

Review of Doravirine Resistance Patterns Identified in Participants During Clinical Development

Elizabeth Anne Martin, DO, MPH,^a Ming-Tain Lai, PhD,^b Winnie Ngo, BS,^b Meizhen Feng, MS,^b Donald Graham, BS,^b Daria J. Hazuda, PhD,^b Sushma Kumar, PhD,^c Carey Hwang, MD, PhD,^a Peter Sklar, MD, MPH,^a and Ernest Asante-Appiah, PhD^b

Background: Doravirine (DOR) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of HIV-1 infection in patients with no known DOR resistance-associated mutations. DOR was rationally designed to address limitations associated with other approved NNRTIs, particularly resistance from common NNRTI resistance-associated mutants containing K103N, Y181C, or G190A reverse transcriptase substitutions.

Setting: Data to date from both in vitro studies and clinical trials have been compiled to summarize the resistance profile of DOR.

Methods: We analyzed data from in vitro studies and phase 2 and 3 trials to assess the emergence of resistance-associated mutations and their impact on efficacy among participants treated with DOR.

Results: DOR exhibited a distinct resistance profile compared with efavirenz and rilpivirine in vitro and in vivo; mutant viruses that were resistant to DOR showed limited cross-resistance to efavirenz and rilpivirine. In clinical trials, the development of DOR resistance-associated substitutions in reverse transcriptase was uncommon.

Conclusion: Overall, minimal cross-resistance across NNRTIs was observed for DOR and limited development of DOR-related resistance. These data should assist clinicians in further understanding the resistance profile of DOR, so appropriate treatment decisions can be made for their patients.

Key Words: clinical trial, doravirine, NNRTI, replication capacity, resistance

(*J Acquir Immune Defic Syndr* 2020;85:635–642)

INTRODUCTION

Almost 40 million people worldwide are presently living with HIV-1 infection, ~62% of whom are receiving antiretroviral therapy (ART).¹ Currently, 22 individual agents and 22 combination regimens are approved by the US Food and Drug Administration for the treatment of HIV-1.² Non-nucleoside reverse transcriptase inhibitors (NNRTIs)—as one of the components of single-tablet regimens or in combination with other antiviral agents—comprise more than one-quarter of these options. The most common initial HIV treatment regimens generally include 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus an integrase strand transfer inhibitor, an NNRTI, or a boosted protease inhibitor (PI).²

Doravirine (DOR) is an NNRTI approved in the United States, Europe, Canada, and elsewhere in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients with no ART history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and no known DOR resistance-associated mutations.

DOR was rationally designed to address limitations associated with other approved NNRTIs, such as resistance from common NNRTI resistance-associated substitutions in reverse transcriptase (RT), eg, K103N, Y181C, and G190A, the central nervous system (CNS) toxicity observed with efavirenz (EFV), and the food requirement and high baseline viral load exclusion associated with rilpivirine (RPV).^{3–6} In this article, we present the data compiled to date regarding DOR resistant-associated mutations and build on a recent review⁷ by including data previously unpublished. These data should assist clinicians in further understanding the resistance profile of DOR, so appropriate treatment decisions can be made for their patients.

IN VITRO RESISTANCE STUDIES

In vitro studies have shown that DOR has >50-fold improved potency compared with EFV against viruses with the RT K103N substitution. Furthermore, DOR shows >5-fold more potent activity than RPV against viruses with the

Received for publication May 29, 2020; accepted July 28, 2020.

From the Departments of ^aClinical Research; ^bInfectious Disease and Vaccine Research; and ^cGlobal Regulatory Affairs and Clinical Safety, Merck & Co., Inc., Kenilworth, NJ.

Supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

All authors are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, and may hold stock in Merck & Co., Inc., Kenilworth, NJ.

M.-T. Lai: At the time the research was conducted.

Correspondence to: Elizabeth Anne Martin, DO, MPH, Merck Sharp & Dohme Corp., 126 E. Lincoln Avenue, RY34-A484, Rahway, NJ 07065 (e-mail: elizabeth.martin1@merck.com).

Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

RT Y181C substitution in the presence of 100% normal human serum.⁸ In a panel of 96 of the most prevalent NNRTI resistance-associated clinical mutant viruses that was evaluated with DOR and other approved NNRTIs, 16 (17%) of these mutants displayed >10-fold reduction in susceptibility compared with wild-type virus, indicating resistance to DOR, versus 62 (65%), 15 (16%), and 18 (19%) for EFV, etravirine, and RPV, respectively. Among these, only the RT Y188L substitution was shown to confer high-level (>100-fold change) DOR resistance.⁴ The RT Y188L substitution is uncommon among patients for whom NNRTI therapy has failed, possibly because it requires 2 base changes (TTA [tyrosine] to TTA [leucine] or CTT [leucine]) and is associated with low viral replication capacity.^{4,9,10}

To assess the potential of DOR in suppressing common NNRTI resistance-associated mutants under clinically relevant drug concentrations, inhibitory quotients (IQs) were calculated by determining the ratio of the clinical trough concentration over the antiviral half-maximal inhibitory concentration (IC₅₀) for NNRTI mutant viruses with DOR, RPV, and EFV.⁸ IQs have been shown to be good predictors of clinical efficacy for various ART drug classes.¹¹ The IQ values against RT substitutions K103N, Y181C, and K103N/Y181C mutants were 39, 27, and 25, respectively, for DOR, whereas RPV displayed IQ values of 4.6, 1.4, and 0.8, respectively, and EFV showed IQ values of 2.5, 60, and 1.9, respectively. With the exception of Y188L, DOR also exhibited higher IQ values than RPV and EFV against the top 11 most prevalent NNRTI resistance-associated mutants.⁸

Of the 3 main HIV-1 subtypes, subtype B is most commonly found in North America, South America, and Europe, whereas subtypes A and C are most prevalent in Africa; all 3 subtypes are seen in Asia, with different subtypes predominating depending on the region.¹² In *in vitro* resistance selection studies with subtype B virus, DOR has demonstrated a unique resistance pathway. The development of resistance was characterized by the selection of RT mutants with the V106A substitution, followed by the emergence of substitutions of F227L or L234I with escalating DOR concentrations.¹³ By contrast, under the same conditions, RT substitutions L100I and K103N were the major substitutions associated with EFV, and E138K and K101P substitutions were the 2 most common resistance pathways in selection studies with RPV.¹³ The V106A, V106A/L234I, and V106A/L234I/V108I resistance-associated substitutions, which demonstrated 10-fold (single substitution) and >150-fold (double and triple substitutions) resistance to DOR, were susceptible to RPV and EFV, showing <6-fold resistance; the V106A/F227L mutant, which was >150-fold resistant to DOR, exhibited 22-fold resistance to EFV.¹³

Results with subtype A virus were similar to those observed with subtype B; the major resistance pathway started with the development of the RT V106A mutant at a lower DOR concentration, followed by the RT F227L mutant as DOR concentrations increased.¹³ Two resistance pathways were observed with EFV in RT starting with L100I or V106M.¹³ This was followed by the emergence of Y188H/C or V179D and Y188C or L100I substitutions, respectively.¹³ With RPV, RT substitution E138K was the first

major resistance pathway, followed by L100I at a higher RPV concentration; as RPV concentrations further increased, the triple mutant E138K/L100I/V108I emerged.¹³

Two resistance pathways were identified with DOR in the selection studies in subtype C virus: RT substitution V106A followed by F227I, and V106M followed by F227C.¹³ For EFV, the results were similar to those observed with subtype A virus. By contrast, subgroup C virus exhibited a unique resistance pathway with RPV. Although RT E138K was observed as with the other subtypes, it was followed by RT K101E to yield the unique double substitution RT E138K/K101E instead of E138K/L100I.¹³

Resistance selections were conducted with the K103N, Y181C, G190A, E138K, and K103N/Y181C mutant viruses using clinically relevant concentrations of DOR, RPV, and EFV. No viral breakthrough was observed with DOR for any mutant, whereas breakthrough viruses were readily detected with RPV against RT Y181C, K103N/Y181C, and E138K mutants and with EFV against RT K103N and K103N/Y181C containing variants.⁸ These data are consistent with the higher IQ values for DOR at clinically relevant concentrations when compared with EFV and RPV, suggesting that DOR has the potential to possess a higher genetic barrier to the development of resistance compared with RPV and EFV at the drug concentrations achieved in the clinic for each agent. Taken together, DOR exhibited a distinct resistance profile compared with EFV and RPV, and mutant viruses that are resistant to DOR showed limited cross-resistance to EFV and RPV.

OVERVIEW OF THE EFFICACY AND SAFETY OF CLINICAL TRIALS

The clinical picture of DOR has been established in a number of clinical trials. In treatment-naive populations, 3 phase 2 and 2 phase 3 trials have been completed.^{14–18} An additional phase 3 trial examined the effects of switching to DOR after achieving virologic suppression for 6 months.¹⁹ DOR was shown to be efficacious in these trials, with nausea, dizziness, headache, fatigue, diarrhea, abdominal pain, and abnormal dreams as the most common adverse events (AEs).^{20,21}

Treatment-Naive Populations

The initial phase 2b trial that supported the use of DOR in HIV-1-infected treatment-naive adults was a multicenter, double-blind, randomized, dose-ranging trial (P007; NCT01632345) that investigated the safety, tolerability, pharmacokinetics, and efficacy of 4 DOR doses (25 mg, 50 mg, 100 mg, and 200 mg) versus EFV (600 mg), each in combination with emtricitabine (FTC; 200 mg) plus tenofovir disoproxil fumarate (TDF; 300 mg).¹⁴ The 100-mg dose was selected for further study based on the antiviral response and safety profile.¹⁴ At week 96 (secondary efficacy endpoint), 75% of DOR-treated participants achieved HIV-1 RNA <50 copies/mL (Table 1). Rates of CNS-related AEs at week 24 (key safety endpoint) were significantly different between DOR and EFV (27% and 47%, respectively).¹⁴

TABLE 1. Summary of Efficacy Results of DOR Clinical Trials

Study	Phase	Population	Treatments (n)	Participants With HIV-1 RNA <50 copies/mL* at Week 96
P007	2b	Treatment-naïve with plasma HIV-1 RNA ≥1000 copies/mL	DOR + 3 TC/TDF (108) EFV + 3 TC/TDF (108)	75.0% 75.9%
DRIVE-BEYOND	2a	Treatment-naïve with common NNRTI-transmitted resistance mutations†	DOR/3 TC/TDF (10)	100.0%‡
P011	2b	Treatment-naïve with plasma HIV-1 RNA ≥1000 copies/mL	DOR/3 TC/TDF (31) DOR + ISL 0.25 mg (29) DOR + ISL 0.75 mg (30) DOR + ISL 2.25 mg (31)	83.9%§ 89.7%§ 90.0%§ 77.4%§
DRIVE-FORWARD	3	Treatment-naïve with plasma HIV-1 RNA ≥1000 copies/mL	DOR + 2 NRTIs (383) DRV/r + 2 NRTIs (383)	73.1% 66.0%
DRIVE-AHEAD	3	Treatment-naïve with plasma HIV-1 RNA ≥1000 copies/mL	DOR/3 TC/TDF (364) EFV/FTC/TDF (364)	77.5% 73.6%
DRIVE-SHIFT	3	Virologically suppressed for ≥6 mo with 2 NRTIs plus a boosted PI, boosted elvitegravir, or NNRTI	Immediate switch to DOR/3 TC/TDF (447) Baseline regimen, switch at 24 wk (209)	90.8%§ 94.6%

*Trial P007 used HIV-1 RNA <40 copies/mL for primary efficacy endpoint.
 †Eight participants had the RT K103N mutation, and 2 participants had the RT G190A mutation.
 ‡Seven patients completed week 96.
 §Data at 48 weeks.
 ||Data at 24 weeks.
 DRV/r, ritonavir-boosted darunavir.

The phase 2a, multicenter, open-label DRIVE-BEYOND trial (NCT02629822) examined the efficacy, safety, and tolerability of DOR (100 mg) in a fixed-dose combination with lamivudine (3 TC; 300 mg) and TDF (300 mg) in HIV-1–infected treatment-naïve adults with common NNRTI-transmitted resistance mutations.¹⁵ Eight participants had the RT K103N substitution, and 2 participants had the RT G190A substitution. One participant did not meet the inclusion criteria for the efficacy analysis. Although only 8 and 7 of the 9 total participants completed 48 and 96 weeks, respectively, all participants achieved HIV-1 RNA <50 copies/mL, including the 2 who did not complete 96 weeks (Table 1).¹⁵

In a phase 2b, randomized, double-blind, dose-ranging trial (P011; NCT03272347), HIV-1–infected treatment-naïve participants (N = 121) were randomized to receive DOR (100 mg) plus 3 TC (300 mg) and 1 of 3 doses of the novel nucleoside reverse transcriptase translocation inhibitor, islatravir (ISL) (0.25 mg, 0.75 mg, or 2.25 mg), or DOR plus 3 TC and TDF for 24 weeks, after which participants entered the open-label phase for 24 weeks where they received DOR/3 TC/TDF or DOR alone plus 1 of the 3 doses of ISL if virologically suppressed.¹⁶ The proportions of participants with HIV-1 RNA <50 copies/mL ranged from 77% (DOR + ISL 2.25 mg) to 90% (DOR + ISL 0.75 mg) at week 48 (Table 1).¹⁶

In the phase 3 DRIVE-FORWARD trial (NCT02275780), treatment-naïve adults with plasma HIV-1 RNA ≥1000 copies/mL were randomized to receive DOR (100 mg) or darunavir (800 mg) plus ritonavir (100 mg) once daily, with 2 investigator-selected NRTIs.¹⁷ At week 96, DOR was shown to be noninferior to ritonavir-boosted darunavir, with 73% and 66% of participants, respectively, achieving HIV-1

RNA <50 copies/mL [difference, 7.1%; 95% confidence interval (CI): 0.5 to 13.7] (Table 1).²² DOR demonstrated a good safety profile, exhibiting a lipid profile superior to ritonavir-boosted darunavir and favorable CNS tolerability compared with darunavir.

The phase 3 DRIVE-AHEAD trial (NCT02403674) evaluated the fixed-dose combination of DOR (100 mg), 3 TC (300 mg), and TDF (300 mg) with EFV (600 mg) plus FTC (200 mg) and TDF (300 mg) in treatment-naïve adults with plasma HIV-1 RNA ≥1000 copies/mL.¹⁸ At week 96, DOR was found to be noninferior to EFV, with 78% of DOR-treated participants and 74% of EFV-treated participants achieving plasma HIV-1 RNA <50 copies/mL (difference, 3.8%; 95% CI: −2.4 to 10.0) (Table 1).²³ Significantly fewer neuropsychiatric AEs were observed with DOR than with EFV, and DOR exhibited a superior lipid profile to EFV.

Virologically Suppressed Populations

The phase 3 DRIVE-SHIFT trial (NCT02397096) examined the effects of switching to DOR/3 TC/TDF in participants who were virologically suppressed for ≥6 months with 2 NRTIs plus a boosted PI, boosted elvitegravir, or an NNRTI.¹⁹ Participants were either immediately switched to DOR/3 TC/TDF (immediate-switch group) or were switched after another 24 weeks on their baseline regimen (baseline group). At week 24, the proportions of participants with HIV-1 RNA <50 copies/mL were 94% and 95% for the immediate-switch and baseline groups, respectively. At week 48, the proportion of participants with HIV-1 RNA <50 copies/mL was maintained at 91% in the immediate-switch group, demonstrating the noninferiority of switching to DOR versus continuing the baseline regimen

(difference, -3.8% ; 95% CI: -7.9 to 0.3) (Table 1). Rates of AEs and drug-related AEs were higher in the immediate-switch group versus the baseline group at week 24, consistent with what has been observed in other switch trials. A superior lipid profile for low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol was observed in the immediate-switch group compared with continuation of a boosted PI regimen at week 24.

RESISTANCE ANALYSIS ACROSS CLINICAL TRIALS

Treatment-Naive Populations

In the dose-ranging phase 2 P007 trial, 18% ($n = 19/108$) of the 100-mg DOR-treated participants met the criteria for protocol-defined virological failure (PDVF) at week 96; 16 were nonresponders, and 3 were rebounders (Table 2).¹⁴ The trial defined PDVF as either participants who never achieved HIV-1 RNA <40 copies/mL by week 24 (non-responder) or those who, after initial response of HIV-1 RNA <40 copies/mL, had 2 consecutive measurements of HIV-1

RNA ≥ 40 copies/mL at least 1 week apart at or after week 24 (rebounder). Five DOR-treated participants had samples that met resistance testing criteria, 40% ($n = 2/5$) of which were rebounders (Table 3). No phenotypic resistance to DOR was observed, but 1 isolate had RT E138E/G, V179D, and A62V substitutions and showed phenotypic resistance to EFV.

In the DRIVE-BEYOND phase 2a trial, the definition of PDVF differed from that in the P007 trial, with an HIV-1 RNA threshold of ≥ 50 copies/mL. One participant who was nonadherent met PDVF criteria at week 24 and exhibited the RT G190A substitution; this participant also showed resistance to EFV and nevirapine at both baseline and time of PDVF (Tables 2 and 3). Phenotypic analysis at week 24 also showed a 1.7-fold change in susceptibility for DOR compared with wild-type virus, which is within the proposed bounds of susceptibility. Although no phenotypic resistance threshold has been established for DOR, an IC_{50} value 2.5 times higher than that of wild-type virus was used as the assay cutoff—a common cutoff when assessing phenotypic resistance for antiretroviral agents in development. Therefore, no evidence of phenotypic resistance to DOR was observed at the time of PDVF.

TABLE 2. Resistance Analysis Summary of Participants With PDVF at Week 96*

Trial (N)†	PDVF‡ Status	Nonresponder, n (%)	Rebounder, n (%)	Participants With PDVF Who Failed Because of DOR Phenotypic Resistance, n (%)
P007 (N = 108)	Confirmed HIV-1 RNA ≥ 40 and ≤ 200 copies/mL	12 (11.1)	1 (0.9)	0
	Confirmed HIV-1 RNA >200 copies/mL	4 (3.7)	2 (1.9)	
	Total	16 (14.8)	3 (2.8)	
DRIVE-BEYOND (N = 10)	Confirmed HIV-1 RNA ≥ 50 and ≤ 200 copies/mL	0	1 (10.0)	0
	Confirmed HIV-1 RNA >200 copies/mL	0	0	
	Total	0	1 (10.0)	
P011 (N = 31)§	Confirmed HIV-1 RNA ≥ 50 and ≤ 200 copies/mL	1 (3.2)	5 (16.1)	0
	Confirmed HIV-1 RNA >200 copies/mL	0	0	
	Total	1 (3.2)	5 (16.1)	
DRIVE-FORWARD (N = 383)	Confirmed HIV-1 RNA ≥ 50 and ≤ 200 copies/mL	0	19 (5.0)	1 (0.3)
	Confirmed HIV-1 RNA >200 copies/mL	3 (0.8)	12 (3.1)	
	Total	3 (0.8)	31 (8.1)	
DRIVE-AHEAD (N = 364)	Confirmed HIV-1 RNA ≥ 50 and ≤ 200 copies/mL	0	18 (4.9)	6 (1.6)
	Confirmed HIV-1 RNA >200 copies/mL	6 (1.6)	10 (2.7)	
	Total	6 (1.6)	28 (7.7)	
DRIVE-SHIFT (N = 656)	Confirmed HIV-1 RNA ≥ 50 and ≤ 200 copies/mL	NA	5 (0.8)	0
	Confirmed HIV-1 RNA >200 copies/mL	NA	2 (0.3)	
	Total	NA	7 (1.1)	

Analysis of postbaseline data only includes laboratory records collected after the first dose of trial medication through 14 days after the last dose of trial medication.

*Data are at week 48 for trials P011 and DRIVE-SHIFT.

†Number of participants in the DOR group.

‡PDVF was defined as one of the following: (1) nonresponder [confirmed (2 consecutive measures ≥ 1 week apart) HIV-1 RNA ≥ 200 copies/mL at week 24 or 36, or confirmed (2 consecutive measures ≥ 1 week apart) HIV-1 RNA ≥ 50 copies/mL (40 copies/mL for P007 trial) at week 48]; or (2) rebounder [confirmed (2 consecutive measures ≥ 1 week apart) HIV-1 RNA ≥ 50 copies/mL after an initial response of HIV-1 RNA <50 copies/mL at any time during the trial].

§Includes only those patients in the DOR/3 TC/TDF arm.

||Excludes 1 participant who was nonadherent.

NA, not applicable.

TABLE 3. Summary of Genotypic and Phenotypic Resistance From DOR Clinical Trials (Week 96*)

Trial	PDVF or D/C	Wk†	VL (copies/mL)	NNRTI Mutation			NRTI Mutation				
				Genotypic		Phenotypic (Fold Change)	Genotypic		Phenotypic (Fold Change)		
				RT Mutation	DOR	EFV	RT Mutation	3 TC	FTC	TDF	ABC
P007‡	PDVF	36	NA	NA	1.07S	0.70S	NA	NA	0.98S	0.78S	NA
	PDVF	24	NA	None	0.53S	0.49S	None S	NA	1.22S	0.56S	NA
	PDVF	48	1763	None	0.84S	0.64S	None S	NA	1.16S	0.83S	NA
	PDVF	24	20,660	None	0.64S	0.65S	None S	NA	1.24S	0.74S	NA
	PDVF	24	NA	E138E/G, V179D	0.75S	7.14R	A62V	NA	0.87S	0.76S	NA
DRIVE-BEYOND	PDVF	24	5393	G190A, V179V/I	1.71S	3.30R	None	0.66S	0.87S	0.90S	0.79S
P011: No participant met the criteria for virologic testing											
DRIVE-FORWARD	D/C	2	NA	ND	2.88R	NA	ND	1.11S	1.24S	1.21S	0.94S
	D/C	24	7924	None	0.50S	NA	None	1.18S	0.93S	0.77S	0.73S
	D/C	48	2120	None	Failed	NA	None	Failed	Failed	Failed	Failed
	D/C	24	55,708	V106I, H221Y, F227C	>96.6R	NA	M184V	>108.4R	>57.89R	0.42S	3.87S
	PDVF	24	31,896	None	1.11S	NA	None	0.90S	0.86S	1.01S	0.98S
	PDVF	16	847	None	0.69S	NA	None	0.92S	1.05S	0.78S	0.77S
	PDVF	36	16,499	None	0.98S	NA	None	1.21S	1.12S	0.66S	0.82S
	PDVF	24	14,980	None	2.47S	NA	A62V	1.04S	1.04S	1.05S	0.74S
	PDVF	24	13,417	None	0.75S	NA	None	1.17S	0.97S	0.78S	0.81S
	PDVF	24	<40 TND	None	Failed	NA	None	Failed	Failed	Failed	Failed
	PDVF	24	24,002	None	1.01S	NA	None	0.92S	0.75S	0.84S	0.72S
	PDVF	60	1591	V106A, P225H	>95.05R	NA	V118I, M184I	32.00R	35.00R	0.51S	1.18
	PDVF	96	2056	None	0.60S	NA	None	0.72S	0.89S	0.95S	0.99S
	PDVF	96	412	None	0.52S	NA	None	0.91S	1.10S	0.79S	0.72S
	PDVF	72	1024	None	0.52S	NA	None	0.91S	1.34S	0.91S	0.74S
DRIVE-AHEAD	D/C	4	207	Failed	0.64S	0.63S	Failed	0.98S	1.00S	0.85S	NA
	D/C	24	18,724	None	1.37S	0.80S	None	0.98S	0.97S	0.80S	NA
	D/C	4	7469	None	0.41S	0.40S	V118I	0.70S	0.76S	0.62S	NA
	D/C	16	9631	None	0.92S	0.77S	None	0.98S	0.85S	0.82S	NA
	D/C	4	2849	None	1.62S	1.51S	None	1.14S	1.06S	0.92S	NA
	D/C	24	13,901	None	0.79S	0.61S	None	1.20S	1.15S	1.02S	NA
	D/C	4	472	V206I	0.84S	0.53S	None	0.85S	0.90S	0.76S	NA
	D/C	8	110	None	1.80S	1.33S	None	0.96S	1.00S	0.77S	NA
	D/C	48	172,105	None	1.77S	1.20S	None	1.06S	1.07S	0.97S	NA
	D/C	24	246,237	V179D	0.79S	4.30R	None	1.11S	1.16S	0.96S	NA
	D/C	4	410	None	1.30S	1.28S	A62A/V	1.39S	1.21S	1.00S	NA
	D/C	8	652	Failed	Failed	Failed	Failed	Failed	Failed	Failed	NA
	D/C	24	77,133	None	0.97S	0.83S	None	1.15S	0.85S	0.82S	NA
	PDVF	24	10,232	None	1.03S	0.80S	None	1.13S	1.25S	0.82S	NA
	PDVF	96	11,369	None	0.52S	0.55S	None	0.93S	0.96S	0.66S	NA
	PDVF	72	3717	None	0.75S	1.01S	None	1.00S	0.85S	0.88S	NA
	PDVF	36	13,675	None	0.79S	0.81S	A62V	1.05S	0.91S	0.98S	NA
	PDVF	96	591	None	1.35S	0.88S	None	1.42S	1.36S	0.84S	NA
	PDVF	84	618	None	Failed	Failed	Failed	Failed	Failed	Failed	NA

(continued on next page)

TABLE 3. (Continued) Summary of Genotypic and Phenotypic Resistance From DOR Clinical Trials (Week 96*)

Trial	PDVF or D/C	Wk†	VL (copies/mL)	NNRTI Mutation			NRTI Mutation				
				Genotypic	Phenotypic (Fold Change)		Genotypic	Phenotypic (Fold Change)			
					RT Mutation	DOR		EFV	RT Mutation	3 TC	FTC
	PDVF	48	1256	Y188L	>181.58R	>120.04R	M184V, M41L	>102.62R	>82.87R	0.78S	NA
	PDVF	48	93	Failed	1.03S	1.01S	Failed	0.95S	1.05S	0.85S	NA
	PDVF	16	1519	None	0.88S	0.86S	None	1.29S	1.19S	0.77S	NA
	PDVF	36	7498	Y318Y/F	0.35S	0.33S	A62V	0.75S	0.82S	0.78S	NA
	PDVF	84	4969	None	0.99S	0.92S	None	1.18S	1.20S	0.89S	NA
	PDVF	48	475	None	0.65S	0.60S	None	1.13	0.96S	0.98S	NA
	PDVF	24	13,380	V106I, F227C, H221H/Y	>102.28R	4.34S	None	3.43S	2.94S	0.45S	NA
	PDVF	96	3736	None	0.42S	0.55S	None	1.13S	0.94S	0.63S	NA
	PDVF	48	110,949	None	1.42S	1.21S	None	1.20S	1.31S	0.82S	NA
	PDVF	36	131	None	1.36S	1.16S	None	1.11S	1.14S	0.87S	NA
	PDVF	24	34,944	A98G, V106V/I, H221H/Y, F227C	>109.90R	30.00R	M184V	>116.24R	>90.30R	0.58S	NA
	PDVF	24	221,864	None	1.10S	0.76S	None	1.12S	1.09S	0.85S	NA
	PDVF	24	14,791	A98A/G, V106V/I, E138E/G, F227C, F227F/C	>97.08R	18.00R	M184V, V75V/I	>107.12R	>83.63R	0.58S	NA
	PDVF	24	106,092	A98A/G, V106A, V106V/A, E128E/G, P225H, P225P/H, Y318Y/F	>210.82R	4.77R	K65R	12.00R	7.71R	1.59 PS	NA
	PDVF	60	1672	None	1.03S	0.84S	None	0.89S	0.85S	0.85S	NA
	PDVF	24	32,799	V106M, V108V/I, V106M/T, F227F/C, F227C/R	>98.16R	11.00R	K65K/R, M184V	>96.85R	>75.97R	0.42S	NA
DRIVE-SHIFT											
	D/C	4	70,410	None	0.95S		None	1.39S		1.14S	
	PDVF	28	534	None	Failed		None	Failed		Failed	
	PDVF	28	490	None	Failed		None	Failed		Failed	

*Data are at week 48 for DRIVE-SHIFT.

†Weeks at PDVF or D/C.

‡Participants treated with DOR 100 mg/d.

ABC, abacavir; D/C, discontinued; NA, not available; ND, test not performed; PS, partially sensitive; R, resistant; S, susceptible; TND, target not detected; VL, viral load.

In the P011 trial, none of the 121 participants met the definition of PDVF at week 24. At week 48, 5% (n = 6/121) of participants met the criteria for PDVF, including 1 nonresponder (DOR + ISL 2.25 mg) and 5 rebounders (DOR + ISL 0.25 mg and DOR + ISL 0.75 mg, n = 2 each; DOR/3 TC/TDF, n = 1); all confirmatory HIV-1 RNA levels were <80 copies/mL (Table 2). No participants met resistance testing criteria.¹⁶

In the DRIVE-FORWARD trial, 9% (n = 34/383) of DOR-treated participants met the criteria for PDVF at week 96 (Table 2). PDVF was defined similarly to that in DRIVE-BEYOND.¹⁷ Most cases [91% (n = 31/34)] were classified as rebounders, and 61% (n = 19/31) had plasma HIV-1 RNA <200 copies/mL at the confirmation visit. Of those with PDVF, 11 had resistance testing performed; an additional 4 participants in the DOR group who discontinued for reasons other than PDVF also underwent resistance testing (Table 3). The remaining participants who met PDVF criteria or who discontinued for other reasons did not meet resistance testing criteria, defined as exhibiting HIV-1 RNA >400 copies/mL.

Among those with PDVF who were tested, 2 DOR-treated participants developed resistance to DOR: 1 with RT V106I, H221Y, and F227C substitutions who discontinued at week 24 because of noncompliance and 1 with RT V106A/P225Y or V106A/P225H double substitution who was lost to follow-up after week 84. Of the 4 participants who discontinued for other reasons and were tested, 1 who discontinued because of nonadherence exhibited viral resistance to DOR (RT V106I, H221Y, and F227C substitutions) and FTC (RT M184V). The second participant, who discontinued because of rash at week 2, was found to be phenotypically resistant (IC₅₀ 2.8 times higher than wild-type virus), but no genotypic resistance-associated mutations to DOR or other NNRTIs were found. No primary genotypic or phenotypic resistance to FTC, TDF, abacavir, or 3 TC was observed.

In the DRIVE-AHEAD trial, 9% (n = 34/364) of DOR-treated participants met PDVF criteria (Table 2), which was defined the same as that in the DRIVE-FORWARD trial.¹⁸ Of these, 82% (n = 28/34) were rebound cases. A total of 35 DOR-

treated participants (22 with PDVF and 13 without PDVF) had samples available for resistance testing (Table 3). Of those with PDVF, 32% (n = 7/22) had DOR-related resistance mutations; 6 isolates were both genotypically and phenotypically resistant to DOR. Among these, 5 isolates showed RT V106 (V106I, V106V/I, V106A, and V106M/T) substitutions in combination with one or more of A98A/G, H221H/Y, P225P/H, F227 (as F227C or F227C/R), or Y318Y/F RT substitutions, and 1 had genotypic resistance conferred through a Y188L substitution alone. One isolate displayed the Y318Y/F DOR resistance-associated RT substitution but did not show phenotypic resistance. Genotypic resistance to 3 TC was also seen in 71% (n = 5/7) of the isolates from DOR-treated participants with resistance mutations who discontinued due to PDVF. Although 1 participant who discontinued at week 4 because of physician decision was shown to have an RT V106I substitution, the virus remained susceptible to DOR. Two participants had virus with genotypic resistance-associated substitutions to 3 TC and TDF.²³

Virologically Suppressed Populations

Participants in the DRIVE-SHIFT trial who were stable for ≥6 months with 2 NRTIs plus a boosted PI, boosted elvitegravir, or an NNRTI were switched to DOR/3 TC/TDF at day 1 or week 24.¹⁹ Overall, 4% (n = 24/656) of participants entered the trial with RT K103N, Y181C, and/or G190A substitutions.¹⁹ Seven participants met the criteria for PDVF: 6 in the immediate-switch group and 1 in the baseline group (after switching to DOR/3 TC/TDF) (Table 2). None of these participants had RT K103N, Y181C, or G190A substitutions at baseline. Two DOR-treated participants in the immediate-switch group had samples that met the threshold criteria for resistance testing (Table 3). No genotypic or phenotypic resistance to DOR, 3 TC, or TDF was identified among participants in the immediate-switch group. The participant in the baseline group who received ritonavir-boosted darunavir, FTC, and TDF displayed an RT M184M/I substitution. Viral drug resistance testing was also performed in 1 participant in the immediate-switch group who discontinued for reasons other than PDVF; no genotypic or phenotypic resistance was observed. Among the 24 participants with baseline NNRTI resistance-associated mutations, 96% (n = 23/24) had HIV-1 RNA <50 copies/mL at week 48: 91% (n = 10/11) in the immediate-switch group (1 participant with HIV-1 RNA <50 copies/mL discontinued on day 29 because of protocol deviation) and 100% (n = 13/13) in the baseline group.¹⁹

DISCUSSION

Extensive preclinical research was conducted to determine the resistance profile of DOR before any clinical investigations. These in vitro studies suggest that multiple substitutions are necessary for the development of DOR resistance, which may explain the low rate of acquired resistance seen with DOR in those participants who met the criteria for resistance testing in clinical trials. Although the proportion of participants that were eligible for resistance testing throughout the DOR clinical development program was dependent on the threshold of reliable quantification for testing (plasma HIV-1 RNA levels >400 copies/mL), overall,

only 7 (0.8%) of 865 treatment-naive participants in the P007, DRIVE-BEYOND, DRIVE-FORWARD, and DRIVE-AHEAD clinical trials, and none who were virologically suppressed (DRIVE-SHIFT), failed with DOR resistance. This includes 6 (1.6%) of 364 DOR-treated participants in the DRIVE-AHEAD trial and 1 (0.3%) of 383 in the DRIVE-FORWARD trial with complete DOR phenotypic resistance (Table 2). A low rate of DOR resistance-associated mutations has also been found in the general population of treatment-naive patients with HIV-1 infection.²⁴ A large European review of resistance samples from treatment-naive patients found that the prevalence of at least 1 DOR resistance-associated mutation was 1.4%, compared with 7.7%, 11.7%, 4.3%, and 4.3% for RPV-associated, etravirine-associated, nevirapine-associated, and EFV-associated mutations, respectively.²⁴ A second trial out of Italy examined the prevalence of DOR resistance-associated mutations in patients for whom an NNRTI had previously failed using the Antiretroviral Response Cohort Analysis database.²⁵ In this NNRTI-experienced population (N = 6893), intermediate-level (defined as detection of any RT V106A/M, Y188C/H, V108I, and K103N + P225H substitution) and high-level (defined as detection of any RT Y188L, M230L, G190E, V106A/M + F227L, and V106A/M + L234I substitutions) DOR resistance was seen in 12.7% and 6.1%, respectively, and the most common high-level DOR resistance-associated substitution was RT Y188L.²⁵ The multivariable analysis showed that EFV and etravirine use were associated with a higher probability of high-level DOR resistance, whereas RPV use was less associated.

The most prevalent DOR resistance-associated substitutions detected among participants with PDVF in DOR clinical trials were substitutions at RT positions 106 (V106A/I/M) and 227 (F227C). This is consistent with in vitro resistance selection studies in which V106A/M preceded emergence of F227C/L/V in RT in most cases.¹³ The RT V106I substitution emerged in 3 participants compared with 1 participant each for V106A and V106M, often in combination with F227C. Nonetheless, available data suggest that RT V106I is a polymorphism rather than a resistance-associated substitution selected by DOR. First and foremost, in vitro studies show that, in contrast to V106A or V106M, V106I does not confer a potency reduction to DOR.⁴ In addition, the presence of RT V106I does not seem to enhance the replicative capacity of viruses isolated from participants with PDVF (Table 4). Moreover, in a resistance analysis among participants with HIV-1 RT V106I viruses at baseline across 3 phase 2/3 DOR clinical trials in treatment-naive participants infected with subtype B virus and treated in combination with 2

TABLE 4. Replication Capacity of DOR-Resistant Clinical Mutants

Clinical Isolate Mutants	Replication Capacity
A98G/F227C/M184V	22%
A98G/V106I/H221Y/F227C/M184V	6.4%
V106A/P225H/Y318F/K65R	103%
V106I/F227C	2.7%
V106I/H221Y/F227C/M184V	40%
V106M/F227C/M184V/K65R	19.4%
Y188L/M184V	6.4%

NRTIs for 48 weeks, 7 (87.5%) of 8 participants treated with DOR, compared with 4 (57.1%) of 7 participants treated with darunavir, achieved HIV-1 RNA <50 copies/mL. It is highly unlikely that the RT V106I substitution confers a higher level of resistance to the PI (darunavir) than the NNRTI (DOR). Notably, a single transitional base change in the codon in subtype B virus is required to convert valine to isoleucine. Thus, the totality of the data suggests that RT V106I is a polymorphism and not a DOR resistance-associated substitution.

There were no treatment-emergent RT K103N, G190A, or Y181C substitutions in any DOR clinical trial; this is in contrast with the EFV group in DRIVE-AHEAD in which 10 of 12 isolates tested exhibited a RT K103N substitution, and the other 2 had an RT G190E substitution.¹⁸ The absence of these treatment-emergent substitutions supports the in vitro profile of DOR that demonstrated activity against the 3 common NNRTI mutations.

Some participants in the DRIVE-SHIFT trial of a virologically suppressed population, and all participants in the DRIVE-BEYOND trial of treatment-naïve participants, had baseline mutations, including the RT K103N, Y181C, and/or G190A substitutions. Nevertheless, viral suppression was achieved and maintained with no viral resistance to DOR seen among participants whose samples could be tested. These results do not preclude the discovery of additional mutations that may reduce susceptibility to DOR, including when present in combination, as may be reported in the Stanford University HIV Drug Resistance Database (<https://hivdb.stanford.edu/cgi-bin/Phenotypes.cgi?Gene=RT>).

Although additional real-world data are needed to confirm the in vitro and clinical trial results, the distinctive spectrum of RT resistance mutations seen to date suggest that DOR is an NNRTI, with activity against HIV-1 viruses with common NNRTI mutations and a unique, clinically relevant resistance profile. Thus, DOR is a viable treatment option for patients with no prior ART experience or to replace the current ART regimen in those who are virologically suppressed.

ACKNOWLEDGMENTS

The authors wish to thank Hong Wan, PhD, of Merck & Co., Inc., Kenilworth, NJ for statistical analysis and Meredith Rogers, MS, CMPP, of The Lockwood Group (Stamford, CT) for editorial assistance.

REFERENCES

- UNAIDS. Fact sheet: global HIV statistics. 2019. Available at: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. Accessed September 20, 2019.
- AIDSinfo. *FDA-approved HIV Medicines*. US Department of Health and Human Services. 2020. Available at: <https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/58/fda-approved-hiv-medicines/>. Accessed March 18, 2020.
- Adams J, Patel N, Mankaryous N, et al. Nonnucleoside reverse transcriptase inhibitor resistance and the role of the second-generation agents. *Ann Pharmacother*. 2010;44:157–165.
- Lai MT, Feng M, Falgoutyret JP, et al. In vitro characterization of MK-1439, a novel HIV-1 nonnucleoside reverse transcriptase inhibitor. *Antimicrob Agents Chemother*. 2014;58:1652–1663.
- EDURANT (Rilpivirine) Tablets, for Oral Use. *Prescribing Information*. Titusville, NJ: Janssen Therapeutics; 2019.
- Hwang C, Lai MT, Hazuda DJ. Rational design of doravirine: from bench to patients. *ACS Infect Dis*. 2020;6:64–73.
- Pham HT, Xiao MA, Principe MA, et al. Pharmaceutical, clinical, and resistance information on doravirine, a novel non-nucleoside reverse transcriptase inhibitor for the treatment of HIV-1 infection. *Drugs Context*. 2020;9:2019-11-4.
- Feng M, Sachs NA, Xu M, et al. Doravirine suppresses common non-nucleoside reverse transcriptase inhibitor-associated mutants at clinically relevant concentrations. *Antimicrob Agents Chemother*. 2016;60:2241–2247.
- Soriano V, de Mendoza C. Genetic mechanisms of resistance to NRTI and NNRTI. *HIV Clin Trials*. 2002;3:237–248.
- Lai MT, Lu M, Felock PJ, et al. Distinct mutation pathways of non-subtype B HIV-1 during in vitro resistance selection with nonnucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother*. 2010;54:4812–4824.
- Hsu A, Isaacson J, Brun S, et al. Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 2003;47:350–359.
- Bbosa N, Kaleebu P, Ssemwanga D. HIV subtype diversity worldwide. *Curr Opin HIV AIDS*. 2019;14:153–160.
- Feng M, Wang D, Grobler JA, et al. In vitro resistance selection with doravirine (MK-1439), a novel nonnucleoside reverse transcriptase inhibitor with distinct mutation development pathways. *Antimicrob Agents Chemother*. 2015;59:590–598.
- Gatell JM, Morales-Ramirez JO, Hagins DP, et al. Doravirine dose selection and 96-week safety and efficacy versus efavirenz in antiretroviral therapy-naïve adults with HIV-1 infection in a phase IIb trial. *Antivir Ther*. 2019;24:425–435.
- Wong A, Goldstein D, Mallolas J, et al. Efficacy and safety of doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) in treatment-naïve HIV-1 infected adults with transmitted non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations. *J Acquir Immune Defic Syndr*. 2019;82:e47–e49.
- Molina JM, Yazdanpanah Y, Saud AA, et al. Islatravir (ISL, MK-8591) at doses of 0.25 to 2.25 mg QD in combination with doravirine maintains viral suppression through 48 weeks in adults with HIV-1 infection. Presented at: 10th IAS Conference on HIV Science; July 21–24, 2019; Mexico City, Mexico.
- Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naïve adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. *Lancet HIV*. 2018;5:e211–e220.
- Orkin C, Squires KE, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naïve adults with human immunodeficiency virus-1 infection: week 48 results of the DRIVE-AHEAD trial. *Clin Infect Dis*. 2018;68:535–544.
- Johnson M, Kumar P, Molina JM, et al. Switching to doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) maintains HIV-1 virologic suppression through 48 weeks: results of the DRIVE-SHIFT trial. *J Acquir Immune Defic Syndr*. 2019;81:463–472.
- DELSTRIGO (Doravirine, Lamivudine, and Tenofovir Disoproxil Fumarate) Tablets, for Oral Use. *Prescribing Information*. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2019.
- PIFELTRO (Doravirine) Tablets, for Oral Use. *Prescribing Information*. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2019.
- Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naïve adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. *Lancet HIV*. 2020;7:e16–e26.
- Orkin C, Squires K, Molina J-M, et al. Doravirine/lamivudine/tenofovir DF continues to be noninferior to efavirenz/emtricitabine/tenofovir DF in treatment-naïve adults with HIV-1 infection: week 96 results of the DRIVE-AHEAD trial [abstract]. *Open Forum Infect Dis*. 2018;5(suppl 1):S759.
- Soulie C, Santoro MM, Charpentier C, et al. Rare occurrence of doravirine resistance-associated mutations in HIV-1-infected treatment-naïve patients. *J Antimicrob Chemother*. 2019;74:614–617.
- Sterrantino G, Borghi V, Callegaro AP, et al. Prevalence of predicted resistance to doravirine in HIV-1-positive patients after exposure to non-nucleoside reverse transcriptase inhibitors. *Int J Antimicrob Agents*. 2019;53:515–519.