Use of doravirine-based regimens in clinical practice in Europe

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Objectives: We evaluated antiviral effectiveness and safety of doravirine (DOR)-based regimens in people with HIV (PWH) in routine clinical practice.

Design: A retrospective, noninterventional study across 16 sites in five European countries [United Kingdom (UK), France, Spain, Belgium, Netherlands].

Methods: The study was conducted in both treatment-experienced and treatment-naive PWH who either switched to, or initiated DOR-containing antiretroviral therapy (ART). The primary endpoints were virological success (defined as the percentage of participants with HIV RNA <50 copies/ml, using FDA Snapshot method) and virological failure (FDA Snapshot, HIV RNA ≥50 copies/ml) at 48 weeks after initiation of DOR regimen.

Results: Between August 2017 and February 2022, 394 participants were enrolled, 63 naive and 331 treatment-experienced. 75.4% were men, with a median age of 45 years, and 92.2% received DOR in combination with tenofovir disoproxil fumarate and lamivudine or emtricitabine. The proportion of participants with virological success at week 48 after initiation of DOR regimen was 90.6% [95% confidence interval (CI) 87.3–93.3] overall, 87.3% (95% CI 76.5–94.4) in the ART-naive group, and 91.2% (95% CI 87.7–94.1) in the switch group. The proportion of participants with virological failure was 3.3% (95% CI 1.8–5.6) overall, 1.6% (95% CI 0–8.5) in the ART-naive group and 3.6% (95% CI 1.9–6.2) in the switch group. Of the 394 included participants, two (0.5%) were lost to follow-up and 13 (3.3%) discontinued the DOR regimen, four (1%) due to adverse events.

Conclusion: Our results show high levels of efficacy and low levels of side effects in DOR-containing regimens in both treatment-naive and treatment-experienced PWH.

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Introduction

The introduction of antiretroviral therapy (ART) has resulted in highly effective treatment for HIV and a normal life expectancy for treated people with HIV (PWH) [1]. Due to the need for lifelong therapy, focus has shifted to regimens that are convenient and well tolerated [1].

Doravirine (DOR) is a novel nonnucleoside reverse transcriptase inhibitor (NNRTI) with in-vitro activity against both wildtype HIV type 1 (HIV-1) and most common NNRTI-resistant variants (including K103N, Y181C, and G190A) at concentrations achieved with 100 mg once-daily dose [2]. DOR has a unique in-vitro resistance profile among NNRTIs, with lower inhibitory concentration values against NNRTI-resistant variants than other NNRTIs [3–7]. DOR was granted European marketing authorization in November 2018 [8]. DOR, in combination with nucleos(t)ide reverse transcriptase inhibitors (NRTIs), is indicated as a regimen for HIV-1 infection in adults who initiate ART or are virologically suppressed (HIV-1 RNA less than 50 copies/ml) on a stable antiretroviral regimen without present or past evidence of resistance to NNRTIs [9].

Two large phase 3, randomized, controlled, multicentre, double-blind, noninferiority trials studied DOR associated with two NRTIs in comparison with boosted darunavir (DRIVE-FORWARD) or efavirenz (DRIVE-AHEAD) with two NRTIs in naive ART PWH [10–15]. Both trials showed noninferiority of DOR-based regimen compared to darunavir-based or efavirenz-based regimen at 96 weeks on achieving HIV viral load of less than 50 copies/ml, and no major safety concerns were observed. Long-term follow-up up to 192 weeks of these participants confirmed the low rate of virological failure and the good safety profile [12]. DRIVE-SHIFT, a phase 3, randomized, open-label trial, studied switching from a stable antiretroviral regimen to DOR in association with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), and concluded that DOR/3TC/TDF is a well tolerated and efficient regimen for maintaining viral suppression at week 144 after ART switch [16,17]. The gathering of evidence from routine clinical practice from PWH who start or switch to a DOR-containing regimen would further demonstrate the value of this regimen.

We conducted a retrospective cohort study to evaluate the clinical effectiveness, discontinuation, and resistance among PWH receiving DOR in routine clinical practice in five European countries.

Methods

Study design and setting

A retrospective, noninterventional study [DoRavirine Europe real World (DREW)] was conducted among both treatment-experienced and treatment-naive PWH who either switched to, or initiated DOR-containing ART. This multicentre study was conducted across 16 sites in five European countries [United Kingdom (UK), France, Spain, Belgium, and the Netherlands] through collaboration with the NEAT ID Network, a well established network of clinical sites across Europe [18]. Electronic data were collected from these NEAT investigational sites where commercial DOR has been available for at least 12 months and where resistance testing is undertaken routinely as part of standard of care.

Regulatory and/or ethics approvals were obtained as per territory specific requirements for a noninterventional retrospective study, and the study was conducted in accordance with the Declaration of Helsinki.

Participants

Adults ($\geq$18 years) with HIV-1 who received at least one dose of DOR (without initial dose adjustment) were included in the study if they met the following criteria: had been started or switched to DOR for at least 12 months at time of data collection; had a resistance genotype available before starting DOR; had no evidence of DOR-associated resistance mutation at baseline, but other NNRTI-associated resistance mutations were allowed (based on the Stanford algorithm); and were on DOR-containing ART regimen that also contained two fully active nucleos(t)ides and individual had no documented NRTI resistance mutations to the two NRTIs in the combination. Individuals were excluded if DOR was part of their fifth line or higher therapy; they had prior virological failure with agents of the NNRTI class (but other types of virological failure were allowed), no documented resistance testing, and/or no genotype available at DOR initiation; and/or they were enrolled in DOR clinical trials.

Participants were categorized into the following subgroups:

1. ART-naive group – individuals who, at the time of DOR initiation, were HIV treatment-naive.
2. Switch group – individuals who, at the time of DOR initiation, were virologically suppressed (HIV RNA $<$50 copies/ml) for at least 6 months with no evidence of prior virological failure with agents of the NNRTI class.

Data collection

Delegated site staff identified eligible PWH by reviewing patient records. A detailed electronic data collection form was used to collect comprehensive data from clinical sites by appropriately trained and authorized member(s) of the study team. Demographic (e.g. age, sex, ethnicity), clinical (e.g. comorbidities, treatment history, time since diagnosis), virological (e.g. HIV viral load), and immunological (e.g. $CD4^+/CD8^+$ cell count) variables were collected

from the time of the DOR regimen initiation visit (or the most recent data prior to the start of DOR). Data on HIV viral load, $CD4^+/CD8^+$ cell counts, resistance test results, laboratory variables [including creatinine, estimated glomerular filtration rate (eGFR), glucose, alanine transaminase (ALT), aspartate aminotransferase, cholesterol, and triglycerides], and clinical variables (including height, weight, concurrent medication, and important medical events) were collected from the DOR initiation visit and all other available hospital visits in the 12-month post-DOR initiation window.

An 8-week window around the date in question was used to select data at each time-point for the aforementioned variables. The last available measurement while the patient was on DOR-based regimen within the time window was also used. There was a +/− 2-month range around the 12-month data collection window, and data were collected. If there were no viral load data in the window, the latest available data beyond week 48 before data collection ended were used as long as the patient remained under the same DOR-based regimen. Any change in backbone without discontinuation of DOR was not considered discontinuation of study treatment.

Data were collected retrospectively with participants requiring at least 12 months of data from the initiation on DOR to be included in the study. The input of data into the electronic data capture system occurred between 10 October 2022 and 3 March 2023.

Outcomes and definitions

The primary endpoints were virological success (defined as the percentage of participants with HIV RNA <50 copies/ml, using FDA Snapshot method) and study-defined virological failure at 48 weeks after initiation of DOR regimen. Study-defined virological failure was characterized as: two consecutive HIV RNA at least 50 copies/ml after reaching HIV RNA less than 50 copies/ml while on DOR, or one HIV RNA at least 50 copies/ml and DOR regimen was discontinued immediately or at next hospital visit after reaching RNA less than 50 copies/ml. Virological failure could occur at or after week 48 only in the ART-naive group, and at any time point after DOR switch in the switch group. The proportion of participants who discontinued DOR regimen at week 48, and reasons for discontinuation were reported. Treatment discontinuation was defined as discontinuation of DOR (due to adverse events or for other reasons), relocation, or loss to follow-up.

Secondary endpoints included the proportion of participants with clinical decision virological failure (defined using threshold of 200 copies/ml commonly used to make treatment-related clinical decisions) at 48 weeks. In this instance, virological failure was defined as: two consecutive HIV RNA at least 200 copies/ml after reaching HIV RNA less than 50 copies/ml; one HIV RNA at least 200 copies/ml and DOR regimen was discontinued immediately or at next hospital visit, after reaching HIV RNA less than 50 copies/ml. Other secondary endpoints included proportion of participants with low-level viremia (defined as an HIV RNA ≥50 and <200 copies/ml at any time point after reaching an HIV RNA <50 copies/ml or HIV RNA level ≥50 and <200 copies/ml at week 48) and changes in laboratory (e.g. immunological, renal, liver, and lipid markers) and clinical (e.g. weight) parameters from baseline to week 48.

Statistical analyses

Statistical analyses were carried out in IBM SPSS Statistics version 28.0 for Windows. Demographics and baseline characteristics and data on baseline resistance mutations were summarized for the overall cohort and separately by patient category (ART-naive and switch groups). Continuous variables were described using medians and interquartile range (IQR). Categorical variables were described using frequencies and proportions.

The proportion of participants with virological success (HIV RNA <50 copies/ml) at 48 weeks after initiation of DOR regimen was estimated using the FDA Snapshot approach. The proportion of participants with HIV RNA at least 50 copies/ml, discontinued DOR due to adverse events, discontinued DOR for other reasons, and on study but missing data in window were also estimated. The two-sided 95% CIs for the proportions were calculated using the exact Clopper–Pearson method. The proportion and 95% CI of participants who discontinued DOR regimen, had confirmed virological failure (HIV RNA ≥200 copies/ml), and low-level viraemia at week 48 were estimated by Kaplan–Meier estimates for the overall cohort and by patient category. Changes in laboratory and clinical parameters from baseline to week 48 were compared within group using Wilcoxon paired test for the overall cohort and separately by patient category. The last observation carried forward approach was used to fill in missing data. For participants who discontinued DOR regimen but continued to be followed in the study, the last available result before discontinuation was used in the analyses.

Univariable and multivariable Cox proportional hazard models were used to identify baseline factors associated with the incidence of HIV RNA at least 50 copies/ml at any time during the study in the switch group and treatment/follow-up discontinuation at week 48 in the overall cohort. Variables with a univariable *P* value less than 0.20 were retained for the multivariable analysis. Multivariable analyses were adjusted for patient category. The nadir $CD4^+$, nadir $CD8^+$, baseline $CD4^+$, and baseline $CD8^+$ were log transformed for the models. We could not analyse factors associated with virological failure and resistance, as the number of events was too small.

Results

Patient demographic and clinical characteristics

Of 399 individuals enrolled, five (1.3%) (1 ART-naive group and 4 switch group) were excluded, as they did not meet the study eligibility criteria due to the presence of mutations to one or both NRTIs in their current cART and/or DOR mutations at baseline, thus 394 were included in the study (63 ART-naive group and 331 switch group) (Fig. 1). The first participant initiated on DOR on 1 August 2017, whereas the last one initiated on 16 February 2022. Baseline characteristics of the participants are presented in Table 1 and in Table S1 in supplementary material, http://links.lww.com/QAD/D476 for baseline characteristics of the participants according to countries. Participants were mostly men ($n = 297$; 75.4%), with median age of 45 (IQR 37–53) years, and 40.9% ($n = 161$) were White European. Median time since HIV diagnosis was 8.1 (IQR 2.7–13.9) years. Almost 5% ($n = 18$; 4.6%) of participants had a history of previous virological failure. TDF/3TC/DOR was the most common DOR-containing regimen taken by 84.3% ($n = 332$) of participants, and 92.2% of participants overall were on a TDF/XTC-based regimen (i.e. TDF with lamivudine or emtricitabine). Participants had a median of one (IQR 1–1) genotypic resistance test documented prior to baseline, with 30 (7.6%) participants having a history of NRTI and/or NNRTI resistance mutations including 16 participants with NNRTI resistance mutations not conferring resistance to DOR (i.e. K103N in 6, E138 in 10), all but one in the switch group (see Table S2 in supplementary material, http://links.lww.com/QAD/D475 for details of specific resistance mutations). These mutations were primary RAMS (IAS 2022).

For participants in the switch group ($n = 331$), the median duration on their previous ART was 7.3 (IQR 3.9–10.9) years. The last ART before switching to DOR included: 42.3% ($n = 140$) NNRTI; 40.8% ($n = 135$) integrase strand transfer inhibitor (INSTI), and 17.2% ($n = 57$) boosted protease inhibitor. Also, most patients in

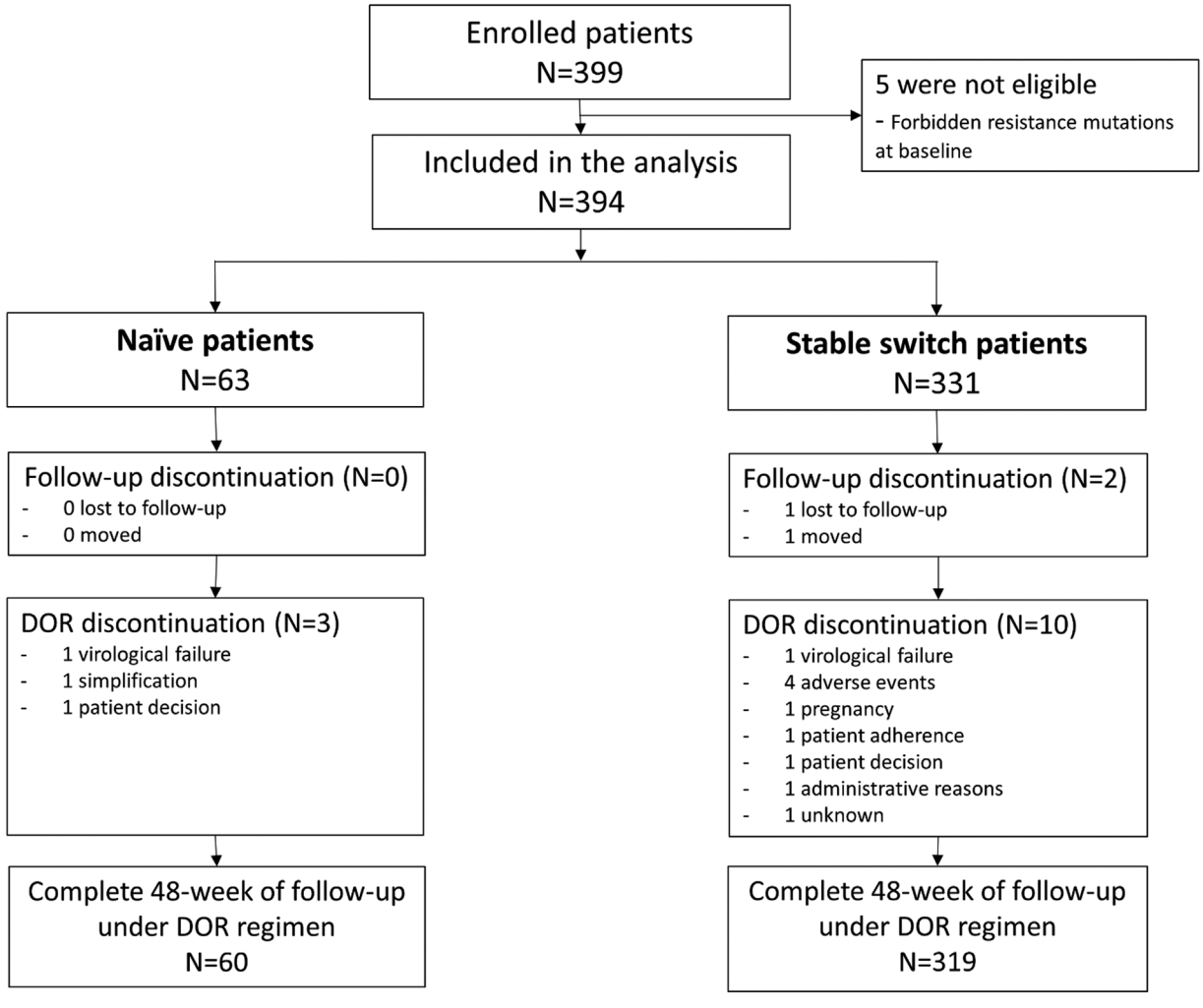

Fig. 1. Study flowchart.

Table 1. Patient demographic and clinical characteristics at doravirine initiation.

	Overall $N=394$	Patient category	
		ART-naive group $N=63$	Switch group $N=331$
Demographics			
Age (years), median (IQR)	45 (37–53)	37 (31–47)	45 (38–54)
Male gender [*n* (%)]	297 (75.4)	49 (77.8)	248 (74.9)
Ethnicity [*n* (%)]			
White European	161 (40.9)	25 (39.7)	136 (41.1)
White mixed	20 (5.1)	5 (7.9)	15 (4.5)
Asian	16 (4.1)	2 (3.2)	14 (4.2)
Black	100 (25.4)	17 (27)	83 (25.1)
Other	97 (24.6)	14 (22.2)	83 (25.1)
Geographical region [*n* (%)]			
UK	185 (47)	35 (55.6)	150 (45.3)
France	160 (40.6)	22 (34.9)	138 (41.7)
Spain	2 (0.5)	0 (0)	2 (0.6)
Belgium	33 (8.4)	6 (9.5)	27 (8.2)
Netherlands	14 (3.6)	0 (0)	14 (4.2)
Clinical characteristics/history			
BMI (kg/m^2) [median (IQR)]	26.1 (22.8–30.4) ($n=198$)	23.4 (22–31.7) ($n=27$)	26.6 (23.2–30.2) ($n=171$)
Comorbidities [*n* (%)]			
HCV co-infection	18 (4.6)	0 (0)	18 (5.4)
HBV co-infection	20 (5.1)	3 (4.8)	17 (5.1)
ESLD	0 (0)	0 (0)	0 (0)
CVD	9 (2.3)	2 (3.2)	7 (2.1)
CKD	2 (0.5)	0 (0)	2 (0.6)
NADM	7 (1.8)	1 (1.6)	6 (1.8)
History of previous virological failure [*n* (%)]	18 (4.6)	0 (0)	18 (5.4)
History of AIDS defining events [*n* (%)]	46 (11.7)	3 (4.8)	43 (13)
HIV information			
Route of HIV infection [*n* (%)]			
MSM	217 (55.1)	32 (50.8)	185 (55.9)
Heterosexual	109 (27.7)	20 (31.7)	89 (26.9)
Other	30 (7.6)	5 (7.9)	25 (7.6)
Unknown	38 (9.6)	6 (9.5)	32 (9.7)
Time since HIV diagnosis (years) [median (IQR)]	8.1 (2.7–13.9)	0.06 (0.03–0.16)	9.3 (4.5–14.8)
Duration on ART (years) [median (IQR)]	NA	NA	7.3 (3.9–10.9) ($n=329$)
CD4+ count (cells/μl) [median (IQR)]	664 (480–860) ($n=393$)	396 (308–622)	689 (526–898) ($n=330$)
CD8+ count (cells/μl) [median (IQR)]	770 (521–1046) ($n=383$)	747 (510.4–1026) ($n=61$)	780 (528–1046) ($n=322$)
CD4/CD8 ratio [median (IQR)]	0.9 (0.6–1.2) ($n=383$)	0.6 (0.3–0.9) ($n=61$)	0.9 (0.6–1.2) ($n=322$)
ART			
Last antiretroviral therapy before switching to DOR[a]			
NRTI use	329 (99.4)	NA	329 (99.4)
TDF	176 (53.2)	NA	176 (53.2)
TAF	81 (24.5)	NA	81 (24.5)
ABC	64 (19.3)	NA	64 (19.3)
FTC	255 (77)	NA	255 (77)
3TC	76 (23)	NA	76 (23)
AZT	2 (0.6)	NA	2 (0.6)
No NRTI in previous ART	2 (0.6)	NA	2 (0.6)
NRTI backbone			
TDF FTC	172 (52)	NA	172 (52)
TDF 3TC	4 (1.2)	NA	4 (1.2)
TAF FTC	81 (24.5)	NA	81 (24.5)
ABC 3TC	64 (19.3)	NA	64 (19.3)
AZT 3TC	2 (0.6)	NA	2 (0.6)
FTC/3TC	6 (1.8)	NA	6 (1.8)
NNRTI use	140 (42.3)	NA	140 (42.3)
EFV	73 (22.1)	NA	73 (22.1)
NVP	14 (4.2)	NA	14 (4.2)
ETR	7 (2.1)	NA	7 (2.1)
RPV	46 (13.9)	NA	46 (13.9)
INSTI use	135 (40.8)	NA	135 (40.8)
DTG	44 (13.3)	NA	44 (13.3)
BIC	21 (6.3)	NA	21 (6.3)

Table 1 (*continued*)

	Overall $N=394$	Patient category: ART-naive group $N=63$	Patient category: Switch group $N=331$
EVG	30 (9.1)	NA	30 (9.1)
RAL	38 (11.5)	NA	38 (11.5)
CABO	2 (0.6)	NA	2 (0.6)
PI use	57 (17.2)	NA	57 (17.2)
DRV	48 (14.5)	NA	48 (14.5)
ATV	9 (2.7)	NA	9 (2.7)
LPV	0 (0.0)	NA	0 (0.0)
Duration on last antiretroviral therapy (years) [median (IQR)]	NA	NA	4 (1.7–7.4) ($n=329$)
Reason for switching to DOR [*n* (%)]			
Adverse event	NA	NA	147 (44.4)
Drug interaction	NA	NA	35 (10.6)
Patient decision	NA	NA	14 (4.2)
Physician decision	NA	NA	16 (4.8)
Pregnancy	NA	NA	16 (4.8)
Rationalisation	NA	NA	5 (1.5)
Simplification	NA	NA	16 (4.8)
Other reason	NA	NA	74 (22.4)
Unknown	NA	NA	8 (2.4)
DOR containing regimen [*n* (%)]			
DOR TDF FTC/3TC	358 (90.9)	56 (88.9)	302 (91.2)
DOR TDF FTC/3TC DTG	5 (1.3)	5 (7.9)	0 (0)
DOR 3TC ABC	16 (4.1)	1 (1.6)	15 (4.5)
DOR TAF FTC	15 (3.8)	1 (1.6)	14 (4.2)
HIV RNA copies/ml at DOR initiation [median (IQR)]	20 (20–30)	19100 (4120–139000)	20 (20–22)

[a]Most participants replaced the third agent NNRTI, PI and INSTI with DOR and kept the NRTI treatment, which is listed under 'DOR containing regimen'.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; BIC, bictegravir; CABO, cabotegravir; CKD, chronic kidney disease; CVD, cardiovascular disease; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ESLD, end-stage liver disease; ETR, etravirine; EVG, elvitegravir; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LPV, lopinavir; NA, not applicable; NADM, non-AIDS-defining malignancy; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; UK, United Kingdom.

the switch group were receiving a backbone of TDF/XTC (53.2%) or tenofovir alafenamide/emtricitabine (24.5%). The most common reasons for switching to DOR included adverse event (44.4%; $n=147$), simplification (22.4%, $n=74$) and drug interactions (10.6%; $n=35$; Table 1).

Primary outcomes

The proportion of participants with virological success (i.e. HIV RNA <50 copies/ml) at week 48 after initiation of DOR regimen was 90.6% (95% CI 87.3–93.3) overall, 87.3% (95% CI 76.5–94.4) in the ART-naive group, and 91.2% (95% CI 87.7–94.1) in the switch group (Table 2). The proportion of participants with study-defined virological failure (HIV RNA ≥50 copies/ml at week 48 after initiation of DOR regimen was 3.3% (95% CI 1.8–5.6) overall, 1.6% (95% CI 0–8.5) in the ART-naive group, and 3.6% (95% CI 1.9–6.2) in the switch group.

Of the 394 included participants, two (0.5%) were lost to follow-up and 13 (3.3%) discontinued the DOR regimen (Fig. 1 and Table 2). Four (1%) participants, all in the switch group, discontinued due to adverse events [hot flashes ($n=1$), nervous system ($n=2$), and abdomen/gastrointestinal tract ($n=1$)]. Other reasons for discontinuation included virological failure ($n=2$), patient decision ($n=2$), simplification ($n=1$), pregnancy ($n=1$), patient adherence ($n=1$), administrative reasons ($n=1$), and unknown ($n=1$). Of the 30 patients with resistance mutations at baseline that did not confer resistance to the study drugs, two had virological failure without selection of new resistance mutations.

Secondary outcomes

The proportion of participants with clinical decision virological failure (HIV RNA ≥200 copies/ml) at week 48 after initiation of DOR was 1.9% (95% CI 0.9–3.9) overall, 1.7% (95% CI 0.2–11.4) in the ART-naive group, and 1.9% (95% CI 0.9–4.2) in the switch group (Table 2 and Fig. 2). Of the seven participants (six switch; one ART-naive) with HIV RNA at least 200 copies/ml, four underwent resistance genotype testing and one (1/4, 25%) in the switch group had a new resistance mutation (K103N, which does not confer resistance to DOR) (Table S3 in supplementary material, http://links.lww.com/QAD/D475). However, the patient's resistance test was undertaken the year before he started DOR when he was started on rilpivirine, emtricitabine, and tenofovir

Table 2. Outcomes at week 48 after initiation of doravirine.

	Overall ($n=394$)		Patient category: ART-naive group ($n=63$)		Patient category: Switch group ($n=331$)	
	N	% (95% CI)	*N*	% (95% CI)	*N*	% (95% CI)
Proportion with discontinuation of DOR regimen or follow-up	15	3.8 (2.3–6.2)	3	4.8 (1.6–14)	12	3.6 (2.1–6.3)
Proportion with VL <50 copies/ml, FDA Snapshot method						
HIV RNA ≥50 copies/ml	13	3.3 (1.8–5.6)	1	1.6 (0.0–8.5)	12	3.6 (1.9–6.2)
HIV RNA <50 copies/ml	357	90.6 (87.3–93.3)	55	87.3 (76.5–94.4)	302	91.2 (87.7–94.1)
Discontinuation due to adverse events	4	1 (0.3–2.6)	0	0 (0–5.7)	4	1.2 (0.3–3.1)
Discontinuation for other reasons	9	2.3 (1–4.3)	2	3.2 (0.4–11)	7	2.1 (0.8–4.3)
On study but missing data in window[a]	11	2.8 (1.4–4.9)	5	7.9 (2.6–17.6)	6	1.8 (0.7–3.9)
Proportion with virological failure (VL ≥200 copies/ml) at week 48	7	1.9 (0.9–3.9)	1	1.7 (0.2–11.4)	6	1.9 (0.9–4.2)
Proportion with low-level viraemia (VL ≥50 and <200 copies/ml) at any time point	20	5.3 (3.4–8.2)	5	8.8 (3.7–19.8)	15	4.7 (2.9–7.7)
Proportion with HIV RNA ≥50 copies/ml at any time during follow-up among switched group	NA	NA	NA	NA	26	8 (5.5–11.6)

ART, antiretroviral therapy; CI, confidence interval; DOR, doravirine; FDA, US Food and Drug Administration; RNA, ribonucleic acid; VL, viral load.

[a]An 8-week window around the date in question were used to select data at each time point for variables of interest. The last available measurement while the patient is on treatment within the time window were also used. If there are no data in the 48-week window, the latest available data beyond week 48 while the patient is still on doravirine were used. Any change in backbone without discontinuation of doravirine was not considered discontinuation of study treatment.

and was likely preexisting at the time DOR was started. The proportion of participants with low-level viraemia during the 48-week follow-up was 5.3% (95% CI 3.4–8.2) overall, 8.8% (95% CI 3.7–19.8) in the ART-naive group, and 4.7% (95% CI 2.9–7.7) in the switch group (Table 2).

Improvements were seen in immunological and lipid markers from baseline to week 48 (Table 3). $CD4^+$ cell count was a median of 56 higher at week 48 compared with baseline ($P<0.001$) in the overall cohort, and $CD4^+/CD8^+$ ratio increased by 0.07 ($P<0.001$). Similar results were evident in the ART-naive and switch groups (Table 3). Total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides decreased by a median of −0.6 ($P<0.001$), −0.4 ($P<0.001$), and −0.2 ($P<0.001$) mmol/l, respectively, in the overall cohort. HDL cholesterol median decreased to a smaller degree,

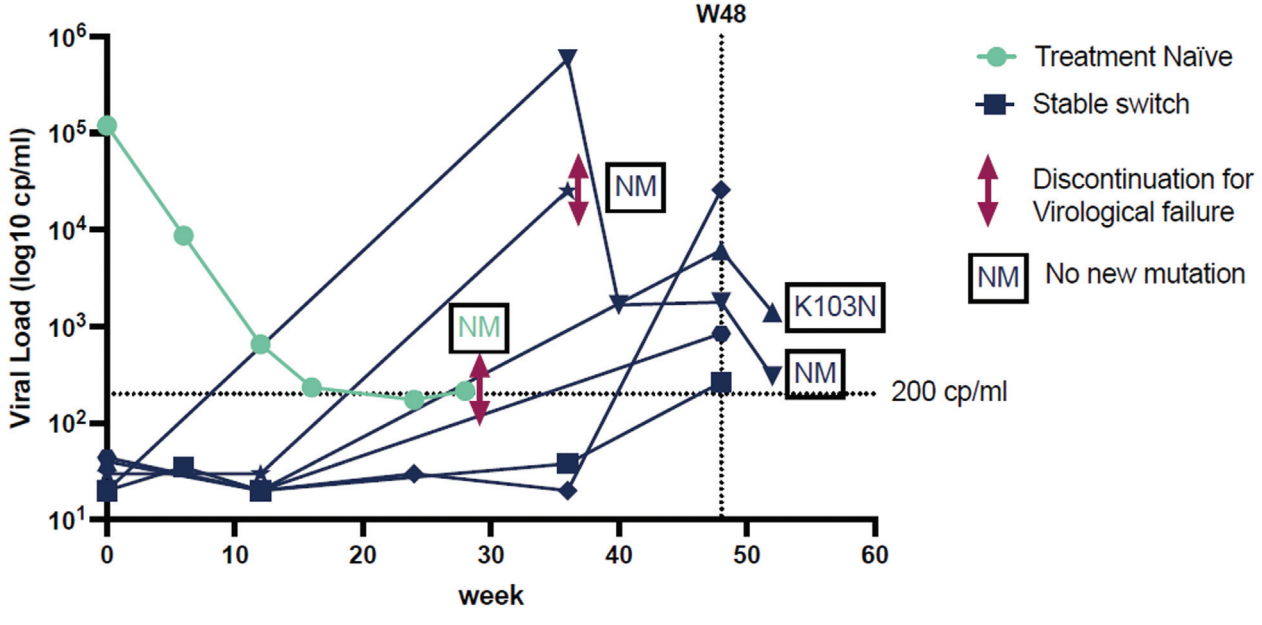

Fig. 2. Confirmed virological failure (viral load ≥200 copies/ml) ($n=7$).

Table 3. Changes in laboratory and biological parameters from baseline to week 48.

	Overall $N=394$	ART-naïve group $N=63$	Switch group $N=331$
$CD4^+$ cell count (cells/μl)	$N=241$	$N=47$	$N=194$
Baseline [median (IQR)]	630 (430–837)	370 (278–622)	670 (499–898)
Change at week 48 [median (IQR)]	56 (−67 to 186)	174 (57–350)	40 (−88 to 150)
P value within group	<0.001	<0.001	0.024
$CD8^+$ cell count (cells/μl)	$N=231$	$N=45$	$N=186$
Baseline median (IQR)	770 (512–1070)	741 (510–1110)	782 (524–1067)
Change at week 48 [median (IQR)]	−20 (−169 to 169)	−80 (−270 to 121)	−11 (−147 to 169)
P value within group	0.411	0.094	0.998
$CD4^+/CD8^+$ ratio	$N=231$	$N=45$	$N=186$
Baseline [median (IQR)]	0.8 (0.6–1.1)	0.6 (0.3–0.9)	0.9 (0.6–1.2)
Change at week 48, median (IQR)	0.07 (−0.06 to 0.26)	0.34 (0.15–0.64)	0.04 (−0.08 to 0.15)
P value within group	<0.001	<0.001	0.004
CD4%	$N=235$	$N=47$	$N=188$
Baseline [median (IQR)]	32.9 (24–37.8)	24.5 (15.7–34.6)	33.2 (26.8–39)
Change at week 48 [median (IQR)]	1 (−2 to 5)	8 (2.6–11.3)	0 (−2.1 to 3)
P value within group	<0.001	<0.001	0.211
CD8%	$N=228$	$N=45$	$N=183$
Baseline [median (IQR)]	40.4 (32–47)	46.4 (38–59)	38.1 (31–45.3)
Change at week 48 [median (IQR)]	−2.0 (−6.1 to 0.1)	−9.9 (−16.3 to 5.7)	−1.1 (−4 to 1)
P value within group	<0.001	<0.001	<0.001
Weight (kg)	$N=163$	$N=26$	$N=137$
Baseline [median (IQR)]	80 (71–93)	75.8 (66.5–93)	81 (72–93)
Change at week 48, median (IQR), *P* value	0 (−3 to 3)	0.6 (−1 to 3.6)	0 (−3 to 2.2)
P value within group	0.482	0.290	0.229
BMI (kg/m^2)	$N=155$	$N=22$	$N=133$
Baseline [median (IQR)]	26.7 (23.2–31.3)	24.6 (22.2–32)	26.9 (23.8–30.4)
Change at week 48 [median (IQR)], *P* value	0 (−0.9 to 0.9)	0.4 (−0.3 to 1.1)	0 (−1 to 0.7)
P-value within group	0.577	0.082	0.210
Creatinine (μmol/l)	$N=285$	$N=43$	$N=242$
Baseline [median (IQR)]	79 (70–92)	74 (64–86)	81 (71–93)
Change at week 48 [median (IQR)]	0 (−7 to 7)	2 (−3 to 9)	0 (−8 to 7)
P-value within group	0.923	0.091	0.490
eGFR ($ml/min/1.73\ m^2$)	$N=285$	$N=43$	$N=242$
Baseline [median (IQR)]	94.7 (82.1–103.4)	102.8 (91.2–111.7)	94.4 (81–102.5)
Change at week 48 [median (IQR)]	−0.7 (−6.3 to 6.2)	−0.7 (−8.6 to 0.1)	−0.7 (−5.7 to 6.9)
P value within group	0.194	0.005	0.810
ALT (U/l)	$N=283$	$N=42$	$N=241$
Baseline [median (IQR)]	28 (19–40)	24 (17–36)	28 (20–40)
Change at week 48 [median (IQR)]	2 (−4 to 9)	0 (−7 to 5)	3 (−3 to 10)
P value within group	<0.001	0.772	<0.001
AST (U/l)	$N=139$	$N=17$	$N=122$
Baseline [median (IQR)]	26 (20.2–33)	26 (20–29)	25.9 (21–33)
Change at week 48 [median (IQR)]	1 (−8 to 11)	−1 (−9 to 7)	2 (−8 to 14)
P value within group	0.067	0.875	0.049
Glucose (mmol/l)	$N=83$	$N=10$	$N=73$
Baseline [median (IQR)]	5.3 (4.9–5.7)	5.4 (4.9–6.1)	5.3 (4.9–5.7)
Change at week 48 [median (IQR)]	0 (−0.6 to 0.5)	−0.2 (−1.3 to 0.2)	0 (−0.5 to 0.5)
P-value within group	0.957	0.333	0.639
Total cholesterol (mmol/l)	$N=108$	$N=18$	$N=90$
Baseline [median (IQR)]	5.2 (4.3–6)	4.6 (3.9–5.4)	5.3 (4.6–6.2)
Change at week 48 [median (IQR)]	−0.6 (−1.1 to 0)	−0.1 (−0.7 to 0.4)	−0.6 (−1.2 to 0.1)
P value within group	<0.001	0.301	<0.001
HDL (mmol/l)	$N=109$	$N=18$	$N=91$
Baseline [median (IQR)]	1.2 (1–1.4)	1.1 (0.9–1.3)	1.2 (1–1.4)
Change at week 48 [median (IQR)]	−0.05 (−0.21 to 0.08)	0.04 (−0.08 to 0.11)	−0.08 (−0.23 to 0.08)
P value within group	0.002	0.653	<0.001
LDL (mmol/l)	$N=102$	$N=18$	$N=84$
Baseline [median (IQR)]	3.2 (2.5–3.9)	2.6 (2.2–3.5)	3.3 (2.7–3.9)
Change at week 48 [median (IQR)]	−0.4 (−0.8 to 0.1)	−0.1 (−0.7 to 0.1)	−0.4 (−0.9 to 0.1)
P-value within group	<0.001	0.500	<0.001
Triglycerides (mmol/l)	$N=109$	$N=18$	$N=91$
Baseline [median (IQR)]	1.4 (0.9–1.8)	1.2 (0.9–1.6)	1.4 (1–1.9)
Change at week 48 [median (IQR)]	−0.2 (−0.8 to 0.2)	−0.1 (−0.8 to 0.9)	−0.2 (−0.8 to 0.1)
P value within group	<0.001	0.913	<0.001

ALT, alanine transaminase; ART, antiretroviral therapy; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; $ml/min/1.73\ m^2$, millilitres of cleansed blood per minute body surface.

−0.05 mmol/l ($P = 0.002$). There was no significant change in body weight at week 48. Changes in renal and clinical parameters did not differ from baseline to week 48 (Table 3). ALT was a median of 2 and 3 UI/l higher at week 48 compared to baseline in the overall cohort ($P < 0.001$) and switch group ($P < 0.001$) respectively, and eGFR decreased by a median of 0.7 ml/min/1.73 m^2 in the ART-naive group ($P = 0.005$).

Multivariable analyses

In the switch group, participants with prior virological failure were 3.6 times (95% CI 1.2–11; $P = 0.027$) more likely to have HIV RNA at least 50 copies/ml at any time during the 48-week follow-up than those without previous virological failure (Table S4 in supplementary material, http://links.lww.com/QAD/D475). In the overall cohort, geographical region, comorbidities, and presence of thymidine analogue-associated mutations (TAMs) were associated with DOR discontinuation by week 48 in multivariable analyses. Participants from Belgium–Spain–Netherlands were more likely to discontinue treatment than French participants (hazard ratio 10.7, 95% CI 1.7–68.0; $P = 0.012$). In addition, participants with comorbidities had an over four (HR 4.2, 1.2–14.6; $P = 0.022$) times higher risk and those with TAMS at baseline over seven (hazard ratio 7.5, 1.4–40.5; $P = 0.019$) times higher risk, respectively, of discontinuing treatment than those without (Table S4 in supplementary material, http://links.lww.com/QAD/D475).

Discussion

Our study evaluated the antiviral effectiveness and safety of DOR-based regimens in routine clinical practice in five European countries. We show the real-life effectiveness of DOR-containing regimens at maintaining virological control in treatment-experienced PWH and inducing it in treatment-naive PWH. Overall, 90.6% of participants achieved virological success (i.e. HIV RNA < 50 copies/ml) at week 48 after initiation of DOR regimen, 91.2% in the switch group and 87.3% in the ART-naive group. The discontinuation rate was low and DOR-containing regimens were well tolerated. None of the participants who had virological failure developed DOR-associated resistance mutations. Moreover, the study did not show any association between the length of time on previous treatment and/or the duration on pre-DOR regimen and the discontinuation and/or failure rates.

Our results are in accordance with other recently published real-life studies on routine clinical practice. In the DRIVE-REAL study in England, which assessed characteristics, treatment patterns, and virological outcomes among PWH initiating DOR in a UK real-life setting without any exclusion criteria for previous failure to NNRTI, 95% (253/266 patients) achieved or maintained viral load suppression (<50 copies/ml), similar to clinical trials in treatment-experienced PWH continuing DOR at 24 weeks [19]. A recent study conducted in a single Italian centre reported that switching to a single-tablet regimen of DOR/TDF/3TC maintained viral suppression in PWH, with high rates of virological suppression (ranging between 93.5 and 98.4%) after 12 months follow-up [20]. It is noteworthy that, in this study, PWH with previous virological failure to lamivudine/emtricitabine or NNRTIs and/or genotypic testing showing reduced sensitivity to lamivudine/emtricitabine or NNRTIs were excluded. Furthermore, a study in five French centres showed a high level of virological success (98%) at week 48 in 50 PWH with a long duration of suppression who were switched to dual therapy of DOR and lamivudine; there was not any exclusion criterium regarding previous failure to NNRTI [21]. These results add important evidence to the efficacy of DOR-containing regimens already demonstrated in clinical trials [10–15].

Our study also showed good tolerability of DOR-containing regimens. The majority of participants in our study remained on a DOR-containing regimen at 48 weeks; only 3.3% discontinued and only 1% due to adverse events. This is similar to the UK DRIVE-REAL study where only 6% discontinued by 6 months, and other studies in Italy where 3.5 and 6.5% treatment-experienced PWH who switched to a DOR-based regimen stopped therapy within 1 year [19,22,23]. The two smaller retrospective cohorts from France and Italy reported 8 and 6.5%, respectively, of PWH who used a DOR-based regimen stopping within 1 year [20,21].

Current ART regimens have been associated with dyslipidaemia, both a leading cause of cardiovascular disease (CVD) and a key risk factor for preventable CVD-related mortality [24]. Given the increased risk of CVD in PWH, a regimen showing no negative effect on lipid profile is an advantage [24]. Apart from a small decrease in high-density lipoprotein (HDL) in the switch group, our study showed improvements in lipid markers from baseline to week 48 following treatment with a DOR-containing regimen. This favourable impact could be related to the switch from a protease inhibitor or an INSTI to DOR or a switch to TDF-based regimen. Other real-life studies have also reported an improved lipid metabolism profile in PWH switching to DOR-based regimens [23,25]. The DRIVE-FORWARD and DRIVE-AHEAD clinical trials showed no increase of fasting serum lipids as opposed to compared drug regimens [10,11,13–15]. We did; however, we saw a slight, although not clinically relevant, increase in ALT levels from baseline to week 48 in the overall cohort and switch group. This is in accordance with the product

profile, which suggests blood tests may show increased levels of liver enzyme (i.e. ALT) [8]. However, second-generation NNRTIs, including DOR, appear generally safe for the liver, even in those co-infected with hepatitis viruses; this is opposed to first generation NNRTIs that have been associated with hepatotoxicity [23,26–30]. Among the few virological failures that were reported, emergence of new resistance mutation occurred in only one of the four patients who had genotypic testing. The emerging mutation was the K103N that does not confer resistance to DOR and was most likely already present when DOR was initiated. In the DRIVE-FORWARD and DRIVE -AHEAD studies of the few naive patients who had emergence of NNRTI mutations at baseline, none had K103N [12].

We found that HIV RNA at least 50 copies/ml at week 48 was associated with prior virological failure, and geographical region, comorbidities, and presence of TAMs were associated with DOR discontinuation or lost to follow-up in multivariable analyses. The association of prior virological failure with virological failure at week 48 and prior TAMs with lost to follow-up could suggest that these patients had poor adherence both in the past and on DOR-containing regimen, but public health policies and patients' profile could differ between countries.

Our study had several strengths. The sample size was relatively large, and the study included 16 centres in five different countries avoiding single centre bias. Some limitations, however, need consideration. There is an inherent risk of bias and confounding given the retrospective observational design of the study. Observational study data are limited to that which is already available at the clinical setting, thus data are less available for specific points in time defined by the study endpoints (i.e. patient appointment times are scheduled more sporadically in the real world than for clinical trials) and safety outcomes. Some clinics collect more detailed and frequent data than others, which makes inter-clinic comparisons more challenging than protocol-led clinical trials. Another limitation is that, at the time of study recruitment, DOR was newly available commercially and primarily indicated for those who are treatment-experienced [8]. There were relatively few treatment-naive group individuals prescribed the drug. Moreover, three quarters of participants were men, 40% White European and our results cannot be extrapolated to a more mixed population. The study pointed to several clinical measures, such as increased $CD4^+$ cell counts and decreased total and LDL cholesterol measures that changed statistically significantly compared to baseline measures. The study could not distinguish if the favourable impact was related to the switch from a protease inhibitor or an INSTI to DOR or a switch to TDF-based regimen; and the study was not designed to demonstrate whether or not these measures contributed to improved clinical health.

In conclusion, the results of our study show high levels of effectiveness and low levels of side effects in DOR-containing regimens in both treatment-naive and treatment-experienced PWH. However, more data is needed to evaluate the risk of resistance emergence in case of virological failure.

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DREW Study Group Clinical Investigators at highest recruiting sites: Casper ROKX, Esteban MARTINEZ, Chris KENYON.

Data sharing: the NEAT ID Foundation acts as the data controller for the study. Data extracted from the eCRF will be kept on a secure network drive of NEAT ID with access to authorized personnel only. Identified only by subject number, live data are pseudo-anonymized at all times and are transferred securely using the NEAT ID file share process. All transfers are fully documented. In keeping with consent of study participants, personal data may be shared with the sponsor, manufacturer, authorities and countries within and outside of the EEA that may offer varying levels of personal data protection. All data will be anonymized. Data may be used in future reports, generated from the study results; or used in scientific presentations at both national and international conferences by research staff authorized by the sponsor. The study protocol is available on Clinicaltrials.gov. This document is redacted of all study staff contact details. Further study data will be made available with publication.

Conflicts of interest

This study received funding from Merck Sharpe and Dohme. J.M.M. has received consulting fees from Gilead Sciences, Merck and ViiV Healthcare, and his institution received grants from Gilead and Merck. K.L. has received consulting and educational activities fees from Gilead, MSD and ViiV Healthcare. F.R. has received consulting fees from Gilead Sciences, MSD and ViiV Healthcare. J.F. has received research grant from GSK. A.P. has received consulting fees from Gilead Sciences, Merck and ViiV Healthcare, and his institution received grants from Gilead, ViiV and Merck. A.R., C.F., D.R., L.A., L.L., T. M. and R.M. have no conflicts of interest to declare.

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