227)
- RAL arm (n=228)

Virologic failure
- HIV-1 RNA ≥ 50 copies per mL in the window
- Discontinued Due to Lack of Efficacy
- Discontinued Due to Other Reasons and Last HIV-1 RNA ≥ 50 c/mL

No data in the W48 window
- Discontinued study/study drug due to AE or death*
- Discontinued study/study drug for other reasons
- On study but missing data in window
Efficacy outcome by baseline characteristics – W48

Primary endpoint ITT: HIV RNA<50 copies/mL at W48 (FDA snapshot)

Baseline HIV RNA levels

- HIV RNA<100,000 copies/mL
  - EFV 600 mg qd: 73%
  - RAL 400 mg bid: 75%
  - EFV 600 mg qd: 64%
  - RAL 400 mg bid: 58%

Baseline CD4

- CD4<50/mm3
  - EFV 600 mg qd: 58%
  - RAL 400 mg bid: 59%
  - EFV 600 mg qd: 69%
  - RAL 400 mg bid: 52%
  - EFV 600 mg qd: 71%
  - RAL 400 mg bid: 73%

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HIV RNA<50 copies/mL under allocated therapy - ITT

De Castro et al. 10th IAS conference. Mexico. Slides MOAB0101

EFV 57.3% (95% IC 50.8-63.7)
RAL 57.9% (95% IC 51.5-64.3)
Median CD4 counts gain - ITT
## Adverse events through W48

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz (N=230)</th>
<th>Raltegravir (N=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, N AE, n patient (%)</td>
<td>1038</td>
<td>208 (90%)</td>
</tr>
<tr>
<td><strong>Grade 3 or 4 AEs, N AE, n patient (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>57</td>
<td>41 (18%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>33</td>
<td>27 (12%)</td>
</tr>
<tr>
<td><strong>Type of grade 3-4 AE, N AE, n patient (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>26</td>
<td>22 (10%)</td>
</tr>
<tr>
<td>ART discontinuation due to drug-related AE</td>
<td>3</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>IRIS</td>
<td>13</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>9</td>
<td>9 (4%)</td>
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<tr>
<td>Hypersensitivity</td>
<td>1</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4</td>
<td>4 (2%)</td>
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</table>
Conclusion

• This study is the first large phase III randomized trial comparing efavirenz to INSTI-based ART in the context of HIV-TB co-infection
• Despite promising virological and PK data from our previous phase II study we failed to demonstrate the non-inferiority of raltegravir 400 mg bid when compared to efavirenz 600mg qd at W48
• Risk factors for virological failure are being analyzed
• Based on these results, efavirenz should still be considered as the preferred first line therapy for HIV/TB co-infected patients
• Raltegravir 400 mg bid may represent an alternative in selected patients
The trial is sponsored and funded by ANRS
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Scientific Committee and Independent Data Monitoring Committee members
ANRS team: C. Rekacewicz, M. de Solère, A. Montoyo
ANRS 12300 REFLATE TB 2 Study Group

<table>
<thead>
<tr>
<th>Brasil</th>
<th>Côte d’Ivoire</th>
<th>France</th>
<th>Mozambique</th>
<th>Vietnam</th>
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<tbody>
<tr>
<td>B. Grinsztejn</td>
<td>E. Messou</td>
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<td>N. Bhatt</td>
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<td>R. Escada</td>
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<td>I. Timana</td>
<td>D. Laureillard</td>
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<td>S. Wagner</td>
<td>DA.Diomandé</td>
<td>O. Marcy</td>
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<td>X. Anglaret</td>
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<td>A. Domergue</td>
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