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# Durability comparison between efavirenz- and rilpivirine-based first line regimens

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ITALIAN COHORT NAIVE ANTIRETROVIRALS
Italian Cohort Naive Antiretrovirals

## Introduction/Summary

- Non-nucleoside reverse transcriptase inhibitors (NNRTI) efavirenz (EFV) and rilpivirine (RPV) have been largely used in recent years in first line combined antiretroviral therapies (cART). Many studies have compared the short term and long-term efficacy and tolerability of the two NNRTI, but a direct head-to-head comparison of durability of EFV and RPV containing regimens has never been performed.
- The aim of this study is to compare the durability of the two NNRTI-based regimens in ART-naïve patients living with HIV (PLWHIV). Secondary endpoints are assessing time to virological suppression in the two groups of PLWHIV and causes of drug discontinuation for the whole study population.

## Study Design

- Observational, prospective, multi-centre study: the Italian Cohort Naive Antiretrovirals Foundation Study (ICONA). We included all patients of the cohort who started first-line cART containing TDF/FTC associated with either RPV or EFV.

## Methods

ICONA collects data starting from the data of entry in the cohort till last available follow-up of all patients aged ≥ 18 years old who agree to participate and sign consent forms ( www.icona.org ).

Inclusion criteria for this particular analysis:

- baseline HIV-RNA load < 100,000 copies/ml,
- age > 18 years
- First line regimen containing tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and either EFV or RPV.

Durability was defined as time between cART initiation and virological failure, discontinuation of any component of first-line regimen for any cause or last available follow-up while on the same cART regimen.

Virological failure was defined as two consecutive HIV-RNA loads > 50 copies/ml after 6 months of therapy

Changing from TDF/FTC plus EFV or RPV to an STR containing the same drugs was not counted as a discontinuation.

Differences among baseline characteristics of PLWHIV starting EFV or RPV were assessed by Chi-square or Kruskal-Wallis tests, as appropriate.

Kaplan-Meier plots were used to compare the cumulative risk of discontinuations and failures according to different causes in the two groups of patients along time. We assumed that the risk of stopping for different reasons were independent.

Relative hazards for discontinuation of EFV with respect to RPV were estimated from fitting a Cox regression model.

## Results

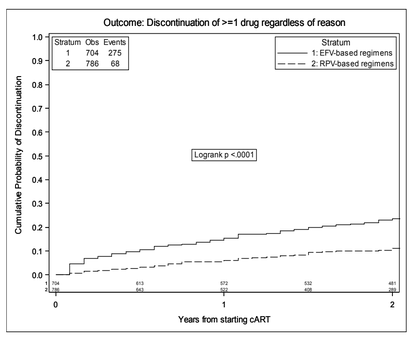
- Overall, 1,490 cART-naïve patients were included, 704 initiating their first cART with EFV and 786 with RPV. General characteristics of the study population are summarized in table 1.
- A total of 343 PLWHIV discontinued their first-line cART, more often EFV (26%) than RPV (13%) by 2 years (log-rank p <0.0001, figure 1).

**Table 1** Characteristics of patients according to drug started at the time of starting the NNRTI-based cART.

| | Regimen started | | |
|---|---|---|---|
| **Characteristics** | RPV-based | EFV-based | p-value* |
| | N= 786 | N= 704 | |
| **Female n(%)** | 136 (17.3%) | 124 (17.6%) | 0.875 |
| **Median age (IQR)** | 33 (27, 39) | 36 (30, 43) | 0.006 |
| **Mode of HIV Transmission, n(%)** | | | 0.074 |
| **IDU** | 53 (6.8%) | 54 (7.7%) | |
| **Homosexual contacts** | 420 (54.0%) | 336 (48.1%) | |
| **Heterosexual contacts** | 260 (33.1%) | 274 (38.9%) | |
| **Other/Unknown** | 45 (5.8%) | 34 (4.9%) | |
| **AIDS diagnosis, n(%)** | 11 (1.4%) | 22 (3.1%) | 0.024 |
| **Positive HBsAg, n(%)** | 1 (0.1%) | 7 (1.0%) | 0.069 |
| **Positive HCVAb, n(%)** | 47 (6.0%) | 58 (8.2%) | 0.112 |
| **Median calendar year of baseline** (IQR)** | 2014 (2014, 2015) | 2011 (2009, 2012) | <.001 |
| **Median CD4 count, cells/mmc (IQR)** | 447 (347, 580) | 340 (257, 421) | <.001 |
| **Median CD4 nadir, cells/mmc (IQR)** | 424 (334, 535) | 317 (243, 396) | <.001 |
| **Median CD8 count, cells/mmc (IQR)** | 983 (719, 1353) | 921 (654, 1258) | 0.005 |
| **Median Viral load, log10 copies/mL (IQR)** | 4.23 (3.81, 4.59) | 4.38 (3.92, 4.74) | 0.004 |
| **CD4 count, <=200 cells/mmc, n(%)** | 37 (4.7%) | 110 (15.7%) | <.001 |
| **Median ime from HIV diagnosis to date of starting cART, months (IQR)** | 13 (2, 46) | 19 (3, 50) | 0.013 |

## Results of 2

**Figure 1:** Cumulative risk of discontinuation of initial cART regimen for any cause

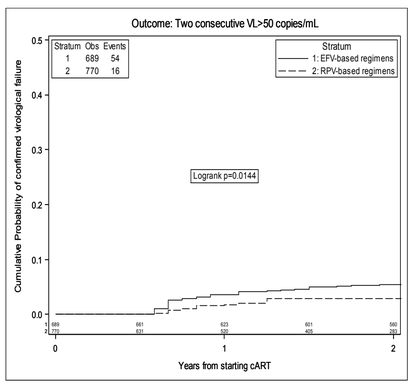



The most frequent reasons for drug discontinuation were intolerance in 34.1% cases (14.3% EFV; 2.0% RPV), toxicity in 21.3% (8.1% EFV; 2.0% RPV), proactive switch ( a change to prevent a possible toxicity and inefficacy) in 10.2% (4.4% EFV; 0.5 % RPV) and inefficacy in 9.9% (2.4% EFV; 2.1% RPV).

### Efficacy

Failure was recorded as cause of discontinuation in 34 patients overall (17 in EFV and 17 in RPV, p = 0.16) : 28 cases of virological failures (14 EFV and 14 RPV), three immunological failures (2 EFV and 1 RPV), two deaths (0 EFV, 2 RPV) and one case of failure not further defined (1 EFV 0 RPV).

**Figure 2:** Virological failures in EFV and RPV.




Patients in EFV were more likely to experience at least one episode of HIV-RNA > 50 copies/ml 23.4% vs 7.0% (p=0.0003) and also virological failure (defined at the time of a confirmed value >50 copies/mL), (7.8% with EFV vs 2.1% with RPV) defined as two consecutive viral loads > 50 copies/ml (p= 0.0144), figure 2.

### Toxicity

Seventy-three PLWHIV (21% of all discontinuations) discontinued their first cART regimen due to toxicity. Toxicity was mainly renal, in 27.4% of cases (15.1% EFV; 12.3% RPV), linked to an increase of cholesterol or triglycerides in 21.9% (20.5% EFV; 1.4% RPV) or hepatic 16.4%, (12.3% EFV; 4.1% RPV), table 2. Incidence of discontinuation for all toxicity reasons was not significantly different in the two groups.

### Intolerance

Intolerance was responsible for the majority (34%) of discontinuations in the present study.

It was due to central nervous system (CNS) side effects in 54.7% (53.8% EFV; 0.9% RPV) and to allergic reactions in 19.7% (17.1% EFV; 2.6% RPV) patients. Intolerance was significantly more frequent in patients taking EFV (p<0.0001), figure 3.

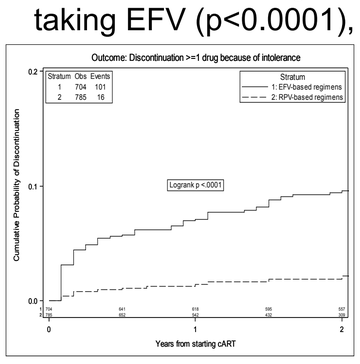



**Figure 3:** Discontinuation of 1 or more drug of initial cART regimen in the two groups of patients.

### Proactive switches and other causes of discontinuations

Proactive switches were responsible for 10.2% of discontinuations and resulted significantly more frequent in patients taking EFV than in those taking RPV (p= 0.0116).

The remaining 24.5% cases of discontinuations were due to other causes, including patient's choice (n=20), drug-drug interactions (n=10), pregnancy or pregnancy planning (n=12), inclusion in clinical trials or end of the study (n=10), adherence to new guidelines advices (n=2), availability of more effective drugs according to clinician's judjment (n=8) and unknown reasons (n=15).

## Adjusted relative hazards

After adjustment for age, gender, nation of birth, mode of HIV transmission, hepatitis co-infection, AIDS diagnosis, baseline CD4+ count, viral load and year of starting cART, patients treated with EFV in their first-line regimen were more likely to discontinue the regimen for any cause (HR 4.09, 95% CI 2.89, 5.80), for toxicity (HR 2.23, 95% CI 1.05, 4.73) and intolerance (HR 5.17, 95% CI 2.66, 10.07) than those starting RPV. Moreover, patients in EFV were 10 times more likely to receive a proactive switch in the first years of therapy than those initiating RPV (HR 10.96, 95% CI 3.17, 37.87), table 2.

**Table 2:** Crude and adjusted relative hazards.

| | Crude and adjusted relative hazards | | | |
|---|---|---|---|---|
| **Outcomes** | Crude RH (95% CI) | p-value | Adjusted* RH (95% CI) | p-value |
| **Discontinuation for any cause** | | | | |
| RPV | 1.00 | | 1.00 | |
| EFV | 2.47 (1.87, 3.26) | <.001 | 4.09 (2.89, 5.80) | <.001 |
| **Discontinuation due to toxicity** | | | | |
| RPV | 1.00 | | 1.00 | |
| EFV | 1.57 (0.86, 2.86) | 0.139 | 2.23 (1.05, 4.73) | 0.037 |
| **Discontinuation due to intolerance** | | | | |
| RPV | 1.00 | | 1.00 | |
| EFV | 4.16 (2.42, 7.16) | <.001 | 5.17 (2.66, 10.07) | <.001 |
| **Discontinuation due to proactive switch** | | | | |
| RPV | 1.00 | | 1.00 | |
| EFV | 3.69 (1.25, 10.87) | 0.018 | 10.96 (3.17, 37.87) | <.001 |
| **Discontinuation due to failure** | | | | |
| RPV | 1.00 | | 1.00 | |
| EFV | 0.61 (0.30, 1.24) | 0.171 | 0.94 (0.33, 2.64) | 0.903 |
| **Single VL>50 copies/mL** | | | | |
| **Regimen** | | | | |
| RPV | 1.00 | | 1.00 | |
| EFV | 1.57 (0.86, 2.86) | 0.139 | 1.19 (0.78, 1.82) | 0.409 |
| **Confirmed VL>50 copies/mL or discontinuation** | | | | |
| RPV | 1.00 | | 1.00 | |
| EFV | 2.48 (1.91, 3.22) | <.001 | 3.21 (2.30, 4.48) | <.001 |

## Conclusion

With the limit of the non-randomized and observational study design, in our comparison of people starting their first TDF/FTC + NNRTI-based cART with a baseline viral load < 100,000 copies/ml, RPV was better tolerated, less toxic and showed longer durability than EFV. In contrast, there was no evidence for a difference in discontinuation rates due to failure by NNRTI group.