Outcomes of efavirenz- and non-efavirenz containing ART in HIV-positive Patients Co-infected with Tuberculosis in Eastern Europe, Western Europe and Latin America

Yanink Caro-Vega1, Anna Schulze2, Anne Marie W. Efsen3, Frank A. Post4, Alexander Panteleev5, Alissandra Skrahin6, Jose M. M7, Enrico Girardi8, Daria N. Podlekareva9, Jens D. Lundgren3, Javier Toibaro10, Simona Todorov11, Hansjakob Furrer12, Joan Caylà13, Marcello Losso14, Robert F Miller15, Amanda McOdl16, Ole Kirk17, Brenda Crabtree-Ramírez17: TB·HIV study group in EuroCoord*

2. Department of Infection and Reproductive Health. London School of Hygiene & Tropical Medicine, London, UK.
3. Centre for Health and Infectious Disease Research (CHIDeR). Department of Infectious Diseases and Rheumatology, CUMIN, Ghent University, Ghent, Belgium.
4. Department of Social Health, Catholic Centre, Kings College Hospital, London, UK.
5. Department of Health, Telethon Institute of Child Health Research, Australia.
6. Clinical Department, Republikaans Ziekenhuis, Rotterdam Centre for Pulmonology and Rheumatology, The Netherlands.
7. Infectious Disease Service, Hospital Clinícal – IRBAPS. University of Barcelona, Barcelona, Spain.
10. St. Cyprian Ivanov Hospital, 'Temporal and Infectious Diseases, Outcomes and 'Cord Districts. University of Medicine and Pharmacy, Bucharest, Romania.
11. Department of Infectious Diseases. Bern University Hospital, University of Bern, Switzerland.

*All authors contributed equally to the study and the writing of this manuscript. All authors had access to and approved the final versions of the manuscript.

Background: Efavirenz (EFV)-based ART has been recommended as a preferred regimen for co-infected HIV/TB patients. In EFV-resistant/ART-experienced patients and in those with contraindications to EFV, recommendations include using 1) boosted protease inhibitors (PI/r) with rifabutin (RB), 2) raltegravir, or increasing the ritonavir boosting dose either with saquinavir or lopinavir, as access to the first two options may be limited in resource-constrained settings. Clinical outcomes between EFV- and non-EFV regimens in HIV/TB co-infected patients have not been well studied.

Methods: Within the TB·HIV Study, we studied the risk of death and undetectable viral load (<400 copies/mL) at 12 months since the date of anti-TB treatment start (baseline), using KM plots and Cox regression analysis. Adult HIV/TB patients were classified in two groups. The EFV group: patients exposed to EFV, 2 weeks or more after their TB diagnosis and the Non-EFV group: patients exposed to ART but not EFV in the same time-frame.

Results: 994 patients were included in the analysis (EFV n=698; non-EFV n=296), approximately half from Eastern Europe. Baseline characteristics are shown in Table 1, stratified by region.

In the KM analysis, not adjusted survival was statistically higher in the non-EFV group at 12 months (Fig. 1). However, in the adjusted Cox regression survival analysis, the hazard ratio was 1.3 (95%CI: 0.8–2.2) for EFV vs non-EFV (Fig. 2). In the same model, the use of rifamycines in any time was associated with a lower risk of death, with an aHR of 0.5 (95%CI: 0.3–0.8) (Table 2). At 12 months, clinical outcomes differed considerably across treatment groups and regions: the percentage of undetectable HIV RNA ranged from 29–76% (p<0.01 in both EFV and non-EFV), and mortality from 1–20% (p<0.05 in both EFV and non-EFV) across the three regions (Fig. 3). A high percentage of patients (14–24%) in all regions became lost to follow-up. However, when adjusted for region, age at TB, gender, CD4 at TB, use of rifamycines, diseminated TB, and ARV naive and probable route of transmission of HIV the probability of virological success at 12 months (~400 copies/mL), was not different between both treatment groups. Median change in CD4 count at 12 months in the EFV group was 104 cells/mL (IQR: 35–205) and 78.5 cells/mL (IQR: 14–157) in the non-EFV group, p<0.001, however, when analyzing naïve patients only no differences were found (EFV 105 cells/mL vs. non-EFV 113 cells/mL, p=0.9).

Conclusion: This study demonstrated that ART regimens in HIV-positive co-infected patients, with undetectable viral load at 12 months differed significantly between regions, with significantly lower mortality and higher rates of viral suppression in Western Europe. Similar rates of mortality and viral suppression were observed with EFV vs. no EFV containing regimens. Although PI were initiated in only 17% of patients, the reasons for the relatively frequent co-administration of PI and RIF deserves to be better understood.

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Region</th>
<th>Eastern Europe</th>
<th>Western/Southern Europe</th>
<th>Latin America</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 35–44 years</td>
<td>13% (n=7)</td>
<td>14% (n=18)</td>
<td>4% (n=4)</td>
<td>11% (n=49)</td>
</tr>
<tr>
<td>Age 45–54 years</td>
<td>26% (n=14)</td>
<td>22% (n=28)</td>
<td>21% (n=21)</td>
<td>21% (n=92)</td>
</tr>
<tr>
<td>Age 55–64 years</td>
<td>42% (n=22)</td>
<td>42% (n=54)</td>
<td>34% (n=34)</td>
<td>35% (155)</td>
</tr>
<tr>
<td>Age 65 or older</td>
<td>19% (n=10)</td>
<td>12% (n=16)</td>
<td>21% (n=21)</td>
<td>14% (n=67)</td>
</tr>
</tbody>
</table>

Table 2: Adjusted Cox Model for Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted hazard ratio (HR)</td>
<td>1.3 (0.8–2.2)</td>
<td>1.3 (0.8–2.2)</td>
</tr>
</tbody>
</table>

174 patients had a Protease Inhibitor (PI) based ARV regimen (106 with RIF, 40 with RB, 28 without a rifamycines). To accommodate PI use, an increasing 26% of patients received RB-based TB therapy (Fig. 3). A total of 44 (4.4%) patients received a PI together with RIF-based TB therapy at baseline.

Conclusion: In this cohort, the use of ART regimens, mortality and proportion of patients with undetectable viral load at 12 months differed significantly between regions, with significantly lower mortality and higher rates of viral suppression in Western Europe. Similar rates of mortality and viral suppression were observed with EFV vs. no EFV containing regimens. Although PI were initiated in only 17% of patients, the reasons for the relatively frequent co-administration of PI and RIF deserves to be better understood.

http://www.tb4h.de/