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ORIGINAL RESEARCH

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

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Objectives

The aim of this study was to compare the durabilities of efavirenz (EFV) and rilpivirine (RPV) in combination with tenofovir/emtricitabine (TDF/FTC) in first-line regimens.

Methods

A multicentre prospective and observational study was carried out. We included all patients participating in the Italian Cohort Naive Antiretrovirals (ICONA) Foundation Study who started first-line combination antiretroviral therapy (cART) with TDF/FTC in combination with RPV or EFV, with a baseline viral load < 100 000 HIV-1 RNA copies/mL. Survival analyses using Kaplan–Meier (KM) curves and Cox regression with time-fixed covariates at baseline were employed.

Results

Overall, 1490 ART-naïve patients were included in the study, of whom 704 were initiating their first cART with EFV and 786 with RPV. Patients treated with EFV, compared with those on RPV, were older [median 36 (interquartile range (IQR) 30–43) years *vs.* 33 (IQR 27–39) years, respectively; $P < 0.001$], were more frequently at Centers for Disease Control and Prevention (CDC) stage C (3.1% *vs.* 1.4%, respectively; $P = 0.024$), and had a lower median baseline CD4 count [340 (IQR 257–421) cells/μL *vs.* 447 (IQR 347–580) cells/μL, respectively; $P < 0.001$] and a higher median viral load [4.38 (IQR 3.92–4.74) $\log_{10}$ copies/mL *vs.* 4.23 (IQR 3.81–4.59) $\log_{10}$ copies/mL, respectively], ($P = 0.004$). A total of 343 patients discontinued at least one drug of those included in the first cART regimen, more often EFV (26%) than RPV (13%), by 2 years ($P < 0.0001$). After adjustment, patients treated with EFV were more likely to discontinue at least one drug for any cause [relative hazard (RH) 4.09; 95% confidence interval (CI) 2.89–5.80], for toxicity (RH 2.23; 95% CI 1.05–4.73) for intolerance (RH 5.17; 95% CI 2.66–10.07) and for proactive switch (RH 10.96; 95% CI 3.17–37.87) than those starting RPV.

Conclusions

In our nonrandomized comparison, RPV was better tolerated, less toxic and showed longer durability than EFV, without a significant difference in rates of discontinuation because of failures.

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Introduction

In recent years, nonnucleoside reverse transcriptase inhibitors (NNRTIs) have been one of the most frequently used classes of drugs in first-line combination antiretroviral therapy (cART) [1]. In current HIV treatment guidelines, integrase strand transfer inhibitor (INSTI)-based regimens are the preferred first-line cART option, 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 < 100 000 HIV-1 RNA copies/mL and CD4 counts > 200 cells/μL [4,6,7].

Efavirenz (EFV) and rilpivirine (RPV) are both possible first-line NNRTIs according to different guidelines, with the limitation of HIV RNA load < 100 000 copies/mL for RPV [3,4,7,8]. RPV is usually preferred to EFV in high-income countries, where EFV use is in decline [9,10] as a consequence of better alternatives increasingly becoming available [11–13], and reports of suicidal ideation and hazard of suicidality [14,15] and an increase in lipid concentrations [13] associated with RPV use. EFV, however, is now available as a generic drug and this could modify policies regarding use of and access to this drug, especially in low-income countries.

Many studies have compared the short- and long-term efficacies and tolerabilities of the two different single-tablet regimen (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 STRs [16]. Only two published studies have specifically assessed RPV durability, both concluding that RPV had a significantly better performance in cART-naïve patients compared with other antiretroviral agents [19,20]. Previous analyses of durability have compared people receiving the two NNRTIs without accounting, in the study entry criteria, for the fact that RPV use is restricted to people with an untreated HIV RNA level < 100 000 copies/mL. This makes the interpretation of the comparisons 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 endpoint was to compare the durabilities of the two drugs in STRs in cART-naïve patients, while secondary endpoints were to assess time to virological suppression in the two groups of PLWHIV and causes of drug discontinuation across the study population.

Methods

The Italian Cohort Naive Antiretrovirals (ICONA) Foundation Study is a multicentre prospective and observational study which has recruited ART-naïve PLWHIV since 1997. The ICONA Study has been approved by the Institutional Review Boards of all the participating centres. ICONA collects data, from the date of entry to the cohort until the last available follow-up, for 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 and 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 considered to occur 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 the first-line regimen defined durability. As the European Medicines Agency (EMA) recommend using an 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 of the drugs used (e.g. changing from TDF/FTC plus EFV or RPV to an STR containing TDF/FTC/EFV or TDF/FTC/RPV) did not count as events and the comparison has been made assuming that all individuals were on an STR. Follow-up of participants who 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 the patient's decision to discontinue the drug in the absence of any clinical or laboratory signs of drug harmfulness), toxicity (defined as adverse effects related to exposure to that drug at the usual doses), simplification (defined in this case as a proactive

switch, i.e. as a change in cART regimen to prevent possible toxicity and inefficacy or to improve adherence or 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.

Statistical analysis

Characteristics of the patients at the time of starting the NNRTI-based regimens were compared using the χ^2 test for categorical variables and Wilcoxon rank sum test for the comparison of the medians of the numeric variables.

Standard survival analysis was used to compare the rates of experiencing treatment failure and virological success according to the regimen started by means of Kaplan–Meier curves and the proportional hazards Cox regression model. Multivariable Cox models were constructed manually by including a set of potential confounders chosen *a priori*. A cause-specific hazard approach was used for the analysis of discontinuation of at least one drug 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.

Results

Overall, 1490 cART-naïve patients were included in the study, of whom 704 were initiating their first cART with EFV and 786 with RPV. Among patients on EFV, a minority immediately started TDF/FTC/EFV in an STR (210/704; 29.8%), while, among the remaining 494 patients, 109 switched to an STR within 3 months (22.1%) and 200 within 6 months (40.5%). In contrast, almost all patients on RPV started cART with TDF/FTC/RPV co-formulated in an STR (780/786; 99.2%).

In terms of sociodemographics, 17% of patients were female, 7% had a history of previous injecting drug use and 87% acquired HIV through sexual transmission [51% men who have sex with men (MSM) and 36% heterosexual contacts], while 5% had other/unknown modes of transmission of HIV infection. Median follow-up was 40 [interquartile range (IQR) 13–59] months for EFV and 17 (IQR 7–28) months 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, compared with those who initiated RPV, were slightly older [median 36 (IQR 30–43) years *vs.* 33 (IQR 27–39) years, respectively; $P < 0.001$], were more frequently at Centers for Disease Control and Prevention (CDC) stage C (3.1% *vs.* 1.4%, respectively; $P = 0.024$), and had a lower median CD4 count [340 (IQR 257–421) cells/μL *vs.* 447 (IQR 347–580) cells/μL, respectively; $P < 0.001$] and median nadir CD4 count [317 (IQR 243–396) cells/μL *vs.* 424 (IQR 334–535) cells/μL, respectively; $P < 0.001$]. All patients had baseline HIV RNA < 100 000 copies/mL as per the inclusion criteria, but patients treated with EFV had a significantly higher median HIV RNA load [4.38 (IQR 3.92–4.74) $\log_{10}$ copies/mL *vs.* 4.23 (IQR 3.81–4.59) $\log_{10}$ copies/mL in PLWHIV treated with RPV; $P = 0.004$]. Calendar year of cART initiation 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 (IQR 3–50) months *vs.* median 13 (IQR 2–46) months for those who started RPV]. General characteristics of the two groups of patients are shown in Table 1.

A total of 343 PLWHIV discontinued their first-line cART. Two hundred and eighteen of these events had occurred by 2 years, more often in participants who started EFV [$n = 159$; 23.6%; 95% confidence interval (CI) 20.4–26.8%] than in those initiating RPV ($n = 59$; 10.1%; 95% CI 7.6–12.7%), which showed an overall higher durability ($P < 0.0001$; Fig. 1). Among people who experienced a treatment discontinuation, the most frequent causes of drug discontinuation were intolerance in 34.1% of cases [101/704 patients on EFV (14.3%); 16/786 patients on RPV (2.0%)], toxicity in 21.3% [57/704 patients on EFV (8.1%); 16/786 patients on RPV (2.0%)], proactive switch in 10.2% [31/704 patients on EFV (4.4%); 4/786 patients on RPV (0.5%)] and failure in 9.9% [17/704 patients on EFV (2.4%); 17/786 patients on RPV (2.1%)]. The numbers and causes of discontinuations are shown in Table 2.

Failure

Failure was recorded as the cause of discontinuation in 34 patients overall: 28 cases of virological failure [14/704 patients on EFV (2.0%); 14/786 patients on RPV (1.8%)], three immunological failures [2/704 patients on EFV (0.3%); 1/786 patients on RPV (0.1%)], two deaths [0/704 patients on EFV (0%); 2/786 patients on RPV (0.2%)] and one case of inefficacy not further defined [1/704 patients on EFV (0.1%); 0/786 patients on RPV (0%)]. Kaplan–Meier curves of discontinuation for failure were not significantly different in patients taking either EFV or RPV (log-rank *P*-value = 0.166; Fig. 1). When we examined the current HIV RNA load values, we found that patients

Table 1 Characteristics of patients according to drug started at the time of starting combination antiretroviral therapy (cART)

Characteristic	Regimen started		
	TDF/FTC/RPV (n = 786)	TDF/FTC/EFV (n = 704)	P-value*
Female [n (%)]	136 (17.3)	124 (17.6)	0.875
Age (years) [median (IQR)]	33 (27–39)	36 (30–43)	0.006
Mode of HIV transmission [n (%)]			
IDU	53 (6.8)	54 (7.7)	0.074
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
HBsAg positive [n (%)]	1 (0.1)	7 (1.0)	0.069
HCV-Ab positive [n (%)]	47 (6.0)	58 (8.2)	0.112
Calendar year of baseline [median (IQR)]	2014 (2014–2015)	2011 (2009– 2012)	< 0.001
CD4 count (cells/μL) [median (IQR)]	447 (347–580)	340 (257–421)	< 0.001
CD4 count nadir (cells/μL) [median (IQR)]	424 (334–535)	317 (243–396)	< 0.001
CD4 count ≤ 200 cells/μL [n (%)]	37 (4.7)	110 (15.7)	< 0.001
CD8 count (cells/μL) [median (IQR)]	983 (719–1353)	921 (654–1258)	0.005
HIV RNA load ($\log_{10}$ copies/mL) [median (IQR)]	4.23 (3.81–4.59)	4.38 (3.92–4.74)	0.004
Time from HIV diagnosis to date of starting cART (months) [median (IQR)]	13 (2–46)	19 (3–50)	0.013

cART, combination antiretroviral therapy; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; EFV, efavirenz; RPV, rilpivirine; IQR, interquartile range; IDU, injecting drug user; HBsAg, hepatitis B virus surface antigen; HCV-Ab, hepatitis C virus antibody.
*χ^2 or Kruskal–Wallis test as appropriate.

on EFV were more likely to experience a confirmed virological failure > 50 copies/mL (7.8% of those on EFV *vs.* 2.1% of those on RPV by 2 years) (log-rank $P = 0.01$), but this finding was not confirmed using a threshold of 200 copies/mL (log-rank $P = 0.427$).

By 2 years, the proportion of PLWHIV with HIV RNA ≤ 50 copies/mL was 99.7% (95% CI 99.2–100.1%) for RPV and 96.3% (95% CI 94.8–97.8%) for EFV (log-rank $P < 0.0001$).

Toxicity

Overall, 21.3% of PLWHIV discontinued their first-line cART regimen because of toxicity. Among those who discontinued at least one drug because of toxicity, the main reason for discontinuation was renal toxicity in 27.4% of cases [11/704 patients on EFV (1.6%); 9/786 patients on RPV (1.1%)], was linked to an increase in cholesterol or triglycerides in 21.9% of cases [15/704 patients on EFV (2.1%); 1/786 patients on RPV (0.1%)] and was hepatic toxicity in 16.4% of cases [9/704 patients on EFV (1.3%); 3/786 patients on RPV (0.4%)] (Table 2). The incidence of discontinuation for all causes of toxicity was not significantly different in the two groups (log-rank $P = 0.136$; Fig. 1).

Intolerance

Intolerance was responsible for the majority (34.1%) of discontinuations in this analysis. Discontinuation for intolerance was attributable to central nervous system (CNS) side effects in 54.7% of cases [61/704 patients on EFV (8.7%); 1/786 patients on RPV (0.1%)] and to allergic reactions in 19.7% [20/704 patients on EFV (2.8%); 3/786 patients on RPV (0.4%)] (Table 2). Intolerance was significantly more frequent in patients taking EFV (log-rank $P < 0.0001$; Fig. 1).

Proactive switches and other causes of discontinuation

Proactive switches were responsible for 10.2% of discontinuations and were significantly more frequent in patients taking EFV than in those taking RPV (log-rank $P = 0.0116$).

The remaining 24.5% of cases of discontinuation were for other causes, including the 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 the end of the study (n = 10; 13.0%), adherence to new guideline advice (n = 2; 2.6%), availability of more effective drugs according to the clinician's judgement (n = 8; 10.4%) and unknown reasons (n = 15; 19.5%).

Relative hazards (RHs) for discontinuation

After adjustment for a number of potential confounders (age, gender, nation of birth, mode of HIV transmission, hepatitis coinfection, AIDS diagnosis, baseline CD4

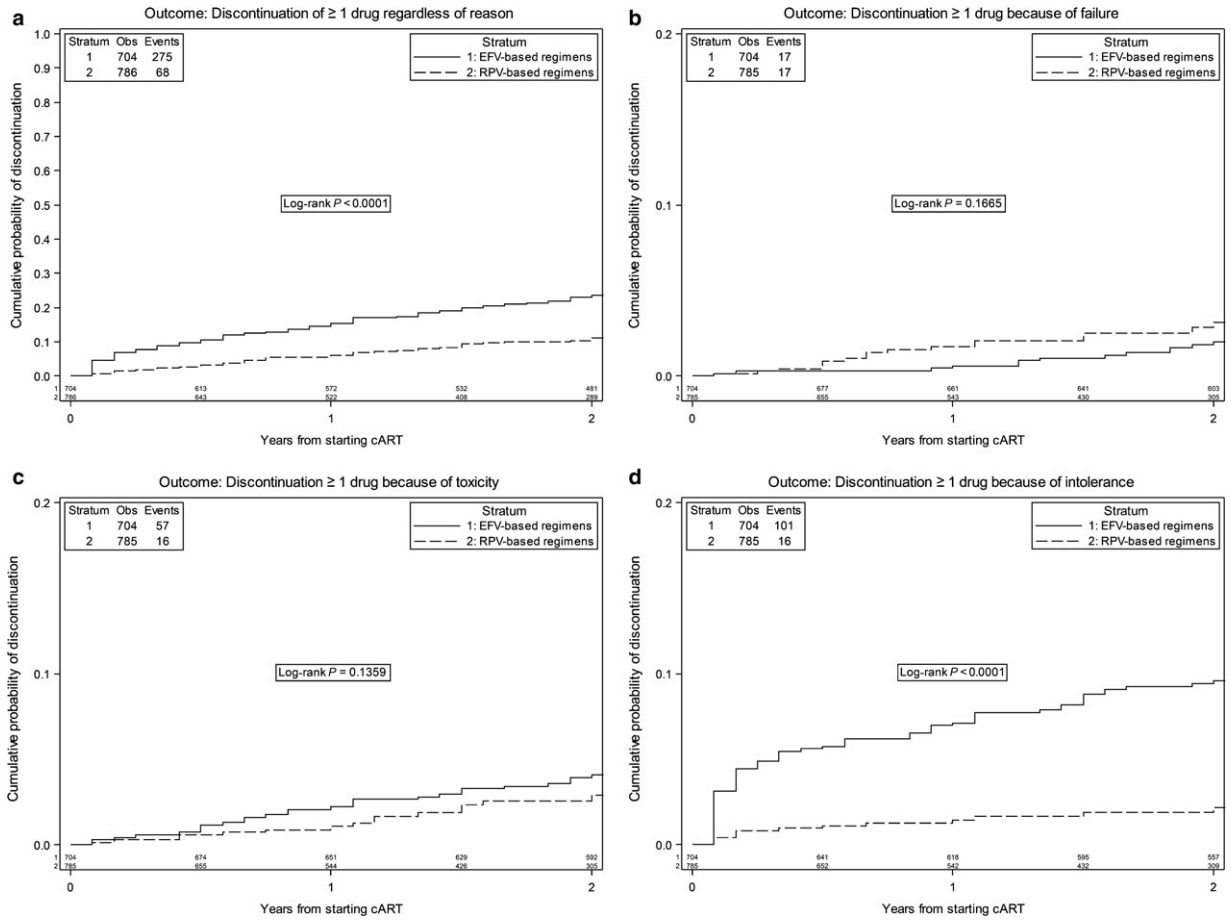

Fig. 1 Cumulative probability of discontinuation of rilpivirine (RPV) and efavirenz (EFV) due to any cause (a), failure (b), toxicity (c) and intolerance (d). cART, combination antiretroviral therapy; EFV, efavirenz; RPV, rilpivirine.

count, HIV RNA load and year of starting cART), patients who started EFV in their first-line regimen were 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 on EFV were > 10 times more likely to undergo a proactive switch in 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 of confirmed virological failure (> 50 copies/mL) nor that of achieving HIV RNA ≤ 50 copies/mL was 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 since the beginning of their therapy ($n = 210$ for TDF/FTC/EFV *vs.* $n = 780$ for TDF/FTC/RPV). The significance of findings for the same variables identified in the general population was confirmed, with the exception of the risk of proactive switch, which was no longer significantly different between the two treatment groups ($P = 0.946$; Table 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 with EFV, in the absence of significant differences in the cumulative chance of achieving HIV RNA load suppression or in the estimated rates of virological failure 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 agent even in ART-naïve patients [1], and combinations of two nucleoside reverse transcriptase inhibitors (NRTIs) plus an NNRTI have previously been reported to have high

Table 2 Causes of discontinuation according to the physicians' records

Reason for discontinuation	Regimen		
	RPV-based (n = 68)	EFV-based (n = 275)	Total (n = 343)
Failure [*n* (%)]	17 (25.0)	17 (6.2)	34 (9.9)
Death	2 (11.8)	0 (0.0)	2 (5.9)
Virological	14 (82.4)	15 (88.2)	29 (85.3)
Immunological	1 (5.9)	2 (11.8)	3 (8.8)
Intolerance [*n* (%)]	16 (23.5)	101 (36.7)	117 (34.1)
CNS	1 (6.3)	63 (62.4)	64 (54.7)
Allergic reactions	3 (18.8)	20 (19.8)	23 (19.7)
Gastrointestinal intolerance	2 (12.5)	4 (4.0)	6 (5.1)
Lipodystrophy	1 (6.3)	2 (2.0)	3 (2.6)
Osteopaenia/osteoporosis	5 (31.3)	6 (5.9)	11 (9.4)
Arthromyalgias	1 (6.3)	0 (0.0)	1 (0.9)
Skin and skin structure diseases	1 (6.3)	1 (1.0)	2 (1.7)
Clinical contraindications	2 (12.5)	5 (5.0)	7 (6.0)
Pro-active switch* [*n* (%)]	4 (5.9)	31 (11.3)	35 (10.2)
Toxicity [*n* (%)]	16 (23.5)	57 (20.7)	73 (21.3)
Cardiovascular	0 (0.0)	1 (1.8)	1 (1.4)
Hepatic	3 (18.8)	9 (15.8)	12 (16.4)
Renal	9 (56.3)	11 (19.3)	20 (27.4)
Peripheral nervous system	0 (0.0)	9 (15.8)	9 (12.3)
Metabolic/increase in lipids	2 (12.5)	17 (29.8)	19 (26.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Adherence [*n* (%)]	0 (0.0)	2 (0.7)	2 (0.6)
Temporary complete interruptions [*n* (%)]	0 (0.0)	4 (1.5)	4 (1.2)
Other [*n* (%)]	14 (20.6)	63 (22.9)	77 (22.4)
Patient's choice	2 (14.3)	18 (28.6)	20 (26.0)
Drug–drug interactions	3 (21.4)	7 (11.1)	10 (13.0)
Pregnancy or pregnancy planning	2 (14.3)	10 (15.9)	12 (15.6)
Inclusion in or discharge from clinical trials	0 (0.0)	10 (15.9)	10 (13.0)
Adherence to new guidelines	0 (0.0)	2 (3.2)	2 (2.6)
Availability of more effective drugs	2 (14.3)	6 (9.5)	8 (10.4)
Unknown	5 (35.7)	10 (15.9)	15 (19.5)

EFV, efavirenz; RPV, rilpivirine; *n*, number of patients; %, percentage calculated using the total number of discontinuations reported; CNS, central nervous system.
*Regimen modification with a viral load ≤ 50 copies/mL to prevent toxicity or to improve adherence/simplify the regimen/reduce pill burden.

Table 3 Crude and adjusted relative hazards (RHs) for discontinuation of efavirenz (EFV) *vs.* rilpivirine (RPV) from fitting a Cox regression model

Outcome	Crude RH (95% CI)	*P*-value	Adjusted* RH (95% CI)	*P*-value
Discontinuation for any reason				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	2.47 (1.87–3.26)	< 0.001	4.09 (2.89–5.80)	< 0.001
Discontinuation because of toxicity				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	1.57 (0.86–2.86)	0.139	2.23 (1.05–4.73)	0.037
Discontinuation because of intolerance				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	4.16 (2.42–7.16)	< 0.001	5.17 (2.66–10.07)	< 0.001
Discontinuation because of proactive switch				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	3.69 (1.25–10.87)	0.018	10.96 (3.17, 37.87)	< 0.001
Single VL > 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	1.57 (0.86–2.86)	0.139	1.19 (0.78–1.82)	0.409
Confirmed VL > 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	2.03 (1.14–3.62)	0.016	0.70 (0.31–1.54)	0.374
Confirmed VL > 50 copies/mL or discontinuation				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	2.48 (1.91–3.22)	< 0.001	3.21 (2.30–4.48)	< 0.001
Success VL ≤ 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	0.83 (0.74–0.92)	< 0.001	0.89 (0.75–1.05)	0.161

CI, confidence interval; TDF, tenofivir disoproxil fumarate; FTC, emtricitabine; VL, viral load.
*Adjusted for age, gender, nation of birth, mode of HIV transmission, hepatitis coinfection status, AIDS diagnosis, baseline CD4 count and viral load and year of starting combined antiretroviral therapy (cART).

durability [21], although recent data demonstrate an even better performance of INSTI-based regimens [22]. EFV was for years the preferred third agent, in international guidelines at least until 2013 [23,24], and in Italian guidelines until 2014 [25], and is still a preferred choice for first-line cART according to the World Health Organization (WHO) [8]. It has high efficacy also in patients with baseline HIV RNA > 100 000 copies/mL, there is extensive experience of its use and it is widely available globally [5]. Also, because of the recognized efficacy of this drug, EFV has been frequently used as the comparator treatment in randomized controlled efficacy trials [26]. RPV has been more recently introduced into clinical practice and it has been studied in comparative trials only *vs.* EFV, in both STRs [16] and regimens that are not co-formulated [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 count > 200 cells/μL [16]. The data from the ICONA cohort document that the proportion of people starting first-line RPV-based regimens has increased in recent years, while use of EFV has declined. This is confirmed in the present analysis, which showed a significant difference in calendar year of starting RPV and EFV. A more recent calendar year of initiation has been previously correlated with a lower risk of treatment discontinuation [21]. It is also possible that people who started EFV delayed therapy initiation until the 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 RPV-containing cART had lower HIV RNA loads and higher CD4 T-cell counts compared with those who started EFV. All these factors demonstrate a tailored use of RPV in PLWHIV enrolled in the ICONA cohort. However, our analysis was controlled for both calendar year and baseline CD4 count, so that a residual confounding

Table 4 Crude and adjusted relative hazards (RHs) for discontinuation of tenofovir disoproxil fumarate/emtricitabine/efavirenz (TDF/FTC/EFV) *vs.* tenofovir disoproxil fumarate/emtricitabine/rilpivirine (TDF/FTC/RPV) in patients who started a single-tablet regimen (STR) of combined antiretroviral therapy (cART), from fitting a Cox regression model ($n = 210$ patients in the TDF/FTC/EFV group; $n = 780$ patients in the TDF/FTC/RPV group)

Outcome	Crude RH (95% CI)	*P*-value	Adjusted* RH (95% CI)	*P*-value
Discontinuation for any reason				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	3.86 (2.80–5.32)	< 0.001	7.86 (5.01–12.32)	< 0.001
Discontinuation because of toxicity				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	2.98 (1.51–5.88)	0.002	2.78 (1.03–7.51)	0.043
Discontinuation because of intolerance				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	5.40 (2.89–10.12)	< 0.001	7.00 (3.01–16.30)	< 0.001
Discontinuation because of proactive switch				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	0.50 (0.05–4.52)	0.535	1.12 (0.04–32.57)	0.946
Single VL > 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	2.98 (1.51–5.88)	0.002	1.80 (0.97–3.34)	0.064
Confirmed VL > 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	1.57 (0.70, 3.55)	0.274	0.51 (0.13, 2.02)	0.335
Confirmed VL > 50 copies/mL or discontinuation				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	3.56 (2.62–4.83)	< 0.001	6.33 (4.09–9.80)	< 0.001
Success VL ≤ 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	0.81 (0.69, 0.96)	0.012	0.88 (0.70, 1.11)	0.279

CI, confidence interval; VL, viral load.
*Adjusted for age, gender, nation of birth, mode of HIV transmission, hepatitis coinfection status, AIDS diagnosis, baseline CD4 count and viral load and year of starting cART.

caused by these imbalances is improbable. RPV is a preferred option in many guidelines as a first-line agent [3,4,7,31], has low costs, the lowest risk of rash among NNRTI-based therapies, and a low risk of metabolic adverse effects, in addition to being co-formulated in the smallest tablet among single-pill regimens [5,32] and showing lower relative risks for neurological events than EFV [16,32]. RPV has also been previously reported to be more durable compared not only with EFV, but also with other modern drugs including an INSTI [i.e. raltegravir (RAL)] [19,20,33]. However, people with baseline HIV RNA > 100 000 copies/mL were not excluded in these other studies. Moreover, in a recent meta-analysis including four randomized controlled trials with EFV as the comparator, RPV was noninferior at 48 and 96 weeks for the endpoint of viral suppression ≤ 50 copies/mL [16,32] and showed no difference in terms of CD4 count change from baseline [16,32], but a higher risk of virological failure [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 HIV RNA < 50 copies/mL to be significantly higher with RPV than with EFV, and also virological failure was less probable in patients treated with RPV. After controlling for possible confounders, neither of these factors was significant, but the probability of virological failure was not different between the two study groups, in contrast to previously reported findings [32]. Moreover, RPV showed a 4-fold lower RH for discontinuation for any cause, while EFV RHs for toxicity and intolerance were 2- and 5-fold higher than those of RPV, respectively, and the RH for proactive switch was nearly 11-fold higher. However, the risks of virological failure (using a definition of confirmed failure of > 50 or > 200 copies/mL) and of discontinuation because of failure were not different in the two groups. Indeed, the risk of treatment failure (e.g. of a confirmed viral load > 50 copies/mL or discontinuation regardless of the reason) was higher in EFV- than in RPV-treated patients (adjusted RH of 3.21), and this was confirmed in the analysis restricted 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 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, discontinued their therapy, and mainly for adverse events related to the CNS [34].

Because all three drugs (TDF/FTC/EFV) will soon be available in generic formulations, their use is an attractive strategy from the point of view of trying to reduce costs for the national health system. This advantage has to be balanced with the potential higher risk of 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. Lastly, whether there is a substantial advantage of the inclusion of tenofovir alafenamide (TAF) in STRs 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, INSTIs are now the preferred first-line third agents according to various guidelines [2–4,31], as there is no evidence of a difference in HIV RNA suppression outcomes compared with EFV [35–37]. In addition, similar to what we found here, INSTI-based regimens were shown to be superior to EFV in maintaining virological suppression and had a lower risk of discontinuation [11,38]. Moreover, a recent analysis of data from 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 other NNRTI-based strategies [3,4,7].

Our analysis has several limitations. First, it was not a randomized comparison and it is possible that unmeasured factors influencing clinicians' treatment choice may have introduced confounding which we could not control for. Secondly, despite having selected patients with HIV RNA < 100 000 copies/mL, we still detected differences in the average viral load, and in CD4 count and calendar year of initiation by treatment group, so that residual confounding cannot be ruled out. Finally, although data are collected in a standardized manner, there is natural variability in how clinicians classify reasons for stopping a drug and in decisions about 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 of the study is that our results reflect what really happens in everyday clinical practice and we were able to compare the two regimens for a large number of outcomes over 2 years from starting cART.

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, was less toxic and showed greater durability than EFV, without significant differences in the rates of virological failure or discontinuation because of failure. We found a lower risk of discontinuation of RPV *vs.* EFV, especially for reasons related to proactive switches. This observation should encourage modelling work to evaluate the cost-effectiveness of initiating EFV instead of RPV as first-line treatment. Also, our data need 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 initiation.

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Appendix 1: The ICONA Foundation study group

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