

First line antiretroviral therapy with efavirenz plus tenofovir disoproxil fumarate/emtricitabine or rilpivirine plus tenofovir disoproxil fumarate/emtricitabine: a durability comparison.

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Running head: EFV vs RPV: a durability comparison

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1 **Abstract**

2

3 **Objective:** This study aimed to compare the durability of efavirenz (EFV) and rilpivirine (RPV)
4 associated to tenofovir/emtricitabine (TDF/FTC) in first-line regimens.

5 **Methods:** Multi-centre, prospective and observational study. We included all patients participating
6 to the Italian Cohort Naïve Antiretrovirals (ICONA) Foundation Study who started first-line cART
7 with TDF/FTC associated with RPV or EFV, with baseline viral load < 100,000 copies/ml. Survival
8 analyses by means of Kaplan-Meier (KM) curves and Cox regression with time-fixed covariates at
9 baseline were employed.

10 **Results:** Overall, 1,490 ART-naïve patients were included, 704 initiating their first cART with EFV
11 and 786 with RPV. Patients treated with EFV were older (median 36 years, IQR 30-43 vs. 33 years,
12 IQR 27-39, $p < 0.001$), more frequently in CDC stage C (3.1% vs. 1.4%, $p = 0.024$), with lower
13 median baseline CD4+T-cells (340 cells/ μ l, IQR 257-421 vs. 447 cells/ μ l, IQR 347-580 $p < 0.001$)
14 and higher viral load, median 4.38 (IQR 3.92-4.74) log₁₀ vs. 4.23 (IQR 3.81-4.59) log₁₀ copies/ml.
15 A total of 343 patients discontinued ≥ 1 drug of those included in first cART, more often EFV (26%)
16 than RPV (13%) by 2 years ($p < 0.0001$). After adjustment, patients treated with EFV resulted more
17 likely to discontinue ≥ 1 drug for any cause (relative hazard (RH) 4.09, 95%CI 2.89-5.80), for
18 toxicity (RH 2.23, 95%CI 1.05-4.73) for intolerance (RH 5.17, 95%CI 2.66-10.07) and for
19 proactive switch (RH 10.96, 95%CI 3.17-37.87) than those starting RPV.

20 **Conclusion:** In our non-randomized comparison, RPV was better tolerated, less toxic and showed
21 longer durability than EFV, without significant difference in discontinuation rates due to failures.

1. Introduction

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been in the recent years one of the most used class of drugs, in first-line combined antiretroviral therapy (cART) [1]. In the current HIV treatment guidelines, integrase strand transfer inhibitors (INSTIs) based regimens are the preferred first-line cART, with strength of recommendation A1 [2-5], but, in some scenarios, NNRTIs are still valid first-line agents, i.e. in patients with HIV-RNA below 100,000 copies/mL and CD4+T-cell counts above 200cells/ μ l [4,6-7].

Efavirenz (EFV) and rilpivirine (RPV) are both possible first line NNRTIs according to different guidelines, with the limitation of <100,000 copies/ml of HIV-RNA load for RPV [3-4,7-8]. RPV is usually preferred to EFV in high-income Countries, where EFV use is in decline [9-10], due to increasing better alternatives now available [11-13], reporting of suicidal ideation and hazard of suicidality [14-15] and increase of lipids [13]. EFV, on the other hand, is now available as a generic drug and this could modify policies of use and access to this drug, especially in low-income Countries.

Many studies have compared the short term and long-term efficacy and tolerability of the two different single table regimens (STR) NNRTI-based cART strategies [13,16-18], but few data are available on the durability of EFV and RPV, the only NNRTIs formulated as single tablet regimens (STR) [16]. Only two published studies have specifically assessed RPV durability, both concluding that RPV had a significantly better performance in cART-naïve patients compared to other antiretroviral agents [19-20]. Previous analyses of durability have compared people receiving the two NNRTI without accounting, for study entry, for the fact that RPV use is restricted to people with an untreated level of HIV-RNA <100,000 copies/mL. This makes the interpretation of the comparison even more difficult [19-20].

The aim of this study was to perform a comparison between RPV and EFV in people living with HIV (PLWHIV) with pre-cART HIV-RNA load <100,000 copies/ml. The primary end point is to

compare the durability of the two drugs in SRT regimens in cART-naïve patients, while secondary endpoints are assessing time to virological suppression in the two groups of PLWHIV and causes of drug discontinuation across the study population.

2. Methods

The Italian Cohort Naive Antiretrovirals Foundation Study (ICONA) is a multi-centre, prospective and observational study cohort, recruiting ART-naïve PLWHIV from the outset, in 1997. ICONA study has been approved by Institutional Review Boards of all the participating centres. ICONA collects data starting from the date 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, in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (1983 revision). Demographic, clinical, laboratory data and information on therapies are collected and recorded online (www.icona.org); sensitive data are collected only in anonymous form.

We performed a retrospective analysis of this prospectively collected database, including all patients who started first-line STR-cART containing tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) plus either RPV or EFV. The date of starting the NNRTI-based cART was the baseline for this analysis. All patients with baseline HIV-RNA load $> 100,000$ copies/mL were excluded from the analysis. In the main analysis, virological failure was set at the time of the first of two consecutive HIV-RNA loads > 50 copies/ml after 6 months of therapy. We also performed sensitivity analyses in which virological failure was defined in the same way but using for HIV-RNA the higher threshold of 200 copies/ml. The time between cART initiation and discontinuation of any component of first-line regimen defined durability. As the European Medicines Agency (EMA) recommend to use the STR containing EFV/FTC/TDF only to maintain viral suppression in patients with plasma HIV RNA < 50 copies/ml, changes in formulations that did not imply a modification in the drugs used (e.g. changing from TDF/FTC plus EFV or RPV to a single tablet

regimen, STR, containing TDF/FTC/EFV or TDF/FTC/RPV) did not count as events and the comparison has been made assuming that all the population was in STR. Follow-up of participants that did not experience virological failure was censored at the date of their last clinical visit.

All causes of treatment modification were classified as reported by the treating physician in the ICONA database, including intolerance (defined as patient's rejection in absence of any clinical and laboratory signs of drug harmfulness), toxicity (defined as an adverse effects related to exposure to that drug at usual doses), simplification (defined in this case as a proactive switch, i.e. as a change in cART regimen to prevent a possible toxicity and inefficacy or to improve adherence/simplify the regimen), and failure (defined as immunological or virological failure or death). Time to virological suppression was defined as the time between cART initiation and the first HIV-RNA load < 50 copies/ml.

2.2 Statistical analysis

Characteristics of the patients at the time of starting the NNRTI-based regimens have been compared using the Chi-square test for categorical variables and Wilcoxon rank sum test for the comparison of median of the numeric variables.

Standard survival analysis have been used to compare the rate of experiencing treatment failure and virological success according to the regimen started by means of Kaplan-Meier curves and proportional hazards Cox regression model. Multivariable Cox models have been constructed manually by including a set of a priori chosen set of potential confounders. A cause-specific hazard approach has been used for the analysis of discontinuing ≥ 1 drugs because of failure assuming that there was no informative censoring for stopping for other reasons. The analyses of failure were performed on an intent-to-treat basis.

3. Results

Overall, 1,490 cART-naïve patients were included, 704 initiating their first cART with EFV and 786 with RPV. Among patients in EFV, a minority directly started TDF/FTC/EFV in STR (210/704, 29.8%), while, among the remaining 494 patients, 109 switched to STR within three months (22.1%) and 200 within six months (40.5%). On the other hand, almost all patients in RPV started cART with TDF/FTC/RPV co-formulated in STR (780/786, 99.2%).

In terms of socio-demographics, 17% were female, 7% had history of previous intravenous drug use and 87% acquired HIV through sexual transmission (51% men who had sex with men (MSM) and 36% heterosexual contacts), while 5% had other/unknown mode of transmission of HIV infection. Median follow-up was 40 months (interquartile range, IQR, 13-59) for EFV and 17 (IQR 7-28) for RPV. Gender distribution and self-reported risk factors for HIV infection were similar in the two study groups, while, at baseline, patients treated with EFV were slightly older (median 36 years, IQR 30-43 vs. 33, IQR 27-39; $p<0.001$), more frequently in CDC stage C (3.1% vs. 1.4%, $p=0.024$), with lower median CD4+T-cell (CD4+) count (340 cells/ μ l, IQR 257-421 vs. 447 cells/ μ l, IQR 347-580; $p<0.001$) and nadir (317 cells/ μ l, IQR 243-396 versus 424 cells/ μ l, IQR 334-535 $p<0.001$) than those who initiated RPV. All patients had baseline HIV RNA $<100,000$ copies/ml as by inclusion criteria, but patients treated with EFV had significantly higher median HIV-RNA load, 4.38 (IQR 3.92-4.74) \log_{10} copies/ml versus 4.23 (IQR 3.81-4.59) \log_{10} copies/ml in PLWHIV treated with RPV ($p=0.004$). Calendar year of cART was significantly different ($p<0.001$) in patients who started EFV (median year 2011, IQR 2009-2012) vs. RPV (median year 2014, IQR 2014-2015). Also, a longer latency period between HIV diagnosis and treatment initiation was found in patients who started EFV, median 19 months (IQR 3-50) vs. median 13 months (IQR 2-46) for RPV. General characteristics of the two groups of patients are shown in Table 1.

A total of 343 PLWHIV discontinued their first-line cART. 218 of these events occurred by 2 years, more often in participants who started EFV ($n=159$, 23.6%, 95% confidence interval, 95%CI 20.4-26.8) than those initiating RPV ($n=59$, 10.1%, 95%CI 7.6-12.7), that showed an overall higher

durability ($p < 0.0001$, Figure 1). Among people who experienced a treatment discontinuation, the more frequent causes of drug discontinuation were intolerance in 34.1% cases (101/704 patients in EFV, 14.3%; 16/786 patients in RPV, 2.0%), toxicity in 21.3% (57/704 patients in EFV, 8.1%; 16/786 patients in RPV, 2.0%), proactive switch in 10.2% (31/704 patients in EFV, 4.4%; 4/786 patients in RPV, 0.5%) and failure in 9.9% (17/704 patients in EFV, 2.4%; 17/786 patients in RPV, 2.1%). Number and causes of discontinuation are shown in Table 2.

3.1 Failure

Failure was recorded as cause of discontinuation in 34 patients overall: 28 cases of virological failures (14/704 patients in EFV, 2.0%; 14/786 patients in RPV, 1.8%), three immunological failures (2/704 patients in EFV, 0.3%; 1/786 patients in RPV, 0.1%), two deaths (0/704 patients in EFV, 0%; 2/786 patients in RPV, 0.2%) and one case of inefficacy not further defined (1/704 patients in EFV, 0.1%; 0/786 patients in RPV, 0%). Kaplan-Meier curves of discontinuation for failures were not significantly different in patients taking either EFV or RPV (logrank p -value=0.166, Figure 1). When we examined the current HIV-RNA load values, patients in EFV were more likely to experience a confirmed virological failure >50 copies/mL, (7.8% with EFV vs 2.1% with RPV by 2 years) (logrank p = 0.01), but the datum was not confirmed using a threshold of 200 copies/mL (logrank p = 0.427).

By 2 years the proportion of PLWHIV with a HIV-RNA ≤ 50 copies/mL were 99.7% (95%CI 99.2-100.1) in RPV and 96.3% (95%CI 94.8-97.8) in EFV (logrank p < 0.0001).

3.2 Toxicity

Overall, 21.3% of PLWHIV discontinued their first-line cART regimen due to toxicity. Among those who discontinued ≥ 1 drug because of toxicity the main reason for discontinuation was renal toxicity, in 27.4% of cases (11/704 patients in EFV, 1.6%; 9/786 patients in RPV, 1.1%), linked to an increase of cholesterol or triglycerides in 21.9% (15/704 patients in EFV, 2.1%; 1/786 patients in RPV, 0.1%) or hepatic 16.4%, (9/704 patients in EFV, 1.3%; 3/786 patients in RPV, 0.4%), Table

2. Incidence of discontinuation for all causes of toxicity was not significantly different in the two groups (logrank p-value=0.136, Figure 1).

3.3 Intolerance

Intolerance was responsible for the majority (34.1%) of discontinuations in this analysis. Discontinuation for intolerance was due to central nervous system (CNS) side effects in 54.7% of cases (61/704 patients in EFV, 8.7%; 1/786 patients in RPV, 0.1%) and to allergic reactions in 19.7% (20/704 patients in EFV, 2.8%; 3/786 patients in RPV, 0.4%) patients, Table 2. Intolerance was significantly more frequent in patients taking EFV (logrank $p < 0.0001$, Figure 1).

3.4 Proactive switches and other causes of discontinuation

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

The remaining 24.5% cases of discontinuations were due to other causes, including patient's choice ($n=20$, 26.0%), drug-drug interactions ($n=10$, 13.0%), pregnancy or pregnancy planning ($n=12$, 15.6%), inclusion in clinical trials or end of the study ($n=10$, 13.0%), adherence to new guideline advices ($n=2$, 2.6%) availability of more effective drugs according to clinician's judgment ($n=8$, 10.4%) and unknown reasons ($n=15$, 19.5%).

3.5 Relative Hazards (RH) for discontinuation

After adjustment for a number of potential confounders (age, gender, nation of birth, mode of HIV transmission, hepatitis co-infection, AIDS diagnosis, baseline CD4+ count, HIV-RNA load and year of starting cART), patients who started with EFV in their first-line regimen resulted more likely to discontinue their regimen for any cause (RH 4.09, 95%CI 2.89-5.80), for toxicity (RH 2.23, 95%CI 1.05-4.73) and for intolerance (RH 5.17, 95%CI 2.66-10.07) vs. those initiating RPV. Moreover, patients in EFV were >10 times more likely to receive a proactive switch over the first 2 years of therapy than those initiating RPV (RH 10.96, 95%CI 3.17-37.87), Table 3. After adjustment, neither the probability for confirmed virological failure (>50 copies/mL) nor for

achievement of HIV-RNA ≤ 50 copies/mL resulted significantly different between the two treatment groups ($p= 0.161$ and $p= 0.374$, respectively). The same analyses were also performed in the subset of patients starting an STR regimen since the beginning of their therapy ($n =210$ for TDF/FTC/EFV vs. $n= 780$ for TDF/FTC/RPV). The significance was confirmed for the same variables identified in the general population, with the exception of the risk of proactive switch, that resulted no longer significantly different in the two treatment groups ($p=0.946$, Table 4).

4. Discussion

In this analysis, we evaluated the durability of EFV and RPV STR formulations as first line cART, in a real-life cohort of PLWHIV with baseline HIV-RNA $< 100,000$ copies/mL.

The main finding of this work is a significantly higher durability of RPV based regimens compared to EFV, in absence of significant differences in the cumulative chance of achieving HIV-RNA load suppression or in the estimated rates of virological failures in patients treated with the two different NNRTI-based regimens.

These findings have high clinical relevance, as NNRTIs are a widely used class of antiretroviral agents even in ART-naïve patients [1] and combinations with 2NRTI + NNRTI have been previously reported to have high durability [21], even if recent data demonstrate an even better performance of INSTI-based regimens [22]. EFV has represented for years the preferred third agents in international guidelines at least until 2013 [23-24] and in Italian guidelines until 2014 [25], and still constitute a preferred choice for first line cART according to WHO [8], it has high efficacy also in patients with baseline HIV-RNA $>100,000$ copies/mL, extensive experience of use and is widely available globally [5]. Also, because of the recognized efficacy of this drug, EFV has been frequently used as the comparator treatment group in randomized controlled efficacy trials [26]. RPV has been more recently introduced in clinical practice and it has been studied in comparative trials only vs. EFV, in both STR [16] and not co-formulated regimens [27-29]; and all these studies consistently showed a higher tolerability of RPV based regimens [27-29], and even a

greater virological potency in the setting of HIV-RNA < 100,000 copies/ml and CD4-T cells > 200 cells/ μ l [16]. The data of the ICONA cohort document that the proportion of people starting RPV-based regimens in first line has increased in recent years, while use of EFV had declined. This is confirmed in this analysis showing a significant difference in calendar year of starting RPV and EFV. A more recent calendar year of initiation has been previously correlated with lower risk of treatment discontinuation [21]. It is also possible that people who started EFV delayed therapy initiation until CD4 count reached a lower threshold, a factor that is associated with worse clinical outcomes [30]. Also, despite the fact that we included only people with a pre-ART HIV-RNA <100,000 copies/mL, patients who started a RPV-containing cART had lower HIV-RNA loads and higher CD4 T-cell counts compared to those who started EFV. All these factors demonstrate a tailored use of RPV in PLWHIV enrolled in ICONA cohort. However, our analysis is controlled for both calendar year and baseline CD4 count, so that a residual confounding due to these imbalances is improbable. RPV has a central role in many guidelines as first-line agent [3-4,7,31], has low costs, the lowest risk of rash among NNRTI-based therapies, and low risk of metabolic adverse effects, in addition to being co-formulated in the smallest tablet among single-pill regimens [5,32], and for showing lower relative risks for neurological events than EFV [16,32]. RPV has also been previously reported to be a more durable regimen compared not only to EFV, but also to other modern drugs including INSTI (i.e. raltegravir, RAL) [19-20,33]. However, people with a baseline HIV-RNA above 100,000 copies/ml have not been excluded in these other studies. Moreover, in a recent meta-analysis including 4 randomized controlled trials with EFV as the comparator, RPV was non-inferior at 48 and 96 weeks for the endpoint of viral suppression \leq 50 copies/mL [32,16], showed no difference in terms of CD4 count change from baseline [32,16], but higher risk of virological failure rates [32].

In our observational study, we selected only patients with baseline HIV-RNA <100,000 copies/mL to minimize the possible differences attributable to higher baseline viral load replication in non-RPV treated patients. In unadjusted analysis, we found the cumulative probability of achieving a

HIV-RNA below 50 copies to be significantly higher with RPV than with EFV and also virological failure resulted less probable in patients treated with RPV. After controlling for possible confounders, both these factors resulted not significant, but the probability of virological failure was not different between the two study groups, differently from what previously reported [32]. Moreover, RPV showed a 4-fold lower relative hazard (RH) for discontinuations for any cause, while EFV RH for toxicity and intolerance were 2 and 5 fold higher than those of RPV, respectively and RH for proactive switch was nearly 11 fold higher. However, the risk of virological failure (using definitions of confirmed failure >50 or >200 copies/mL) and of discontinuation due to failure were not different in the two groups. Indeed, the risk of treatment failure (e.g. of a confirmed VL >50 copies/mL or discontinuation regardless of the reason) was higher in EFV- than RPV-treated patients (adjusted RH of 3.21), and it was confirmed also in the analysis restricted only to patients who started an STR cART (adjusted RH of 6.33). All these results seem to suggest that the difference between the two NNRTI regimens is mainly driven by tolerability and thus adherence to treatment, rather than to antiviral efficacy. Indeed, 24% of patients treated with EFV in our study, and up to one-fifth of all individuals starting TDF/FTC/EFV in general, discontinue their therapy, and mainly for adverse events on CNS [34].

Because all three drugs (TDF/FTC/EFV) will soon be available in generic formulation, it is an attractive strategy from the point of view of trying to reduce cost for the national health system. This advantage had to be balanced with the potential higher risk in discontinuation documented in this and other analyses, which also might impact on cost. Also, the potential impact on adherence of use of generics not in fixed combination needs to be further evaluated. Last, whether there is a substantial advantage of the inclusion of tenofovir alafenamide (TAF) in STR for people who are able to safely tolerate TDF, remains unclear.

Another possible issue is that, although a trial comparing these drugs directly with RPV has never been performed, INSTI are now the preferred first-line third agents according to different guidelines [2-4, 31], as there was no evidence for a difference in HIV-RNA suppression outcomes when

compared to EFV [35-37]. In addition, similar to what we found here, INSTI-based regimens were shown to be superior to EFV in maintaining virologic suppression and lower risk of discontinuation [11,38]. Moreover, a recent analysis of the data of an observational cohort, showed no evidence for a difference in the 4-year risk of AIDS-defining illness or death comparing raltegravir and EFV [39].

Altogether, these results suggest that in the selected population of patients with low HIV-RNA loads and high CD4-T cell counts, use of RPV might have some advantages over the choice of other NNRTI-based strategies [3-4,7].

Our analysis has several limitations. First, it is not a randomized comparisons and it is likely that unmeasured factors influencing clinicians' treatment choice might have introduced confounding which we could not control for. Second, despite having selected patients with HIV-RNA < 100,000 copies/mL, we still detected differences in the average viral load, CD4 count and calendar-year at initiation by treatment group, so that residual confounding cannot be ruled out. Finally, although data are collected in standardized manners, there is a natural variability in how clinicians might classify reasons for stopping a drug and in deciding which of the possible reasons was the most important. There was also a not negligible proportion of switches for which the reason was unknown.

Despite these limitations, one advantage is that our results reflect what really happens in the everyday clinical practice and we were able to compare the two regimens for a large number of outcomes over 2 years from starting cART.

4.1 Conclusions

In conclusion, in our patients starting their first TDF/FTC-based cART with a baseline HIV-RNA load < 100,000 copies/ml, RPV was better tolerated, less toxic and showed longer durability than EFV, without significant difference in rate of virological failure or discontinuation due to failure. We found a lower risk of discontinuation of RPV vs. EFV especially for reasons related to proactive switches. This observation should encourage proper modeling work to evaluate the cost-

effectiveness of initiating EFV instead of RPV in first-line. Also, our data needs to be confirmed in randomized studies conducted in more contemporary patients receiving EFV or INSTI-based regimens with both CD4 cell count >200 cells/uL and HIV-RNA <100,000 copies/mL before cART.

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