Predictors for choosing a doravirine-based versus an INSTI-based regimen in ART-naïve and ART-experienced people with HIV in real-world setting: data from the Icona Cohort.

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ABSTRACT

Rationale

Doravirine (DOR) is an attractive new option both for people with HIV (PWH) ART-naive and for those who seek treatment simplification with suppressed HIV-RNA. We used real-world data to examine pattern of use of DOR-containing regimens in these settings.

Methods

All PWH enrolled in the ICONA cohort after January 2020 who initiated a 3-drug regimen (3-DR) with DOR or an INSTI-based as first ART or as switching ART, while HIV-RNA ≤50 copies/ml were included. We used univariable and multivariable logistic regression models to identify demographic factors, immuno-virological and laboratory markers associated with the prescription of 3-DR DOR instead of INSTI-based regimens.

Results

A total of 5,803 PWH were included; 1,958 were in the first regimen (80 DOR, 1,878 INSTI) and 3,854 (387 DOR, 3,458 INSTI) were virologically suppressed ART-experienced. In the first line, 3-DR DOR was more frequently started in PWID, and its use was also associated with higher BMI, higher LDL levels, and less advanced HIV disease compared to PWH initiating an INSTI-based regimen. In the switch setting, older age, Italian origin, higher eGFR and AST levels were all strongly associated with 3-DR DOR use, as well as higher a CD4/CD8 ratio (only compared to 3-DR INSTI), while the association with lipid abnormalities was attenuated.

Conclusions

Our analysis shows that among PWH in care in Italy, those with less advanced HIV disease but with other fragilities and potential risk factors for comorbidities are more likely to use DOR- instead of INSTI-based regimens, regardless of prior treatment history.

INTRODUCTION

Doravirine (DOR) is a new-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) currently available in two formulations: a single-tablet regimen (STR) in fixed-dose combination with lamivudine and tenofovir disoproxil fumarate (DOR/3TC/TDF), or a single drug.

Randomized clinical trials have demonstrated the efficacy and tolerability of DOR-containing regimen, both as first-line,[1–3] and as switching regimen in virologically suppressed (HIV-RNA< 50 copies/mL) people with HIV (PWH) on stable antiretroviral treatment (ART) and as compared to boosted-protease inhibitors or NNRTI or elvitegravir/cobicistat triple regimen.[4]

Based on these findings, the drug was approved both as a first-line therapy for ART-naïve and as a switch strategy for virologically suppressed PWH.[5,6]

However, trials directly comparing DOR to integrase inhibitor (INSTI)-containing regimens are still ongoing.[7,8] Real-world data of DOR are limited to few studies with small sample size and follow-up and the comparison using real-world data with INSTI is also lacking, mainly because of the recent introduction of the compound in clinical practice.[9–11] PWH initiating DOR are likely to be different from those starting INSTI-based regimens and an imbalance in important predictors of outcome may bias these real-life comparisons.

The analysis aimed to investigate the drivers of starting DOR or switching to DOR versus a standard INSTI-based regimen in an Italian setting.

METHODS

This is a retrospective, observational study of prospectively collected electronic medical data from the ICONA Cohort, which includes 61 centers all over Italy. The details of the cohort have been published elsewhere.[12]

We included in the analyses PWH enrolled in ICONA who, after January 2020 (date of availability of DOR in Italy) started a first-line ART with a DOR-including 3-drug regimen (3-DR) or an INSTI-

based regimen (*ART-Naïve*) or switched for the first time from any other regimen either to a 3-DR DOR-based or to an INSTI-based regimen (2-DR or 3-DR), after reaching HIV-RNA below 50 copies/mL *(ART-experienced).* Dual regimens with both DOR+INSTI were excluded from the analysis because they could not be assigned to a single group. We used the March 2024 Icona database update. The baseline was the time of the first ART start for the ART-naïve patients and the time of first switch after January 2020 for the ART-experienced.

The endpoints were: starting a 3-DR DOR-based vs. a 2-DR or 3-DR INSTI-based regimen (from ART-naive), and switching for the first time to 3-DR DOR vs. a 2-DR INSTI-based or vs. a 3-DR INSTI-based regimen in ART-experienced. Chi-square or U-Mann-Whitney tests were used to compare baseline characteristics for ART-naïve and experienced. Standard unadjusted and adjusted logistic regression models were used to identify baseline factors associated with the probability of the outcomes. Factors for which we were interested in studying the association between DOR start/switch were adjusted in the multivariable analysis for age, sex, geographical region and calendar year. Two sensitivity analyses have been done: one for ART-experienced PWH naïve to both INSTI and DOR at January 2020 and the second one including only STR regimens.

RESULTS

A total of 5,803 PWH were included; 1,958 (33.7*%)* were on their first ART regimen, 3,845 (66.3%) switched their ART regimen while HIV-RNA ≤50 copies/mL. Their median age was 46 years (interquartile range, IQR: 36-55), 1,058 (18.2%) were females, most were infected by sexual route, people who inject drugs (PWID) were 376 (6.5%). Complete baseline data according to ART history are shown in Supplemental Table 1.

A total of 1,958 PWH initiated their first ART regimen in the studied period (DOR 80, INSTI 1,878). The prevalence of exposure and the odds ratio of initiating 3-DR DOR as first line from fitting a logistic regression model are summarized in Table 1. After adjustment for sex, age, calendar year of ART initiation and geographical region, females had a marginally statistically higher probability of

initiating DOR-including regimens (adjusted odds ratio, AOR 1.70, 95% confidence interval, CI 0.99-2.93); having acquired HIV via injecting drugs (AOR 3.96, 95%CI 1.96- 8.00 vs. the heterosexual route), BMI >30 kg/m^2 (AOR 3.98, 95%CI 1.39-11.37 vs. BMI 12-25), LDL-cholesterol >100 mg/dL (AOR 2.01, 95% CI: 1.06-3.82 vs. LDL ≤100) were all associated with a higher probability of starting DOR-including regimens.

PWH with more advanced HIV infection, documented by higher HIV-RNA copy levels, had a lower probability of starting ART with DOR-including regimens: HIV-RNA >100,000 copies/ml AOR 0.23 (95%CI 0.12-0.43) vs. HIV-RNA<10,000 copies/ml. Conversely, higher CD4 counts were associated with a higher probability of starting ART with DOR-including regimens: CD4 201-350/mm^3 AOR: 2.83 (95%CI: 1.36-5.90) and CD4>350/mm^3 AOR 3.32 (95%CI 1.74-6.34) vs. CD4 <=200/mm^3 (Table 1).

Over the study period, we observed a total of 387 PWH switching to 3-DR DOR-containing and 3,458 switching to INSTI-containing regimens (2,151 on 2-DR and 1,307 on 3-DR INSTI). Previous ART regimens included NNRTIs in 22.3% of cases, INSTI in 62.9%, multiple/other classes in 4.7% and PIs in 10.1%.

Tables 2-A and 2-B show the association analysis comparing the characteristics of participants switching to 3-DR DOR-containing regimens vs. 2-DR INSTI (n=2,151; Table 2-A) and vs. 3-DR INSTI (n=1,307 Table 2-B). There was some evidence that the adjusted probability of switching to DOR vs. 2-DR INSTI was higher in older PWH (aged 41-55 and >55: AOR 2.00, 95%CI 1.52-2.64 and AOR 1.36, 95%CI 0.98-1.88 vs age 18-40). PWH who switched to DOR were more likely to have triglycerides plasma levels >200 mg/dL (AOR 1.38, 95%CI 1.00-1.91 vs. ≤200 mg/dL) and AST >40 UI/ml vs 2-DR INSTI (AOR: 2.00, 95%CI 1.35-2.94). Overweight individuals (BMI 25-29 Kg/m^2) had a 34% higher chance of switching to 3-DR DOR (AOR 1.34, 95%CI 1.02-1.77 vs BMI 12-25 kg/m^2). In this setting of ART-experienced group PWH with higher CD4 counts were instead less likely to switch to 3-DR DOR compared to 2-DR INSTI (vs. CD4<200 cells/mmc, CD4 201-350 cells/mmc AOR 0.36, 95%CI 0.15-0.85 and >350 CD4/mmc AOR 0.53, 95%CI 0.26-1.07). PWH

with better renal functionality had a higher chance to switch to 3DR-DOR compared to 2DR-INSTI (compared to eGFR <60: eGFR>90 ml/min AOR=7.24, 95%CI 3.22-16.24 and eGFR 60-90 AOR 4.41, 95%CI 1.99-9.74) (Table 2-A). In the sensitivity analysis that included only both INSTI- and DOR-naïve ART-experienced patients, only the age between 41 and 50 years maintained the association with the switch to 3-DR DOR versus 2-DR INSTI, while having undergone more than 4 lines of ART had a lower probability of starting DOR (Supplementary Table S-2A). When comparing PWH who switched to DOR to those who switched to 3-DR INSTI, we observed a similar picture. Namely, there was still a strong association with age (AOR 2.03, 95%CI 1.27-3.25 comparing 41-55 with 18-40 years old) and AST>40 U/L (AOR 1.55, 95%CI 1.02-2-38 vs. ≤40 U/L) with switching to 3-DR DOR. Higher CD4 count (CD4>350 cells/mm^3 AOR 1.76, 85%CI 0.90-3.46) vs. CD4 <200/mm^3) and CD4/CD8 ratio (CD4/CD8≥1: AOR 1.30, 95%CI 1.01-1.67 vs. <1) were associated with 3-DR-DOR start compared to 3-DR INSTI. Interestingly, PWH born outside Italy had a lower probability of switching to 3-DR DOR (AOR 0.65, 95%CI 0.45-0.93 vs 3-DR INSTI). Finally, individuals with ≥4 ART lines were less likely to switch to 3-DR DOR (AOR 0.69, 95%CI 0.51-0.93) (Table 2-B). 3DR-DOR was chosen over 3DR-INSTI for ART-experienced PWH without renal impairment (compared to eGFR <60: eGFR>90 ml/min AOR=5.46, 95%CI 2.33-12.75 and eGFR 60-90 AOR 4.89, 95%CI 2.13-11.24). In the sensitivity analysis of DOR- and INSTI-naïve patients, older age (>55 years old), CD4/CD8 > 1 and ART-lines >4 were associated with a lower probability of starting 3-DR DOR vs. 3-DR INSTI, while PWH with >2 years from HIV diagnosis had a higher probability of starting 3-DR DOR (Table S-2B). We also performed a second sensitivity analysis comparing only DOR- and INSTI- including STRs, showing the same predictors of the main analyses for both ART-naïve and experienced (Supplementary Table S3 and Table S4A-B).

DISCUSSION

Our real-world analysis of PWH seen for care in 61 infectious disease clinics in Italy showed that individuals with less advanced HIV disease but with other vulnerabilities (older age, intravenous

recreational drug use) and metabolic comorbidities (overweight, dyslipidemia) were more likely to receive DOR-based regimens than INSTI-based regimens. In these individuals, HIV infection had been adequately controlled, as they showed lower viral load and higher CD4 counts than PWH using INSTI-based regimens. Indeed, participants who started DOR in our cohort had very high CD4 counts associated with low risk of clinical progression. Randomised studies convincingly show that DOR is effective and has a very safe profile,[1–4] and this may have induced clinicians to use it especially in fragile individuals requiring ART but not severely immune-depressed.

In virologically controlled ART-treated participants, both 2-drug and 3-drug regimens were frequently used as simplification switches. In our analysis, demographic variables, such as age and Italian origin, were key determinants of switching to DOR instead of INSTI-based regimens. Metabolic complications and immunological impairment also appeared to be the reasons for choosing DOR over INSTI, although these associations were less supported by the data.

Our analysis is important as it shows that there are several predictors of treatment response that are imbalanced in participants using DOR- vs. INSTI-based regimens and is useful to guide future real-world data analyses comparing treatment response.

A recent French observational study including 50 PWH switching to DOR while virologically controlled demonstrated the safety and efficacy of the drug in a 48-week follow-up, while a large study from the ATHENA cohort confirmed the non-inferiority at 2-year of switching to DOR vs continuing the regimen in virologically suppressed PWH [13,14] Indeed, our data demonstrate that these studies that have shown that DOR is effective, very well tolerated and associated with a reduction of lipid abnormalities and of weight gain had an impact on real-world prescription patterns.[3,15] This is also consistent with the European HIV treatment guidelines (EACS), recommending the use of NNRTI class drugs such as DOR for patients with metabolic distress to prevent cardiovascular diseases.[5] It should be emphasized that there are no restrictions in the international guidelines or in the product's registration characteristics regarding baseline HIV-RNA and CD4 cell counts for the use of DOR as first-line. Therefore, our results of a preferential use in

less advanced individuals could be justified, beyond a perceived lower virological potency not supported by now by randomized or any emulated clinical trials, to the need to perform the genotypic resistance test before starting DOR, which cannot be executed rapidly in all Italian centers. Overall, a small proportion of individuals have used DOR-including regimens in both naïve and virologically suppressed PWH. Possible reasons might be the absence of RCT or real-world emulated trials comparing DOR- to second-generation INSTI-based regimens in ART-naïves and the lack of availability of DOR in STR with tenofovir alafenamide (TAF).[16] It is indeed well known the benefit of TDF on lipids that is combined with the favourable lipid profile of DOR in the available STR, resulting in a preferable choice of this regimen in PWH with lipid abnormalities, particularly LDL-cholesterol.[4,10,17,18] The attenuated association between DOR use and elevated lipids in pre-treated PWH might be explained by the use of antihyperlipidemic not collected in this study.

The TDF-associated renal toxicity may have indeed triggered a conservative switch to INSTI over DOR in ART-experienced PWH with evidence of kidney impairment.[19] Although only <10% of DOR is eliminated through renal pathways thus, the impact on renal biomarkers should be minimal and, indeed, real-life findings showed a reduction in serum creatinine while on DOR.[18,20]

Our study has several limitations: first, determinants of 2DR DOR-based regimen use could not be evaluated because in most cases DOR is associated with INSTI; 2DR with DOR combined with INSTI and recently also with 3TC have shown in observational cohorts promising findings on efficacy, tolerability and durability.[13,21] Second, we cannot exclude the possibility that some of the associations could be still affected by confounding bias; third, missing data for some of the investigated variables may have also introduced selection bias; fourth, Icona does not collect detailed information on the reasons for initiating a new regimen, on the historical genotype for evaluating NNRTI or INSTI resistance, and on patient’s adherence, which could provide important insights into the clinician's reasons for choosing DOR. Finally, our study aimed to evaluate the drivers of initiating or switching to DOR-based regimen, but the virological and treatment outcomes of the clinicians' decision were not analysed because of low statistical power. However, the current results indicate

that such a comparison will be feasible, as a larger number of PWH using DOR cumulates, to provide a more complete assessment of the role of DOR-based regimens in the current treatment management of PWH.

The main strengths of our analysis are the large number of participants using a relatively new treatment strategy, representing one of the largest published cohorts of PWH treated with DOR-based regimen and the broad inclusion criteria reflecting the real-life clinical picture of PWH seen for care in Italy.

In conclusion, in first-line ART DOR- are preferred to INSTI-based regimens in individuals with less advanced HIV disease but with other frailties such as those using injectable drugs, obesity, and dyslipidaemia. In contrast, older age and longer duration of HIV infection, more than individuals' immunological and lipid profile, appeared to be the key determinants of use of DOR- instead of INSTI-based regimens in the suppressed switching setting.

While awaiting the results of randomized comparisons of the response to DOR, our data show that comparisons using real-world data are feasible and should be warranted.

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DATA AVAILABILITY

The datasets generated during the current study are not publicly available because they contain sensitive data to be treated under data protection laws and regulations. Appropriate agreement of data sharing can be arranged after a reasonable request to the corresponding author.

CONTRIBUTIONS

Conception: ADM, AT, AS, AA, ACL; Study Design: ADM, AT, MP, FB, AS, ACL; Accessing and verifying data: AT, ACL; Statistical Analysis: ACL; Acquisition of data: EQ-R, MFabbiani, MFerrara; Patients' enrolment: EQ-R, MFabbiani, SLC, NS, SR; Draft of the manuscript: ADM, AT, ACL; Review of the article and critical revision for important intellectual content: all the Authors; Reading and final approval of the submitted version: all Authors.

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