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


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**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 before or up to 3 months 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.


| TABLE 1 Baseline Characteristics | Eastern Europe | | | Western/Southern Europe | | | Latin America | | | All Patients | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | non EFV (n=114, 23%) | EFV (n=386,77%) | p | non EFV (n=131, 47%) | EFV (n=14, 53%) | p | non EFV (n=51, 27%) | EFV (n=165, 73%) | p | non EFV (n=296, 29%) | EFV (n=698, 71%) | p |
| Patient age at TB diagnosis (years) | 34 (29 – 38) | 36 (31 – 41) | <0.001 | 40 (33 – 46) | 40 (33 – 48) | 0.121 | 42 (35 – 46) | 38 (29 – 44) | 0.044 | 37 (32 – 46) | 37 (31 – 43) | 0.315 |
| Male | 84 (74%) | 308 (80%) | 0.207 | 80 (61) | 96 (65%) | 0.544 | 29 (57%) | 126 (76%) | 0.012 | 193 (65%) | 530 (76%) | <0.001 |
| HIV Infection Route, n(%) | | | 0.132 | | | 0.182 | | | 0.001 | | | <0.001 |
| IDU | 61 (53%) | 240 (62%) | | 30 (23%) | 21 (14%) | | 11 (21%) | 21 (13%) | | 102 (34%) | 282 (40%) | |
| Heterosexual | 28 (24%) | 98 (25%) | | 53 (40%) | 64 (43%) | | 28 (55%) | 73 (44%) | | 109 (37%) | 235 (34%) | |
| MSM | 2 (1.8%) | 6 (1.5%) | | 14 (11%) | 27 (18%) | | 6 (12%) | 62 (37%) | | 22 (7%) | 95 (14%) | |
| Other | 15 (13%) | 26 (7%) | | 32 (24%) | 34 (23%) | | 6 (12%) | 5 (3%) | | 53 (18%) | 65 (9%) | |
| Unknown | 8 (7%) | 16 (4.1%) | | 2 (1.5%) | 1 (0.7%) | | 0 (0%) | 4 (2%) | | 10 (3%) | 21 (3%) | |
| CD4 at TB diagnosis | 119 (34 – 228) | 83 (30 – 178) | 0.081 | 132(32-367) | 127(45-283) | 0.66 | 100 (50 – 258) | 77 (29 – 183) | 0.122 | 119 (36 – 314) | 90 (31 – 202) | 0.005 |
| RNA at TB diagnosis, n(%) | | | 0.064 | | | <0.001 | | | 0.004 | | | <0.001 |
| >100,000 copies/mL | 22 (19.3%) | 121 (31.3%) | | 20 (15.3%) | 45 (30.6%) | | 3 (5.88%) | 46 (28%) | | 45 (15%) | 212 (30%) | |
| Undetectable | 4 (3.5%) | 8 (2%) | | 3 (2.3%) | 10 (6.8%) | | 2 (3.9%) | 9 (5%) | | 9 (3%) | 27 (4%) | |
| Unknown | 74 (65%) | 207 (54%) | | 96 (74%) | 66 (45%) | | 44 (86%) | 98 (59%) | | 214 (72%) | 371 (53%) | |
| Hepatitis C* | 58 (51%) | 241 (62%) | 0.035 | 29 (22%) | 27 (18%) | 0.527 | 9 (18%) | 22 (13%) | 0.59 | 96 (32%) | 290 (41%) | 0.009 |
| Type of TB, n(%) | | | 0.165 | | | 0.468 | | | 0.181 | | | 0.695 |
| Disseminated | 75 (66%) | 217 (56%) | | 80 (61%) | 85 (58%) | | 23 (45%) | 97 (59%) | | 178 (60%) | 399 (57%) | |
| Extra-pulmonary | 5 (4%) | 28 (7%) | | 18 (14%) | 28 (19%) | | 8 (16%) | 24 (14%) | | 31 (10%) | 80 (11%) | |
| Pulmonary | 34 (30%) | 141 (36%) | | 33 (25%) | 33 (23%) | | 20 (39%) | 44 (27%) | | 87 (29%) | 218 (31%) | |
| TB drug used++, n(%) | | | <0.001 | | | <0.001 | | | 0.005 | | | <0.001 |
| Rifampicin | 84 (74%) | 343 (89%) | | 92 (70%) | 138 (94%) | | 44 (86%) | 160 (97%) | | 220 (74%) | 641 (92%) | |
| Rifabutin | 5 (4%) | 9 (2.3%) | | 37 (28%) | 3 (2%) | | 2 (4%) | 0 (0%) | | 44 (15%) | 12 (1.7%) | |
| Other | 25 (22%) | 34 (8.8%) | | 2 (1.5%) | 6 (4%) | | 5 (10%) | 5 (3%) | | 32 (11%) | 45 (6.4%) | |
| ARV regimen+, n(%) | | | <0.001 | | | <0.001 | | | <0.001 | | | <0.001 |
| Protease Inhibitor | 68 (60%) | 0 (0%) | | 77 (59%) | 0 (0%) | | 29 (57%) | 0 (0%) | | 174 (59%) | 0 (0%) | |
| Integrase Inhibitor | 24 (21%) | 0 (0%) | | 43 (33%) | 0 (0%) | | 6 (12%) | 0 (0%) | | 73 (25%) | 0 (0%) | |
| Other | 22 (19%) | 0 (0%) | | 11 (8%) | 0 (0%) | | 16 (31%) | 0 (0%) | | 49 (16%) | 0 (0%) | |

TB= Tuberculosis, IDU= Intravenous drug use, MSM= Men who have sex with men.

Continuous variables are reported as medians (interquartile range).

* Status at TB diagnosis

+ Other regimens include schemes based on other Non-nucleoside reverse-transcriptase inhibitors such as Nevirapine or Etravirine, and schemes with only nucleotide analog reverse-transcriptase inhibitors.

++ Other TB drugs included drugs not based on Rifamycines

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, Table 2). In the same model, the use of rifamycines in any time was assocciated 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 Rifamycins, disseminated Tb, being ARV naïve and probable route of transmission of HIV the probability of virological success at 12 months (<400 c/mL), was not different between both treatment groups. Median change in $CD4^+$ count at 12 months in the EFV group was 104 cells/$mm^3$ (IQR: 35-205) and 78.5 cells/$mm^3$ (IQR: 14-157) in the non-EFV group, p<0.001, however, when analyzing naïve patients only no differences were found (EFV 105 cells/$mm^3$ vs. non-EFV 113 cells/$mm^3$, p= 0.9).

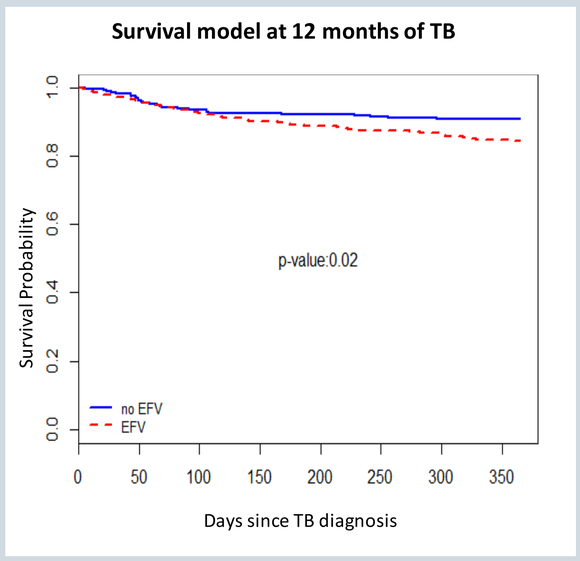


Figure 1. Non Adjusted survival probability at 12 months, marginally higher in non-EFV group in Kaplan-meier analyses.

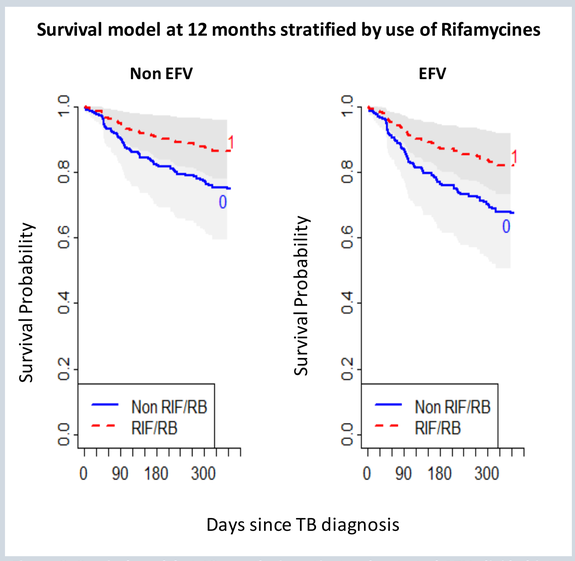


Figure 2. Survival model at 12 months in patients who started ARV, divided into those who recieved an anti-TB drug regimen based on Rifampicine or Rifabutin, Stratified by naive status.

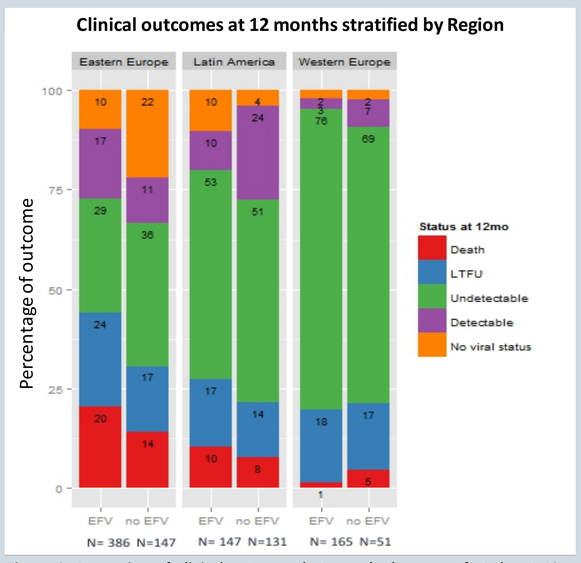


Figure 3. Proportion of clinical outcomes between both group of study, at 12 months stratified by region.

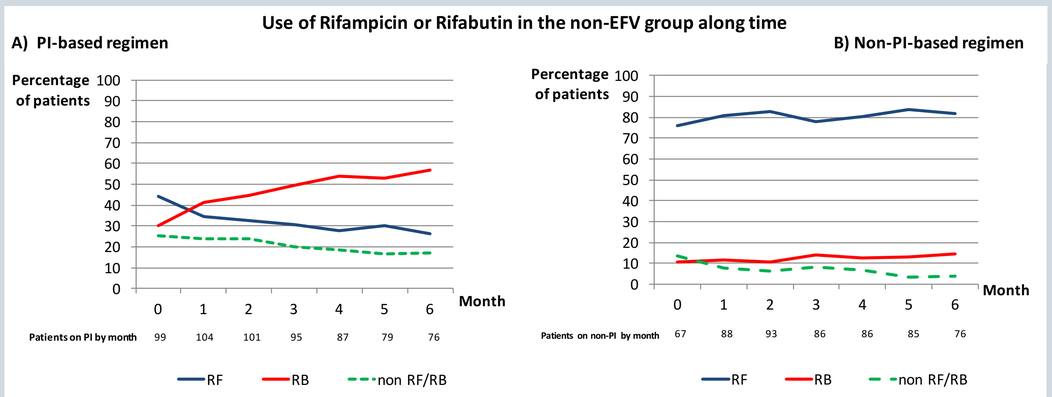


Figure 4. Use of Rifampicin or Rifabutin in the non-EFV group. Panel A) Percentage of patients on PI based regimen and use of either Rifampicin, Rifabutin or anti-TB drug without containing Rifamycines. Panel B) Percentage of patients on a non-PI-based regimen with concomitant use of Rifampicin, Rifabutin or anti-TB drug without containing Rifamycines. RF= Rifampicin, RB= Rifabutin, non- RF/RB= an anti-TB regimen without containing Rifamycines, non-PI= an ARV regimen based on Integrase inhibitor or 3 to 4 nucleoside analogue reverse-transcriptase inhibitor (NRTI).

**Table 2. Adjusted Cox Model for Mortality**

| Variable | HR | 95 % confidence interval | *p* value |
|---|---|---|---|
| Age 30 *vs* 20 years | 1.25 | 0.72 – 2.17 | 0.1325 |
| Age 40 *vs* 20 years | 1.56 | 0.65 – 3.73 | |
| Age 50 *vs* 20 years | 1.91 | 0.84 – 4.32 | |
| Gender - Male *vs* Female | 0.97 | 0.62 – 1.53 | 0.9227 |
| TB Disseminated *vs* non- Disseminated | 1.26 | 0.86 – 1.85 | 0.2175 |
| IDU *vs* non IDU | 1.25 | 0.83 – 1.88 | 0.2782 |
| Rifamycins *vs* No Rifamycins | 0.48 | 0.29 – 0.80 | 0.0051 |
| EFV *vs* non-EFV | 1.37 | 0.86 – 2.17 | 0.1778 |
| CD4 at TB 100 *vs* 50 cells/$mm^3$ | 0.59 | 0.49 – 0.70 | <.0001 |
| CD4 at TB 200 *vs* 50 cells/$mm^3$ | 0.31 | 0.21 – 0.45 | |
| CD4 at TB 350 *vs* 50 cells/$mm^3$ | 0.25 | 0.16 – 0.39 | |
| Region - Western/Southern Europe *vs* Eastern Europe | 0.16 | 0.07 – 0.34 | <.0001 |
| Region - Latin America *vs* Eastern Europe | 0.46 | 0.27 – 0.77 | |

All variables included at TB diagnosis. Continuous variables were included in the models using restricted cubic splines. The model was stratified by naïve status.

174 patients had a Protease Inhibitor (PI) based ARV regimen (106 with RIF, 40 with RB, 28 without a Rifamycins). To accommodate PI use, an increasing 26 % of patients received RB-based TB therapy (Fig 5). 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.

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