

## **Durability of rilpivirine-based versus integrase inhibitor-based regimens in a large cohort of naïve HIV-infected patients starting antiretroviral therapy**

Roberta Gagliardini<sup>a,#,\*</sup>, Nicola Gianotti<sup>b,#</sup>, Franco Maggiolo<sup>c</sup>, Alessandro Cozzi-Lepri<sup>d</sup>, Andrea Antinori<sup>a</sup>, Silvia Nozza<sup>b</sup>, Giuseppe Lapadula<sup>c</sup>, Andrea De Luca<sup>f,†</sup>, Cristina Mussini<sup>g</sup>, Andrea Gori<sup>h</sup>, Annalisa Saracino<sup>i</sup>, Massimo Andreoni<sup>j</sup>, Antonella d'Arminio Monforte<sup>k</sup>, on behalf of the ICONA Foundation Study Group

<sup>#</sup>Both authors contributed equally to this work

<sup>a</sup>Lazzaro Spallanzani National Institute for Infectious Diseases IRCCS, Rome, Italy

<sup>b</sup>Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy

<sup>c</sup>Infectious Diseases, ASST Papa Giovanni XXIII, Bergamo, Italy

<sup>d</sup>Infection and Population Health, Institute of Global Health, University College London, London, United Kingdom

<sup>e</sup>Infectious Diseases, Ospedale San Gerardo - ASST Monza-Brianza, Monza, Italy

<sup>f</sup>Infectious Diseases, Siena University Hospital, Siena, Italy

<sup>g</sup>Infectious Diseases, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy

<sup>h</sup>Infectious Diseases Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

<sup>i</sup>Infectious Diseases, Università degli Studi "Aldo Moro" di Bari, Bari, Italy

<sup>j</sup>Institute of Infectious Diseases, University of Rome Tor Vergata, Rome, Italy

<sup>k</sup>Clinic of Infectious Diseases, S. Paolo Hospital, University of Milan, Milan, Italy

\*Correspondence to: UOC Immunodeficienze Virali, INMI Lazzaro Spallanzani, IRCCS  
via Portuense 292 - 00149 Rome, Italy. Tel.: +039 0655170368 or +039 3331045103; fax: +39 06  
55170477; [Email: roberta\\_gagliardini@yahoo.it](mailto:roberta_gagliardini@yahoo.it) (Roberta Gagliardini)

**Running head:** Durability of first-line RPV vs. INSTI-based ART

## Abstract

**Objectives:** Comparisons between rilpivirine (RPV) and integrase strand transfer inhibitors (INSTIs) in antiretroviral therapy (ART)-naïve HIV-infected individuals are currently lacking. This study aimed to compare, in an observational cohort setting, the durability of treatment of RPV-based and INSTI-based first-line regimens.

**Methods:** Patients who started first-line ARTs based on RPV or INSTIs, with HIV-RNA < 100 000 copies/mL and CD4 cell count > 200 cells/ $\mu$ L were included. The primary endpoint was the cumulative probability of treatment failure (TF = virological failure [confirmed HIV-RNA > 50 copies/mL] or discontinuation of the anchor drug in the regimen), as assessed by Kaplan-Meier method. A multivariable Cox regression was used to control for potential confounding.

**Results:** Of the 1991 included patients, 986 started ART with an RPV-based and 1005 with an INSTI-based regimen. The median (IQR) follow-up was 20 (10, 35) months. The cumulative 2-year probability of TF with RPV (9.1% [95% 7.2, 11.1]) was lower than that observed in the INSTIs group (16.6% [13.8, 19.4],  $P = 0.0002$ ) but not when compared with dolutegravir (DTG) alone. Starting ART with an INSTIs-based regimen vs. RPV was associated with a higher risk of TF after controlling for potential confounding factors (AHR [95% CI]: 1.64 [1.28, 2.10];  $P < 0.001$ ). The results were similar when restricting the analysis to single-tablet regimens, although the probability of virological success was higher for INSTIs and DTG.

**Conclusions:** In ART-naïve patients with low viral loads and high CD4 counts, the risk of treatment failure was lower in those who started RPV-based vs. INSTIs-based regimens other than DTG-based ones.

**Keywords:** Antiretroviral naïve; Rilpivirine; Dolutegravir; Elvitegravir; Raltegravir; Single-tablet regimen

## **Introduction**

Rilpivirine (RPV)-based triple regimens are safe and effective, both in patients starting first-line antiretroviral therapy (ART) [1-3] and in those switching from another effective antiretroviral regimen [4-6]. They are currently approved for use in any treatment line in the absence of drug resistance. RPV-based regimens are not recommended for patients starting first-line ART with a baseline HIV-RNA > 100 000 copies/mL or, according to the Italian HIV treatment guidelines, [7] for those with a CD4+ counts < 200 cells/ $\mu$ L.

Early randomised comparisons between RPV and efavirenz (EFV) in ART-naïve patients with HIV-RNA > 100 000 copies/mL who started these non-nucleoside reverse transcriptase inhibitors (NNRTI) in combination with two nucleoside analogues showed a higher risk of virological failure (VF) in the RPV arm [1,2]. In these studies, VF was defined as never suppressed (HIV-RNA < 50 copies/mL before week 48) or rebounder (having viral load  $\geq$  50 copies/mL at two consecutive assessments after achieving two consecutive HIV-RNA < 50 copies/mL). However, this result was not confirmed in a further open-label randomised controlled trial (RCT) in ART-naïve patients receiving RPV and EFV as single-tablet regimens (STR) [3]. In patients with viral loads < 100 000 the combination of RPV/tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) was eventually proven to be superior to EFV/TDF/FTC, mainly because of a better tolerability profile [3,8]. Unfortunately, RPV-based first-line regimens have never been compared in RCTs to regimens based on ARV drug classes other than NNRTI.

Network meta-analyses of RCTs [9-11] showed a superiority of DTG vs. RPV in terms of viral efficacy, but no differences in treatment discontinuation due to adverse events or treatment emergent serious adverse events. In contrast, there was no difference between RPV and the other drugs in the integrase strand transfer inhibitors (INSTIs) class. However, this was indirect evidence derived from Bayesian modelling, so direct evidence, although based on real-life data, might help to reduce the knowledge gap.

This study aimed to compare the durability of RPV-based and INSTIs-based first-line regimens in HIV-infected patients with HIV-RNA < 100 000 copies/mL and CD4 cells counts > 200 cells/ $\mu$ L.

## **Methods**

### ***Study population***

The ICONA Foundation Study is a multi-centre prospective observational study of HIV-1-infected patients, which was set up in 1997. Eligible patients are those starting ART when they are naïve to antiretrovirals, regardless of the reason for which they had never previously been treated and of the stage of their disease. The ICONA Foundation study has been approved by Institutional Review Boards of all the participating centres; data from patients are anonymised. All patients sign a consent form to participate in ICONA, in accordance with the ethical standards of the committee on human experimentation and the Declaration of Helsinki (last amendment October 2013). Demographic, clinical, laboratory data, and type of therapy are collected for all participants and recorded using electronic data collection [www.icona.org]. In particular, demographic and socio-behavioural data, initiation and discontinuation dates of each antiretroviral drug, reasons for discontinuation, HIV-RNA, CD4+ cell counts, renal and liver function tests, blood cell counts, AIDS-defining diseases, main non-HIV-related diseases, and deaths are recorded for all ICONA enrolled patients. Patients are prospectively followed-up at each of the clinical sites participating in the study and HIV viral load monitoring in cohort participants is performed at least twice a year, according to study protocol and Italian guidelines [7]. Data are collected during patients' routine appointments. Dates of start and stop of each antiretroviral are collected together with the main reason for discontinuation, as reported by the treating physician.

The database for this analysis was put together retrospectively, selecting only patients who started ART after January 2012 and with HIV-RNA < 100 000 copies/mL, CD4 cells counts > 200 cells/ $\mu$ L, with an RPV-based or INSTIs-based first-line regimen, and having one or more

virological follow-up visits thereafter. All considered regimens were composed by two nucleoside reverse transcriptase inhibitors (NRTIs) and one anchor drug (RPV or INSTIs). Data were frozen for the analysis on 30th April 2019.

### ***Virological analyses***

Viral load was assessed in each centre according to local procedures, using an assay with a sensitivity of at least 50 HIV-RNA copies/mL (Biomerieux NucliSENS EasyQ HIV-1 v.2.0, Siemens VERSANT HIV-1 RNA 1.5 Assay kPCR, Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test or v.2.0, Abbott RealTime HIV-1).

### ***Endpoints***

The primary study endpoint was defined as the cumulative probability of treatment failure (TF, a composite endpoint of virological failure [VF, defined as two consecutive HIV-RNA > 50 copies/mL after > 6 months from starting ART] or discontinuation of the anchor drug [ignoring changes in NRTI]). Secondary endpoints were the risk of treatment discontinuation, regardless of the reason for stopping the anchor drug, the probability of HIV-RNA < 50 copies/mL (virological success), and a single HIV-RNA > 50 copies/mL after 6 months from starting ART (virological rebound). An alternative discontinuation endpoint was also considered in which stops of the anchor drug due to simplification were not counted as events.

A sensitivity analysis for the primary endpoint was conducted after restricting the analysis to i) INSTIs patients who started DTG; and ii) patients who started ART with an STR; and iii) INSTIs patients who started elvitegravir (EVG)-containing regimens. A sensitivity analysis where treatment failure was defined as a composite endpoint of VF (defined as two consecutive HIV-RNA > 200 copies/mL after > 6 months from starting ART) or discontinuation of the anchor drug (ignoring changes in NRTI) was also performed. Changes in body weight, total and HDL cholesterol, and eGFR from pre-ART level to 2 years after therapy initiation were also investigated.

## *Statistical analysis*

Differences between groups in characteristics at baseline were assessed by means of  $\chi^2$  or Wilcoxon rank sum (Mann-Whitney) test, as appropriate. Standard survival analysis was used to estimate the time to the primary study endpoint; between-group differences were evaluated by the log-rank test. Kaplan-Meier curves were employed to estimate the time to event with corresponding 95% confidence interval (CI). Unadjusted and adjusted relative hazards of the different endpoints were calculated from fitting Cox regression models and tabulated. For both primary and secondary outcomes, estimates were adjusted for the following potential confounding time-fixed factors measured at baseline: age, gender, country of birth, mode of HIV transmission, CD4+ count and HIV-RNA, year of starting ART, HCV antibodies, and HBsAg status. The Missing Indicator Method was used to handle missing data [12]. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## **Results**

A total of 1991 patients were included in this analysis: 986 started a triple RPV-based and 1005 a triple INSTIs-based regimen (45.1% with dolutegravir, 39.9% with EVG/cobicistat and 15% with raltegravir). **Table 1** shows in detail the patients' baseline characteristics. TDF + XTC (lamivudine or emtricitabine) was used in 93.7% of RPV-based regimens and 57.8% of INSTIs-based regimens, tenofovir alafenamide (TAF)/emtricitabine in 2.7% and 8%, and abacavir + XTC in 3.5% and 34.3%, respectively ( $P < 0.001$ , **Table 2**). Other significant between-group differences at baseline were observed with respect to mode of HIV transmission (homosexual contacts were more frequent in the INSTIs group: 61.7% vs. 55.3% in the RPV group,  $P = 0.017$ ); co-infection with HBV (0.3% vs. 0.1% in the RPV group;  $P < 0.001$ ) or with HCV (5.8% with positive serology in the RPV group vs. 4.4% in the INSTIs group;  $P < 0.001$ ); time since HIV diagnosis (longer in the RPV group: 11 [interquartile range, IQR 2, 43] vs. 2 [IQR 1, 17] months in the INSTIs group;  $P < 0.001$ ); viral load

(higher in the INSTIs group: 4.34 [IQR 3.87, 4.69] vs. 4.20 [IQR 3.73, 4.56] log<sub>10</sub> copies/mL in the RPV group;  $P < 0.001$ ); and calendar year of ART initiation (more recent in the INSTIs group: 2016 [IQR 2015, 2017] vs. 2015 [IQR 2014, 2016] in the RPV group;  $P < 0.001$ ).

### ***Primary endpoint (treatment failure)***

Over a median (IQR) follow-up of 29 (14, 44) months in the RPV and 16 (8, 26) in the INSTI group, the cumulative probability of treatment failure was higher in the INSTIs group ( $P = 0.0002$ , [Figure 1](#)). In more detail, by 2 years of follow-up, TF occurred in 78 patients who started ART with an RPV-based regimen and 124 who started ART with an INSTI-based regimen. Corresponding 2-year percent probabilities (95% CI) of TF were 9.1% (7.2, 11.1) and 16.6% (13.8, 19.4), respectively. Considering the entire period of observation, TF occurred in 125 patients who started ART with an RPV-based and 145 who started ART with an INSTIs-based regimen. In contrast, after restricting the comparison to RPV-based vs. DTG-based regimens, no evidence for a between-group difference in terms of risk of TF was observed. Two-year percent probabilities (95% CI) of TF were 9.1% (7.2, 11.1) with RPV and 8.5% (5.7, 11.3) with DTG ( $P = 0.22$ , [Figure 2, panel A](#)). In the sensitivity analysis restricted to patients who started an STR regimen ( $n = 1575$ , [Figure 2, panel B](#)), the 2-year percent probabilities (95% CI) of TF were 16.7% (14.1, 19.3) in the RPV group and 37.9% (32.6, 43.2) in the INSTIs group ( $P < 0.0001$ ). Even in this sub-analysis, when the comparison of RPV-based with DTG-containing ART were limited, there was no longer evidence of a difference, and 2-year percent probabilities (95% CI) were 16.7% (14.1, 19.3) with RPV and 12.8% (6.9, 18.7) with DTG ( $P = 0.1870$ ).

After adjusting for age, gender, nation of birth, mode of HIV transmission, hepatitis coinfection, year of starting ART, baseline CD4<sup>+</sup> count and HIV-RNA, treatment with an INSTIs-based vs. RPV-based regimen (AHR [95% CI]: 1.64 [1.28, 2.10];  $P < 0.001$ ) was independently associated with a higher risk of TF, as defined in the primary endpoint ([Table 3](#)). Results were similar in the analysis restricted to only patients using STR formulations. After excluding stops due to pro-



active switch (simplifications), risk of treatment failure remained higher in INSTIs-based vs. RPV-based regimens (aHR 1.49 [1.26, 1.77];  $P < 0.001$ ). Even considering a different definition of TF (confirmed HIV-RNA  $> 200$  copies/mL or discontinuation of the anchor drug), treatment with an INSTIs-based vs. RPV-based regimen (AHR [95% CI] 1.80 [1.39, 2.33];  $P < 0.001$ ) was independently associated with a higher risk of TF. In contrast, after limiting the comparison of RPV-based to DTG-based regimens only, the use of a DTG-based regimen appeared to be associated with lower risk of TF (overall and when restricting to STR regimens) and of discontinuation for any reason, although the results were compatible with the null hypothesis of no difference (Table 4). In the comparison of RPV-based with EVG-based regimens, the corresponding 2-year percent probabilities (95% CI) of TF were 9.1% (7.2, 11.1) for RPV and 9.9% (6.6, 13.3) for EVG (Supplementary Figure 1), while treatment with EVG had an AHR of 1.20 (0.82, 1.77) of TF versus RPV in the adjusted analysis (Supplementary Table 1).

## ***Secondary endpoints***

### ***3.2.1 Discontinuation of anchor drug***

Overall, discontinuation of any drug in the regimen (regardless of the reason) occurred in 340 (34.5%) patients who started ART with an RPV-based regimen and in 386 (38.4%) who started ART with an INSTIs-based regimen. Discontinuation of the anchor drug before year 2 occurred in 70 (7.1%) patients who started ART with an RPV-based regimen and in 110 (10.9%) who started ART with an INSTIs-based regimen (Supplementary Table 2). Toxicity/intolerance was the reason for discontinuation before year 2 in 27 (38.6% among patients who discontinued) patients in the RPV group and 44 (40%) in the INSTIs group; proactive switch in three (4.3%) and 17 (15.5%); failure in 10 (14.3%) and four (3.6%); adherence in 0 (0%) and three (2.7%); and other causes (patient's choice, drug-drug interactions, pregnancy or pregnancy planning, inclusion or discharge from clinical trials or unknown) in 30 (42.9%) and 42 (38.2%), respectively. Two-year percent probability (95% CI) of discontinuation due to toxicity/intolerance was 4.8% (3.3, 6.3) for the RPV group and 9.1% (7.0,

11.2) for the INSTIs group. After controlling for potential confounding factors, participants initiating INSTIs retained a higher risk of discontinuation for any reason compared with those starting RPV-based regimens. Even if not statistically significant, the use of an INSTI-based rather than RPV-based regimen seemed to also be associated with a higher risk of discontinuation for toxicity/intolerance (AHR 1.38 [1.00, 1.90],  $P = 0.053$ ) (Table 3).

### 3.2.2 Virological efficacy

Time to achieve an HIV-RNA  $\leq 50$  copies/mL was faster in participants who started an INSTIs-based regimen than in those treated with RPV-based regimens ( $P < 0.0001$ ): 6 months after the start of ART, the probability (95% CI) of achieving  $\leq 50$  HIV-RNA copies/mL was 78.1% (75.4, 80.7) in the RPV vs. 83.2% (80.8, 85.5) in the INSTIs group ( $P < 0.0001$ ). However, by 12 months they were 94.8% (93.4, 96.2) vs. 94.7% (93.2, 96.1) and 24 months 99.1% (98.4, 99.7) vs. 99.3% (98.7, 99.9); thus, the difference was largely attenuated. Similarly, there was no evidence for a difference by treatment groups in the cumulative probability of pure VF  $> 50$  copies/mL ( $P = 0.625$ ): by 2 years of follow-up, VF occurred in 18 patients (2.3 [95% CI 1.2, 3.3]) who started an RPV-based and 14 (1.9 [95% CI 0.9, 3.0]) who started an INSTIs-based regimen. For viral success and VF endpoints, similar results were obtained comparing RPV-based with DTG-based regimens (data not shown). Like in the main comparison with the whole INSTIs class, the use of a DTG-based vs. RPV-based regimen was associated with a higher probability of virological success (aHR 1.31 [1.16, 1.49];  $P < 0.001$ ) (Table 4). The results of the adjusted analyses are shown in Table 3: the use of an INSTIs-based vs. RPV-based regimen was associated with a higher probability of virological success (AHR 1.24 [1.13, 1.37];  $P < 0.001$ ), while there was no evidence of a difference in the risk of confirmed virological failure and virological rebound by treatment group (Table 3).

### 3.2.3 Evolution of weight, metabolic profiles and renal function

Patients who started INSTIs-based regimens showed a significantly higher increase in total cholesterol and HDL vs. RPV-containing regimens, with partial clinical significance, while there was no evidence for a between-group difference in body weight and eGFR changes (Supplementary Table 3).

## Discussion

This study aimed to compare the durability of RPV, mainly combined with FTC/TDF, with that of INSTIs-based first-line regimens in the target population of HIV-infected patients starting their first-line ART with  $< 100,000$  HIV-RNA copies/mL and CD4 cells counts  $> 200$  cells/ $\mu$ L. It is highly unlikely that an RCT comparing RPV with INSTIs class will be ever performed, as these drugs were released several years ago.

Overall, it was found that RPV-based regimes had a longer durability than those based on INSTIs, with a lower risk of discontinuation and TF retained by 2 years from starting ART. It is believed that this is the first analysis showing that the durability of regimens based on RPV appear to be longer than that of those based on INSTIs, even when restricting to participants using STR formulations and when switches of the anchor drug due to simplification were not counted as events.

Interestingly, the higher risk of TF observed in patients who started ART with an INSTIs-based regimen was mainly attributable to treatment discontinuation: indeed, there was no evidence of a difference with regards of the risk of pure virological failure. In another large observational study that also included EFV in the comparison, no difference in virological success and a different composite treatment outcome (defined as HIV-RNA  $< 200$  copies/ mL with no regimen change and no AIDS/death events) were detected [13]. In the current analysis, this difference seemed to be mainly driven by raltegravir and EVG, as there was no longer evidence of a difference when comparing RPV-based with DTG-based regimens only. This finding is not unexpected, as INSTIs have non-homogeneous profiles and are different in terms of genetic barrier, toxicities, pill burden, food

restrictions and drug-drug interactions' potential. Indeed, a recent retrospective analysis from the cohort showed that first-line regimens with dolutegravir were associated with lower risk of treatment failure than first-generation INSTIs [14].

Rates of treatment discontinuation for INSTIs (7.2% by 1 year) were higher than those observed in clinical trials (2-3% by 48 weeks) [15-19]; this was probably due to the open option of simplification, even in the absence of tolerability issues in everyday clinical practice in Italy [20]. The main reported causes of discontinuation in the INSTIs group were combined reasons (including availability of more effective drugs, adherence to new guidelines, patients' choice, and inclusion in clinical trials in 38.2% of patients), toxicity/intolerance (40% of patients), and a proactive switch/simplification (11.1%). While this testifies the frequent occurrence of simplification to newer regimens or regimens with lower pill burden (and, when possible, to STRs) in clinical practice [20], it must be underlined that proactive switches were not the most common reason for discontinuing the INSTIs and were also often suggested by the treating physician because of subclinical toxicity or in order to prevent untoward effects (i.e. switches to a dual regimen).

By 1 year of starting ART, 2.3% of patients who started rilpivirine and 5.1% of those starting the INSTIs-based regimens had discontinued the anchor drug due to toxicity/intolerance. The estimate for RPV is in agreement with that seen in randomised clinical trials of first-line antiretroviral therapies [1-3]. Rates of discontinuations for toxicity/intolerance were similar to those that were reported in a similar analysis that included only INSTI regimens [14].

Although TDF was more frequently used in combination with RPV vs. INSTIs, the current study observed similar frequency of discontinuation due to kidney toxicity among patients treated with INSTIs. One possible explanation for this finding is the fact that TDF concentrations could be boosted by cobicistat in the EVG-based regimen of the INSTIs group [21]. Interestingly, a high

discontinuation rate for CNS toxicity among patients treated with INSTIs (nine of 1005 patients, < 1%) was not observed.

The results of this analysis are in apparent contrast with those from another large cohort, which showed lower rates of regimen discontinuation and virologic failure in patients initiating ART with an INSTIs-containing regimen compared with those who initiated ART with a protease inhibitor or a NNRTI [22]. However, a different definition for both VF and TF was used in that analysis and also patients receiving “old” NNRTI-based regimens, not considered in the current analysis, were included: for instance, many patients in the UNC Center for AIDS Research Clinical Cohort were treated with efavirenz-based combinations, including those of efavirenz with zidovudine and lamivudine. It is known that the genetic barrier and tolerability of rilpivirine are different to that of efavirenz [1-3]. On the other hand, the very low rate of discontinuation found in the current analysis among patients who started ART with RPV is consistent with data from RCTs [3,8].

The reduction of HIV viral load < 50 copies/mL was more rapid with INSTIs or DTG regimens, which is consistent with the results from a number of clinical trials showing that the decline in HIV-RNA plasma concentrations in the first weeks after starting treatment with these drugs is typically steeper than with any other antiretroviral drug class [15-17,19]. Theoretically, this could have a potential benefit in terms of reduction of HIV transmission, even if the clinical implications of this observation are still being debated. Overall, the current study confirmed that a virological suppression < 50 HIV-RNA copies/mL at one year was achieved by > 90% of patients, and was independent from the rapidity of the initial HIV-RNA decline in plasma. In line with these findings, rates of VF were extremely low and almost identical in both groups, which again was consistent with the data shown by clinical trials [1-3,15-17,19].

Before drawing final conclusions, a few limitations of this studies need to be mentioned. One key limitation was the observational study design. Although the analysis was restricted to people with a viral load < 100 000 copies/m and CD4 > 200 cells/ $\mu$ L, there was still some imbalance in participants' virological profile at ART initiation between the treatment groups. However, these

baseline differences were not clinically significant and these imbalances were controlled for by means of multivariable analysis. Confounding was controlled for using standard regression techniques. Although the results of fitting a marginal model in this simple case of time-fixed confounding and a linear predictor with no interactions, and uninformative censoring, large differences from the two approaches were not expected. It is however possible that residual confounding by indication was present, and adherence, presence of psychiatric comorbidities, use of proton-pump inhibitors or antipsychotic agents were probably unmeasured confounders. Another possible limitation was the infrequent use of TAF in the regimens studied, especially in the RPV group, which could have jeopardised the generalisability of the results to more contemporary cohorts of patients initiating ART. Nevertheless, TDF is still currently used and its utilisation in the clinics might even increase over time.

## **Conclusions**

In this large cohort of patients who started ART with  $< 100\,000$  HIV-RNA copies/mL and CD4 cell counts  $> 200$  cells/ $\mu$ L, the risk of treatment failure was lower in patients who started ART with an RPV-based regimen than in those who initiated an INSTIs-based regimen. This difference was mainly driven by toxicity rather than virological efficacy. Of note, there was no evidence of a difference when the comparison was limited to DTG-based regimens. Overall, these data support the current guidelines for the continued recommendation of RPV/(TAF or TDF)/FTC in the special situation of  $< 100\,000$  HIV-RNA copies/mL and CD4 cell count  $> 200$  cells/ $\mu$ L as a possible valid alternative to INSTIs-based regimens in certain clinical situations (7,23). Support from randomised comparisons are still lacking, so while RCTs must be conducted, we are currently forced to rely on results from observational data.

## **Acknowledgments**

## **Icona Foundation Study Group**

BOARD OF DIRECTORS: A d'Arminio Monforte (President), A Antinori (Vice-President), M Andreoni, A Castagna, F Castelli, R Cauda, G Di Perri, M Galli, R Iardino, G Ippolito, A Lazzarin, GC Marchetti, G Rezza, F von Schloesser, P Viale.

SCIENTIFIC SECRETARY: A d'Arminio Monforte, A Antinori, A Castagna, F Ceccherini-Silberstein, A Cozzi-Lepri, E Girardi, A Gori, S Lo Caputo, F Maggiolo, C Mussini, M Puoti, CF Perno.

STEERING COMMITTEE: A Antinori, F Bai, A Bandera, S Bonora, M Borderi, A Calcagno, MR Capobianchi, A Castagna, F Ceccherini-Silberstein, S Cicalini, A Cingolani, P Cinque, A Cozzi-Lepri, A d'Arminio Monforte, A Di Biagio, R Gagliardini, E Girardi, N Gianotti, A Gori, G Guaraldi, G Lapadula, M Lichtner, A Lai, S Lo Caputo, G Madeddu, F Maggiolo, G Marchetti, E Merlini, C Mussini, S Nozza, CF Perno, S Piconi, C Pinnetti, M Puoti, E Quiros Roldan, R Rossotti, S Rusconi, MM Santoro, A Saracino, L Sarmati, V Spagnuolo, V Svicher, L Taramasso.

STATISTICAL AND MONITORING TEAM: A Cozzi-Lepri, I Fanti, L Galli, P Lorenzini, A Rodano, M Macchia, A Tavelli.

COMMUNITY ADVISORY BOARD: A Bove, A Camposeragna, M Errico, M Manfredini, A Perziano, V Calvino.

BIOLOGICAL BANK INMI: F Carletti, S Carrara, A Di Caro, S Graziano, F Petroni, G Prota, S Truffa.

PARTICIPATING PHYSICIANS AND CENTERS: Italy A Giacometti, A Costantini, V Barocci (Ancona); G Angarano, L Monno, E Milano (Bari); F Maggiolo, C Suardi (Bergamo); P Viale, V Donati, G Verucchi (Bologna); E Quiros Roldan, C Minardi, (Brescia); F Franzetti, C Abeli (Busto Arsizio); L Chessa, F Pes (Cagliari); B Cacopardo, B Celesia (Catania); J Vecchiet, K Falasca (Chieti); A Pan, S Lorenzotti (Cremona); L Sighinolfi, D Segala (Ferrara); P Blanc, F Vichi (Firenze); T Santantonio, S Ferrara (Foggia); M Bassetti, E Pontali, A Alessandrini, N Bobbio, G Mazzarello

(Genova); M Lichtner, L Fondaco (Latina); S Piconi, C Molteni (Lecco); A Chiodera, P Milini (Macerata); G Nunnari, G Pellicanò (Messina); A d'Arminio Monforte, M Galli, A Lazzarin, G Rizzardini, M Puoti, A Gori, A Castagna, ES Cannizzo, MC Moioli, R Piolini, D Bernacchia, A Poli, C Tincati (Milano); C Mussini, C Puzzolante (Modena); P Bonfanti, G Lapadula (Monza); V Sangiovanni, I Gentile, V Esposito, G Di Flumeri, G Di Filippo, V Rizzo (Napoli); AM Cattelan, S Marinello (Padova); A Cascio, C Colomba (Palermo); D Francisci, E Schiaroli (Perugia); G Parruti, F Sozio (Pescara); MA Di Pietro, A Vivarelli (Pistoia); C Lazzaletti, R Corsini (Reggio Emilia); M Andreoni, A Antinori, R Cauda, A Cristaudo, C Mastroianni, V Mazzotta, S Lamonica, M Capozzi, A Mondì, A Cingolani, M Rivano Capparuccia, G Iaiani, A Latini, G Onnelli, MM Plazzi, G De Girolamo, A Vergori (Roma); M Cecchetto, F Viviani (Rovigo); G Madeddu, A De Vito (Sassari); B Rossetti, F Montagnani (Siena); A Franco, R Fontana Del Vecchio (Siracusa); C Di Giuli (Terni); GC Orofino, G Di Perri, S Bonora, M Sciandra (Torino); C Tascini, A Londero (Udine); V Manfrin, G Battagin (Vicenza); G Starnini, A Ialungo (Viterbo). Foundation Study Group

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The Icona Foundation is supported by unrestricted grants from Gilead Sciences, Janssen, MSD Thera Technologies and ViiV Healthcare. The funders had no role in study design, data collection, analysis, decision to publish or preparation of the manuscript.

### **Transparency declaration**

RG: speakers' honoraria/educational activities for ViiV Healthcare, Merck Sharp and Dohme and Gilead Sciences, advisor for ViiV Healthcare and Janssen-Cilag. NG: advisor for Gilead Sciences, AbbVie and Janssen-Cilag and speakers' honoraria from Gilead Sciences, ViiV, Bristol-Myers Squibb, Merck Sharp and Dohme, Roche, AbbVie, Boehringer Ingelheim, and Janssen-Cilag. AA: consultancies for Bristol-Myers Squibb, ViiV, Gilead, Abbvie, Merck Sharp and Dohme and Janssen-Cilag, grants from Gilead Sciences, Janssen-Cilag and Bristol-Myers Squibb and travel grants from



Abbvie. GL: received speaker or consultancy grants from Janssen-Cilag, Gilead and Bristol-Myers Squibb and travel grants from Bristol-Myers Squibb, ViiV and Gilead. ADL: board membership for Gilead and ViiV, consultancies for Abbvie, Merck, Teva and Janssen, grants from ViiV and Merck, service in speakers's bureau for Gilead and travel grants from ViiV and Janssen. CM: member of boards for Gilead, BMS, ViiV, Abbvie, MSD and have been member of speaker's bureau for Gilead. AG: member of the advisory boards of Gilead, ViiV, Bristol-Myers Squibb, Janssen-Cilag, Merck Sharp-Dome and Abbvie, received speaker grants from Gilead and travel grants from Gilead, ViiV, Bristol-Myers Squibb, Janssen-Cilag and Merck Sharp-Dome. MA: speaker fees, travel grants, and consulting fees from Abbvie, Bristol-Myers-Squibb, Gilead Sciences, Merck Sharp & Dohme, ViiV Healthcare, and Janssen-Cilag. Ad'AM: member of boards for Abbvie, BMS, Gilead, Janssen, ViiV, MSD. ACL, SN, AS: no potential conflict of interest to declare.

## References

1. Molina JM, Cahn P, Grinsztejn B, Lazzarin A, Mills A, Saag M, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naïve adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet* 2011;378:238-46.
2. Cohen CJ, Andrade-Villanueva J, Clotet B, Fourie J, Johnson MA, Ruxrungtham K, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naïve adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* 2011;378:229-37.
3. Cohen C, Wohl D, Arribas JR, Henry K, Van Lunzen J, Bloch M, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV-1-infected adults. *AIDS* 2014;28:989-97.
4. Palella FJ Jr, Fisher M, Tebas P, Gazzard B, Ruane P, Van Lunzen J, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. *AIDS* 2014;28:335-44.
5. Orkin C, DeJesus E, Ramgopal M, Crofoot G, Ruane P, LaMarca A, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. *Lancet HIV* 2017;4:e195-204.
6. DeJesus E, Ramgopal M, Crofoot G, Ruane P, LaMarca A, Mills A, et al. Switching from efavirenz, emtricitabine, and tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. *Lancet HIV* 2017;4:e205-13.
7. Antinori A, Di Biagio A, Marcotullio S, Sarmati L, Andreoni M, Angarano G, et al.

Evidence-based renewal of the Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons. *New Microbiol* 2018;41(4):247-55.

8. Molina JM, Clumeck N, Redant K, Rimsky L, Vanveggel S, Stevens M, et al. Rilpivirine vs. efavirenz in HIV-1 patients with baseline viral load 100,000 copies/ml or less: week 48 phase III analysis. *AIDS* 2013;27:889-97.

9. Kanters S, Vitoria M, Socias ME, Ford N, Forrest J, Popoff E. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. *Lancet HIV* 2016;3(11):e510-20.

10. Patel DA, Snedecor SJ, Tang WY, Sudharshan L, Lim JW, Cuffe R et al. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naïve HIV-1-infected patients: a systematic review and network meta-analysis. *PLoS One* 2014;9(9):e105653.

11. Snedecor SS, Radford M, Kratochvil D, Grove R, Puneekar Y. Comparative efficacy and safety of dolutegravir relative to common core agents in treatment-naïve patients infected with HIV-1: a systematic review and network meta-analysis. *BMC Infect Dis* 2019;19(1):484.

12. Groenwold RH, White IR, Donders AR, Carpenter JR, Altman DG, Moons KG. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. *CMAJ* 2012;184(11):1265-9.

13. A Mocroft, B Neesgard, R Zangerle, A Rieger, A Castagna, V Spagnuolo. Treatment outcomes of integrase inhibitors, boosted protease inhibitors and nonnucleoside reverse transcriptase inhibitors in antiretroviral-naïve persons starting treatment. *HIV Medicine* 2020;21:599-606.

14. D'Arminio Monforte A, Cozzi-Lepri A, Di Biagio A, et al. Durability of first-line regimens including integrase strand transfer inhibitors (INSTIs): data from a real-life setting. *J Antimicrob Chemother* 2019;74:1363-7.

15. Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JV, Berger DS, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve

patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009;374:796-806.

16. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013;369:1807-18.

17. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naïve adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet* 2014;383:2222-31.

18. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* 2015;385:2606-15.

19. Squires K, Kityo C, Hodder S, Johnson M, Voronin E, Hagins D, et al. Integrase inhibitor versus protease inhibitor based regimen for HIV-1 infected women (WAVES): a randomised, controlled, double-blind, phase 3 study. *Lancet HIV* 2016;3:e410-20.

20. Di Biagio A, Cozzi-Lepri A, Prinapori R, Angarano G, Gori A, Quirino T, et al. Discontinuation of Initial Antiretroviral Therapy in Clinical Practice: Moving Toward Individualized Therapy. *J Acquir Immune Defic Syndr* 2016;71:263-71.

21. Cattaneo D, Minisci D, Baldelli S, Mazzali C, Giacomelli A, Milazzo L, et al. Effect of Cobicistat on Tenofovir Disoproxil Fumarate (TDF): What Is True for TAF May Also Be True for TDF. *J Acquir Immune Defic Syndr* 2018;77:86-92.

22. Davy-Mendez T, Eron JJ, Zakharova O, Wohl DA, Napravnik S. Increased Persistence of Initial Treatment for HIV Infection With Modern Antiretroviral Therapy. *J Acquir Immune Defic Syndr* 2017;76:111-15.

23. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at <https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf>. [Accessed 12 October 2020].

**Figure 1.** Cumulative probability of treatment failure in the overall population by study group.

Abbreviations: RPV, rilpivirine; INSTI, integrase strand transfer inhibitor

**Figure 2.** Cumulative probability of treatment failure among RPV-based and DTG-based regimens (panel A), and comparison between RPV-based and the whole INSTI class but restricting to only patients who started ART with a single tablet regimen (panel B).

Abbreviations: RPV, rilpivirine; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor

**Supplementary Figure 1.** Cumulative probability of treatment failure among RPV-based and EVG-based regimens.

Abbreviations: RPV, rilpivirine; EVG, elvitegravir