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Prevalence of predicted resistance to doravirine in HIV-1-positive patients after exposure to non-nucleoside reverse transcriptase inhibitors ☆

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ABSTRACT

This study investigated the prevalence of doravirine (DOR) resistance mutations in non-nucleoside reverse transcriptase inhibitor (NNRTI)-experienced patients. DOR resistance was assessed in samples from NNRTI-experienced patients who underwent genotypic testing for virological failure from the Antiretroviral Response Cohort Analysis (ARCA) database. Intermediate DOR resistance was defined as detection of any of V106A/M, Y188C/H, V108I, and K103N+P225H. High-level DOR resistance was defined as detection of any of Y188L, M230L, G190E, V106A/M+F227L, and V106A/M+L234I. Overall, 6893 patients were included in the study: 64.2% had experienced efavirenz (EFV), 54.4% nevirapine (NVP), 6.8% etravirine (ETR), 7.7% rilpivirine (RPV) and 0.7% delavirdine. Among NNRTI-experienced patients, 12.7% and 6.1% of subjects had intermediate and high-level DOR resistance, respectively. The most common DOR resistance mutation was Y188L. In multivariable analysis, previous EFV use (OR = 1.52, 95% CI 1.15–2.02) and ETR use (OR = 1.91, 95% CI 1.34–2.73) were associated with detection of high-level DOR resistance, whilst RPV use was associated with a lower probability of high-level DOR resistance (OR = 0.39, 95% CI 0.22–0.71). Moreover, EFV use (OR = 1.76, 95% CI 1.19–2.58) and ETR use (OR = 1.72, 95% CI 1.10–2.68) were associated with detection of the Y188L mutation, whereas RPV use was not (OR = 0.16, 95% CI 0.05–0.50). In Italy, DOR resistance is uncommon among NNRTI-experienced patients, confirming a distinguishing resistance pattern within NNRTIs. However, previous EFV and ETR experience poses a higher risk of DOR resistance. These results support the use of DOR in NNRTI-experienced patients.

1. Introduction

Antiretroviral therapy (ART) has consistently improved over time in terms of efficacy, safety and tolerability. In the most recent update to the human immunodeficiency virus (HIV) treatment guidelines by the US Department of Health and Human Services [1], the non-nucleoside reverse transcriptase inhibitors (NNRTIs)

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efavirenz (EFV) and rilpivirine (RPV) are no longer recommended as preferred first-line regimens and are recommended only in certain clinical situations, mainly due to their side effects [2–4] and low genetic barrier to resistance [5,6]. As a matter of fact, K103N and Y181C are the top two most prevalent NNRTI-associated mutations in NNRTI-experienced patients [7], greatly impairing the activity of most, if not all, NNRTIs. Thus, desirable characteristics for a new NNRTI to be used in NNRTI-experienced subjects should include fewer toxic effects and drug–drug interactions, better tolerability, a higher genetic barrier to resistance and lack of cross-resistance within the class.

Doravirine (DOR) is an investigational NNRTI recently approved by the US Food and Drug Administration (FDA) with once-daily dosing. DOR shows similar potency against different HIV subtypes [8] and has a distinct resistance profile [9]. The safety profile of DOR was assessed in two large phase 3 trials in treatment-naïve HIV-1-infected patients and DOR was generally well tolerated, showing a better neuropsychiatric safety profile than EFV and a better lipid profile than ritonavir-boosted darunavir [10,11].

In cell culture, DOR showed excellent activity against wild-type HIV-1 and the most prevalent NNRTI-associated resistant mutants, with the exception of Y188L [9]. In addition, in vitro studies suggest that mutant viruses selected by DOR, mostly involving substitutions at codon 106, 227 and 234, may remain susceptible to EFV and/or RPV, and conversely that mutants selected by EFV or RPV may remain susceptible to DOR [9,12].

Early clinical assessment suggests that DOR has the potential to fulfil a significant and growing medical need by providing a next-generation NNRTI for the treatment of HIV-1 infection. In fact, in a phase 2b clinical trial, DOR 100 mg once daily demonstrated high efficacy and a safer neuropsychiatric profile compared with EFV 600 mg once daily [13]. In a phase 3 trial, the emergence of NNRTI resistance at virological failure of DOR therapy was observed only in 6 patients (1.6%), which was one-half of the cases compared with the comparator EFV arm [10]. In agreement with in vitro resistance selection studies [10], mutations occurred at codons 106, 188, 221, 225, 227 and 318. Moreover, DOR was non-inferior to darunavir in a 48-week phase 3 trial of treatment-naïve patients, showing a more favourable effect on lipids and no emergent resistance in the seven patients with protocol-defined virological failure who underwent resistance testing [11]. Among 40 patients who discontinued treatment early with detectable virus, only one non-adherent participant developed DOR resistance [11].

There has been limited investigation of the prevalence of mutations associated with resistance to DOR both in NNRTI-naïve and -experienced patients. Thus, the aim of this study was to assess the prevalence and factors associated with mutations that have been linked to genotypic resistance to DOR in the HIV-1-positive Italian population before and after treatment with NNRTIs using a large national resistance database.

2. Methods

This study was a cross-sectional analysis of resistance mutations from the Antiviral Response Cohort Analysis (ARCA) database [14] including patients treated with any NNRTI-containing regimen since 1999 and who underwent genotypic resistance tests (GRTs) before and after NNRTI treatment.

ARCA has been approved by the Southeast Tuscany Ethics Committee, and all patients included in ARCA provided written informed consent to use their data for research purposes.

To assess DOR resistance, all NNRTI mutations detected in the patients' history after the first NNRTI use were considered. Sequences analysed were all RNA sequences. Therefore, from the ARCA database, all patients with at least one GRT performed after virological failure (defined as two consecutive HIV-RNA >50 copies/mL or one HIV-RNA >1000 copies/mL) and with a pre-GRT history of NNRTI use were selected. When more than one post-NNRTI treatment GRT was available, the cumulative GRT was considered. The prevalence of DOR resistance was analysed separately in NNRTI-naïve (patients treated with a NNRTI but before NNRTI use) and in NNRTI-experienced patients (after NNRTI use).

The definition of resistance to DOR was based on previous DOR resistance studies, and the Stanford University HIV Resistance Database algorithm (HIVdb algorithm) was also checked [15]. High-level DOR resistance was defined in the presence of the following mutations or mutation patterns: (i) Y188L [8,12]; (ii) M230L [12,16]; (iii) G190E [17]; (iv) association of V106A or V106M with F227L [17]; and (v) association of V106A or V106M with L234I [12]. Moreover, intermediate resistance to DOR was defined in the presence of one of the following mutations or mutation patterns: (i) V106A or V106M [12]; (ii) V108I [8]; (iii) Y188C or Y188H [15]; and (iv) association of K103N and P225H [8].

The correlation with demographic, clinical and laboratory data as well as with the type of NNRTI used was assessed by multivariable logistic regression in NNRTI-experienced patients. Logistic regression was performed separately for intermediate and high-level DOR resistance as dependent variables using IBM SPSS Statistics v.23.0 (IBM Corp., Armonk, NY).

Table 1
General characteristics of patients ($n = 6893$) included in the study.

Characteristic	n (%)[a]
Male sex	4606 (66.8)
Age at GRT test (years) [median (IQR)]	38 (33–43)
Mode of HIV transmission	
Heterosexual/MSM	3569 (51.8)
IVDU	2179 (31.6)
Other/unknown	1145 (16.6)
HCV infection	2302 (33.4)
CD4$^+$ T-cell nadir [median (IQR)]	154 (53–264)
Non-B HIV subtype	837 (12.1)
No. of ART regimens [median (IQR)]	7 (4–11)
Months of NNRTI treatment [median (IQR)]	32 (12–85)
NNRTI use	
Delavirdine	47 (0.7)
Efavirenz	4424 (64.2)
Nevirapine	3750 (54.4)
Etravirine	469 (6.8)
Rilpivirine	528 (7.7)

GRT, genotypic resistance test; IQR, interquartile range; HIV. human immunodeficiency virus; MSM, men who have sex with men; IVDU, intravenous drug user; HCV, hepatitis C virus; ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor.

[a] Data are n (%) unless otherwise stated.

3. Results

3.1. Patients

Overall, 6893 patients were included in the study (Table 1). Of note, all patients had a history of NNRTI treatment and underwent resistance testing after treatment failure, of whom 3850 (55.9%) were tested for NNRTI failure; moreover, 2192 patients (31.8%) were treated with more than one NNRTI. The most commonly used NNRTIs were EFV and nevirapine (NVP), whilst the number of patients with GRT after the use of etravirine (ETR) or RPV was lower. A total of 47 patients who had been treated with the NNRTI delavirdine, which was available in Italy for a short time at the end of 1990s, were also included. Moreover, 12.1% of viruses harboured non-B HIV subtype.

Table 2a
Prevalence of intermediate resistance to doravirine in non-nucleoside reverse transcriptase inhibitor (NNRTI)-experienced patients ($n = 6893$) before and after NNRTI-containing treatment

	Prevalence [n (%)]	
	Before NNRTI treatment	After NNRTI treatment
Overall	21 (0.3)	878 (12.7)
Single patterns[a]		
V106A/M	3 (0.04)	194 (2.8)
V108I	17 (0.2)	519 (7.5)
Y188C/H	1 (0.01)	62 (0.9)
K103N+P225H	1 (0.01)	164 (2.4)

[a] 1 patient before NNRTI treatment and 61 patients after NNRTI treatment had more than one intermediate resistance pattern.

Table 2b
Prevalence of high-level doravirine resistance in NNRTI-experienced patients ($n = 6893$) before and after NNRTI-including treatment

	Prevalence [n (%)]	
	Before NNRTI treatment	After NNRTI treatment
Overall	8 (0.12)	421 (6.1)
Single patterns[a]		
Y188L	1 (0.01)	250 (3.6)
M230L	3 (0.04)	68 (1.0)
G190E	3 (0.04)	36 (0.5)
V106A/M+F227L	2 (0.03)	74 (1.1)
V106A/M+L234I	0 (0.0)	0 (0.0)

[a] 1 patient before NNRTI treatment and 15 patients after NNRTI treatment had more than one full resistance pattern.

Table 3
Adjusted logistic regression for association with high-level doravirine resistance in non-nucleoside reverse transcriptase inhibitor (NNRTI)-experienced patients

Variable	OR	95% CI	*P*-value
Male sex	1.12	0.97–1.28	0.117
Age (each year)	1.00	0.99–1.01	0.445
IVDU (vs. other)	0.80	0.61–1.05	0.109
HCV infection	0.95	0.73–1.23	0.681
No. of ART regimens (each)	**1.02**	**1.00–1.04**	**0.049**
CD4$^+$ T-cell nadir <200/mm^3	**1.48**	**1.21–1.62**	**<0.001**
Overall time on NNRTI (months)	**0.99**	**0.98–1.00**	**0.019**
Non-B HIV subtype	0.77	0.53–1.12	0.169
Delavirdine use	1.09	0.38–3.14	0.877
Efavirenz use	**1.52**	**1.15–2.02**	**0.004**
Nevirapine use	1.07	0.83–1.40	0.595
Etravirine use	**1.91**	**1.34–2.73**	**<0.001**
Rilpivirine use	**0.39**	**0.22–0.71**	**0.002**

OR, odds ratio; CI, confidence interval; IVDU, intravenous drug user; HCV, hepatitis C virus; ART, antiretroviral therapy; HIV, human immunodeficiency virus.

Table 4
Adjusted logistic regression for association with detection of Y188L mutation in non-nucleoside reverse transcriptase inhibitor (NNRTI)-experienced patients

Variable	OR	95% CI	*P*-value
Male sex	**1.24**	**1.08–1.43**	**0.003**
Age (each year)	0.99	0.98–1.01	0.192
IVDU (vs. other)	**0.60**	**0.42–0.88**	**0.004**
HCV infection	1.27	0.92–1.76	0.149
No. of ART regimens (each)	**1.05**	**1.02–1.07**	**<0.001**
CD4$^+$ T-cell nadir <200/mm^3	**1.59**	**1.22–2.07**	**0.001**
Overall time on NNRTI (months)	0.99	0.98–1.00	0.052
Non-B HIV subtype	0.65	0.39–1.09	0.104
Delavirdine use	1.18	0.49–4.28	0.498
Efavirenz use	**1.76**	**1.19–2.58**	**0.004**
Nevirapine use	0.82	0.58–1.14	0.237
Etravirine use	**1.72**	**1.10–2.68**	**0.017**
Rilpivirine use	**0.16**	**0.05–0.50**	**0.002**

OR, odds ratio; CI, confidence interval; IVDU, intravenous drug user; HCV, hepatitis C virus; ART, antiretroviral therapy; HIV, human immunodeficiency virus.

The prevalence of intermediate and high-level DOR resistance before and after any NNRTI-including treatment is reported in Tables 2a and 2b.

In naïve patients, before any NNRTI treatment, detection of any DOR resistance was uncommon (0.3% and 0.09% for intermediate and high-level resistance, respectively). In contrast, among NNRTI-experienced patients, 6.1% of patients harboured high-level DOR resistance and 12.7% harboured intermediate resistance, suggesting low cross-resistance with other NNRTIs. High-level resistance was mainly due to Y188L, whilst other DOR resistance mutations such as M230L, G190E or V106A/M-related patterns were less common. In NNRTI-experienced patients, high-level DOR resistance was less frequent in non-B HIV subtypes versus B subtype (4.3% vs. 6.3%); among the non-B HIV subtypes, C subtype accounted for the highest frequency (9 DOR-resistant of 66 patients with subtype C; 13.6%). Regarding the single mutation Y188L, this was found significantly less frequently in the whole group of non-B subtypes (2.2% vs. 3.7% in B subtype; $P < 0.05$), whereas it was higher in viruses with C subtype (9.1%; $P < 0.05$ vs. B subtype).

In the multivariable logistic regression in NNRTI-experienced patients, previous EFV and ETR use were associated with the detection of high-level DOR resistance (Table 3).

By contrast, RPV use was associated with a significantly lower probability of high-level DOR resistance when adjusted for other NNRTIs used. Among the other variables considered, a higher number of previous ART regimens and a lower CD4$^+$ T-cell nadir were associated with a higher risk of high-level DOR resistance, whilst a longer time on NNRTI was associated with a lower risk of high-level resistance.

Since the Y188L mutation was the most frequent NNRTI mutation associated with high-level DOR resistance, a sensitivity analysis on Y188L was performed (Table 4). The results were similar, since previous EFV and ETR use were associated with the detection of Y188L mutation, whilst RPV use was associated with a lower probability. Moreover, male sex, lower CD4$^+$ T-cell nadir and higher number of previous ART treatments were also associated with increased risk of 188L mutation, whilst being an intravenous drug user (IVDU) was associated with a lower risk of detecting Y188L. HIV subtype was not associated with DOR resistance in any model.

4. Discussion

Information about the selection of drug resistance mutations affecting the efficacy of DOR in patients experienced to NNRTIs in the clinical setting is currently lacking. NNRTIs in use are significantly cross-resistant to one another and, indeed, second-line NNRTI therapy following NNRTI failure has been challenging, apart from ETR. As DOR has a different resistance pattern with respect to older NNRTIs, we investigated whether previous NNRTI use could impair the activity of DOR.

Overall, DOR resistance was uncommon in NNRTI-naïve patients. This is not surprising because the resistance profile of DOR is not affected by the mutations most commonly detected as a result of transmitted NNRTI resistance (i.e. K103N and Y181C) [18]. On the other hand, although the case file included heavily pretreated patients, as shown by a median number of seven previous ART regimens, only 6.1% of patients harboured high-level DOR resistance, mainly due to Y188L. Although Y188L is included among the mutations conferring high-level resistance to EFV and NVP, its occurrence is significantly less common than the widespread

K103N and Y181C mutations likely because two base changes are required to generate the Y188L mutant [19,20]. Nevertheless, previous EFV and ETR failure still poses a higher risk of detection of Y188L mutation and therefore of DOR resistance; conversely, having used RPV is associated with a significantly lower risk of resistance compared with other NNRTIs because in the case of failure, mutations emerge that are not associated with resistance to DOR.

It is not even surprising that a higher risk of DOR resistance was associated with a higher number of ART regimens and a lower $CD4^+$ T-cell nadir, which are characteristics of patients who have longer history of HIV infection.

Furthermore, the results show that a longer time on NNRTI is associated with a lower risk of high-level DOR resistance. A possible explanation is that resistance to NNRTIs occurs early in the case of failure, therefore a longer time on NNRTI may mean more adherence and consequently less probability to develop NNRTI resistance [21]. Indeed, IVDUs were less likely to develop a Y188L mutation. This mutation is associated with EFV use and high pharmacological pressure, so IVDUs, who are generally less adherent to ART, could less likely develop the Y188L mutation [22].

Finally, HIV subtype did not appear to influence the onset of DOR resistance. Small but significant differences were found for Y188L (more frequent in C subtype, less frequent in the other non-B subtypes), V106M (more frequent in C subtype) and V106A (overall less frequent in non-B subtypes). However, due to the general small number of DOR resistance found, the results should be confirmed by specific studies with a larger number of patients with non-B subtypes.

Hence, DOR is expected to be a valuable option for treating both drug-naïve and NNRTI-experienced patients.

Limitations of this study include a low representation of patients treated with ETR and RPV and the fact that DOR resistance was defined based on in vitro studies [9,12] in the absence of a reference mutation list derived from clinical studies [10]. The full potential of DOR use after NNRTI experience should thus be reappraised along with a definition of its resistance profile in vivo.

5. Conclusions

In conclusion, in Italy DOR resistance is nearly absent in patients never treated with NNRTIs. DOR resistance is also uncommon in NNRTI-experienced patients, confirming a distinguishing resistance pattern within NNRTIs. DOR resistance is mainly related to detection of the Y188L mutation, generally uncommon after NNRTI failure, so that previous EFV and ETR use was found to be associated with a higher risk of DOR resistance, whilst previous RPV use was found associated with a significantly lower risk of DOR resistance. These results support potential large DOR use even in NNRTI-experienced patients as the prevalence of mutations conferring resistance to DOR remains low in patients presenting mutations against the NNRTIs currently in use. However, the role of DOR in vivo must be confirmed by clinical observations, as patients harbouring NNRTI-resistant viruses have been excluded from completed clinical trials to date.

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Competing Interests

GS has received funds for speaking at symposia and advisory boards organised on behalf of Gilead Sciences, Merck Sharp & Dohme, Janssen-Cilag, AbbVie and ViiV Healthcare; FM has served as a consultant on advisory boards for AbbVie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline and Tibotec, has received lecture fees from Bristol-Myers Squibb, Gilead, GlaxoSmithKline and Merck Sharp & Dohme, and has received research and educational grants from AbbVie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline and Jansen-Cilag; MA has received funds for speaking at symposia organised on behalf of Gilead Sciences, Merck, Janssen-Cilag, AbbVie and ViiV Healthcare and a research institutional grant from Merck Sharp & Dohme; AA has received personal fees for consultancy from Bristol-Myers Squibb, Gilead Sciences, ViiV Healthcare, Janssen-Cilag, Merck Sharp & Dohme and AbbVie and research institutional grants from Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag and ViiV Healthcare; MZaz has received grants from ViiV Healthcare and Gilead Sciences and personal fees from ViiV Healthcare, Janssen-Cilag and Gilead Sciences; MZac has received grants for speaking at symposia and advisory boards from AbbVie, Gilead Sciences, Merck Sharp & Dohme, ViiV Healthcare and Janssen Cilag. All other authors declare no competing interests.

Ethical Approval

This research was conducted in accordance with the Declaration of Helsinki as well as national and institutional standards. ARCA has been approved by the Southeast Tuscany Ethics Committee on 21 July 2014, and all patients included in ARCA provided written informed consent for use of their data for research purposes.

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