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Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial

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Background: Doravirine is a novel, nonnucleoside reverse transcriptase inhibitor with demonstrated efficacy in treatment-naive adults with HIV-1.

Methods: In this open-label, active-controlled, noninferiority trial, adults with HIV-1 virologically suppressed for ≥6 months on 2 nucleoside reverse transcriptase inhibitors plus a boosted protease inhibitor, boosted elvitegravir, or a non-nucleoside reverse transcriptase inhibitor were randomized (2:1) to switch to once-daily, single-tablet doravirine 100 mg with lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg (DOR/3TC/TDF) or to continue their current therapy (Baseline Regimen) for 24 weeks. The primary endpoint was the proportion of participants with HIV-1 RNA <50 copies/mL (defined by the FDA Snapshot approach), with the primary comparison between DOR/3TC/TDF at week 48 and Baseline Regimen at week 24 and a secondary comparison between the groups at week 24 (noninferiority margin, −8%).

Results: Six hundred seventy participants (447 DOR/3TC/TDF, 223 Baseline Regimen) were treated and included in the analyses. At week 24, 93.7% on DOR/3TC/TDF vs 94.6% on Baseline Regimen had HIV-1 RNA <50 copies/mL [difference −0.9 (−4.7 to 3.0)]. At week 48, 90.8% on DOR/3TC/TDF had HIV-1 RNA <50 copies/mL, demonstrating noninferiority vs Baseline Regimen at week 24 [difference −3.8 (−7.9 to 0.3)]. In participants on ritonavir-boosted protease inhibitor at entry, mean reductions in fasting LDL-C and non-HDL-C at week 24 were significantly greater for DOR/3TC/TDF vs Baseline Regimen ($P < 0.0001$). Adverse events occurred in 68.9% on DOR/3TC/TDF and 52.5% on Baseline Regimen by week 24, leading to treatment discontinuation in 2.5% and 0.4%, respectively.

Conclusions: Switching to once-daily DOR/3TC/TDF is a generally well-tolerated option for maintaining viral suppression in patients considering a change in therapy.

Registration: ClinicalTrials.gov NCT02397096.

Key Words: doravirine, HIV-1, treatment-experienced, noninferiority

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INTRODUCTION

Viral suppression greatly reduces the risk of HIV-1 transmission, disease progression, and development of drug-resistant HIV-1 strains.[1] Among persons living with HIV and receiving antiretroviral therapy (ART), only 62%–73% achieve durable viral suppression.[2–4] Adherence to ART is among the key determinants of viral suppression; however, only 53.6% of patients receiving ART report optimal treatment adherence.[5] Poor adherence may be related to adverse drug effects, high pill burden, complex dosing schedules, food requirements, and/or drug–drug interactions. Current treatment guidelines recommend switching treatment-experienced patients receiving complex or poorly tolerated regimens to once-daily regimens to increase adherence, improve quality of life, and reduce the likelihood of virologic failure.[6,7]

Doravirine is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) with the potential to be an important option in the switch setting. Doravirine is active in vitro against the most common NNRTI-resistant variants at concentrations achieved with once-daily dosing[8,9] and has a favorable resistance profile that is unique among NNRTIs.[10] Doravirine can be taken with or without food[11] and can be coadministered with statins, oral contraceptives, and gastric acid modifiers.[12–14] In phase 3 trials in treatment-naive adults with HIV-1 infection, doravirine 100 mg given with 2 nucleoside reverse transcriptase inhibitors (NRTIs) demonstrated noninferior efficacy to ritonavir-boosted darunavir with 2 NRTIs,[15] and doravirine 100 mg in a single-tablet regimen with lamivudine (3TC) 300 mg and tenofovir disoproxil fumarate (TDF) 300 mg (DOR/3TC/TDF) demonstrated noninferior efficacy to efavirenz/emtricitabine/TDF.[16] In both trials, the doravirine regimen demonstrated a favorable lipid profile and was generally well tolerated for up to 48 weeks. Doravirine also demonstrated a superior neuropsychiatric profile compared with efavirenz in 2 randomized controlled trials.[16,17]

METHODS

Study Design

DRIVE-SHIFT (MK-1439A Protocol 024; NCT02397096) is a phase 3, open-label, randomized, active-controlled, noninferiority trial to evaluate switching from a stable antiretroviral regimen to the once-daily, single-tablet regimen DOR/3TC/TDF (see Supplemental Digital Content, http://links.lww.com/QAI/B313). The trial was conducted in conformance with ICH Good Clinical Practice guidelines and applicable regulations regarding the protection of human participants in biomedical research. The protocol was approved by the independent ethics committee for each study site, and all participants provided written informed consent before any study procedures were performed.

Participants were enrolled at 122 hospitals and clinics in Europe, North America, Latin America, and Asia. Adults with HIV-1 and no history of virologic failure were eligible if they had been virologically suppressed for ≥6 months on a stable regimen consisting of a ritonavir- or cobicistat-boosted protease inhibitor (PI) (atazanavir, darunavir, or lopinavir), cobicistat-boosted elvitegravir, or an NNRTI (efavirenz, nevirapine, or rilpivirine), each in combination with 2 NRTIs. Participants receiving an NNRTI were on their first antiretroviral regimen. For participants receiving a boosted PI or boosted elvitegravir as their second antiretroviral regimen, HIV-1 RNA was <40 copies/mL when the first regimen was changed.

At screening, participants were required to have HIV-1 RNA <40 copies/mL (Abbott RealTime Assay) and calculated creatinine clearance ≥50 mL/min (the Cockcroft–Gault equation). Pretreatment HIV-1 genotyping was required for participants receiving a boosted PI or boosted elvitegravir. Exclusion criteria included resistance to doravirine, 3TC, or TDF (see Supplemental Digital Content, http://links.lww.com/QAI/B313), acute hepatitis, decompensated liver disease, liver cirrhosis, and use of systemic immunosuppressive therapy or immune modulators within 30 days before study treatment. Participants using lipid-lowering agents had to be on a stable dose at enrollment.

Procedures

Randomization was determined by a computer-generated allocation schedule and stratified by antiretroviral class used in the baseline regimen (ritonavir-boosted PI vs cobicistat-boosted PI vs either cobicistat-boosted elvitegravir or an NNRTI) and by use of lipid-lowering therapy (yes/no) for participants receiving ritonavir-boosted PI. Participants were randomly assigned (2:1) to switch to DOR/3TC/TDF on day 1 [Immediate Switch Group (ISG)] or to continue their baseline regimen until week 24 and then switch to DOR/3TC/TDF [Delayed Switch Group (DSG)]. DOR/3TC/TDF was taken orally once daily at approximately the same time each day and without regard to food. Each participant completed a medication diary to document adherence to study therapy. Changes in study therapy dosage were not allowed, although study therapy could be interrupted for toxicity management.

Plasma HIV-1 RNA quantification was performed at all visits by the central laboratory using the Abbott RealTime HIV-1 assay. CD4$^+$ T-cell count (absolute and percentage) was determined at day 1 and weeks 12, 24, 36, and 48 by the central laboratory using standard procedures.

Protocol-defined virologic failure (PDVF) was defined as 2 consecutive measurements of HIV-1 RNA ≥50 copies/mL at least 1 week apart. Participants with confirmed PDVF were discontinued from the trial, regardless of adherence to study therapy. Viral drug resistance testing was performed for participants with confirmed PDVF and for those who discontinued early for other reasons, if their HIV-1 RNA was >400 copies/mL. For this analysis, postbaseline genotypic viral resistance to DOR was defined as any of the following mutations in the RT gene: A98G, L100I, K101E, V106A, V106I, V106M, V108I, E138K, Y188L, G190A, G190S, H221Y, P225H, F227C, F227L, F227V, M230I, M230L, L234I, P236L, and Y318F. Postbaseline genotypic and phenotypic resistance to 3TC and TDF was assessed by Monogram Biosciences. Because the threshold for phenotypic resistance to DOR has not yet been defined, a 2.5-fold change

in IC50 vs wild-type virus was used as a broad assay reproducibility threshold for potential phenotypic resistance to DOR.

Primary and Secondary Outcome Measures

The primary efficacy outcome was the proportion of participants with HIV-1 RNA <50 copies/mL [as defined by the Food and Drug Administration (FDA) Snapshot approach], with the primary comparison at week 48 in the DOR/3TC/TDF ISG vs week 24 in the Baseline Regimen DSG. Because the longer assessment period for the DOR/3TC/TDF ISG could lead to more nontreatment-related dropouts (which are counted as treatment failures), an additional efficacy comparison was performed based on the week 24 assessments for both groups; this secondary analysis was not included in the multiplicity strategy.

Other measurements for efficacy included the proportion of participants with HIV-1 RNA ≥50 copies/mL, the change from baseline in CD4$^+$ T-cell counts, and the development of viral resistance to study drugs. Safety evaluations included the change from baseline in fasting serum lipids (in participants whose regimen at screening was a ritonavir-boosted PI), the incidence of adverse events (AEs), and changes in laboratory safety tests (hematology and chemistry). Laboratory values were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric AEs (Version 2.0, November 2014), and an increase in grade from baseline was classified as a laboratory abnormality.

Statistical Analysis

All randomized participants who received at least 1 dose of study therapy were included in the efficacy analyses, which used the FDA Snapshot approach (all missing data were treated as failures regardless of the reason). The difference between treatment groups in the proportion of participants with HIV-1 RNA <50 copies/mL and the associated 95% confidence interval (CI) were calculated using the stratum-adjusted Mantel–Haenszel method. If the lower bound of the 2-sided 95% CI was above −8 percentage points, switching to DOR/3TC/TDF was considered noninferior to the baseline regimen. With 440 participants in the DOR/3TC/TDF ISG and 220 in the Baseline Regimen DSG, the study had 80% power to demonstrate the primary hypothesis that switching to DOR/3TC/TDF through 48 weeks is noninferior to continuing the baseline regimen through 24 weeks, at an overall 1-sided 2.5% alpha level and assuming a true response rate of 85% for both treatment groups.

To evaluate the consistency of the virologic response, the difference between treatment groups (with a nominal, unadjusted 95% CI) was calculated for subgroups based on age (≤median, >median), sex, geographic region, race, ethnicity, hepatitis B or C coinfection, baseline CD4$^+$ T-cell count (<200 cells/mm^3, ≥200 cells/mm^3), antiretroviral class in the baseline regimen, duration of previous antiretroviral regimen (≥12 months, <12 months), and history of NNRTI-class mutations (K103N, Y181C, or G190A in participants receiving a boosted PI or elvitegravir at baseline).

The proportion of participants with HIV-1 RNA ≥50 copies/mL (as defined by the FDA Snapshot approach) was also analyzed at both comparison time points, consistent with recent FDA guidance on assessment of noninferiority in antiretroviral switch trials.[18] For this endpoint, a margin of 4 percentage points was used to assess the noninferiority of a switch to DOR/3TC/TDF through 48 weeks compared with continuation of the baseline regimen through 24 weeks.

For participants whose baseline regimen included a ritonavir-boosted PI, the change in fasting lipids from baseline to week 24 was analyzed using analysis of covariance models adjusted by the baseline lipid level, use of lipid-lowering therapy, and treatment group. If noninferiority for the primary efficacy analysis was established, the hypotheses on fasting low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) were tested sequentially. For participants with missing lipid data, the last lipid observation after randomization was carried forward. If lipid-lowering therapy was modified during the study, the last lipid measurement before the modification was carried forward.

RESULTS

Of 852 individuals screened between June 17, 2015 and February 10, 2017, 450 were randomized to the DOR/3TC/TDF ISG and 223 to the Baseline Regimen DSG; 447 and 223 participants, respectively, received at least 1 dose of study therapy and were included in the efficacy and safety analyses. Demographics and baseline clinical characteristics were balanced between the treatment groups (Table 1). The study population was primarily men (84.5%) and white (76.4%), with a median age of 43 years (range, 21–71). At baseline, 70.4% of participants were receiving a boosted-PI regimen, and the median CD4$^+$ T-cell count was 628 cells/mm^3 (range, 82–1928). Sixty-one participants discontinued study therapy by week 48: 40 (8.9%) from the ISG and 21 (9.4%) from the DSG. The most common reasons for early discontinuation were AEs and withdrawal of consent (Fig. 1).

Efficacy

At week 24, the proportion of participants with HIV-1 RNA <50 copies/mL was 93.7% (419/447) in the DOR/3TC/TDF ISG and 94.6% (211/223) in the Baseline Regimen DSG (Fig. 2, Panel A). At week 48, HIV-1 RNA <50 copies/mL was maintained in 90.8% (406/447) of the DOR/3TC/TDF ISG (Fig. 2, Panel B), demonstrating that switching to DOR/3TC/TDF is noninferior to continuing the baseline regimen for 24 weeks [difference (95% CI), −3.8 (−7.9 to 0.3)]. Of the 209 participants in the Baseline Regimen DSG who switched to DOR/3TC/TDF at week 24, 198 (94.7%) had HIV-1 RNA <50 copies/mL at week 48 (see Supplemental Digital Content, http://links.lww.com/QAI/B313).

TABLE 1. Baseline Demographics and Clinical Characteristics

	Immediate Switch (N = 447)	Delayed Switch (N = 223)
Age (yrs), median (range)	43 (21–71)	42 (22–71)
Male, n (%)	372 (83.2)	194 (87.0)
Race/ethnicity, n (%)		
White	344 (77.0)	168 (75.3)
Black or African American	56 (12.5)	34 (15.2)
Asian	17 (3.8)	8 (3.6)
Other race*	30 (6.7)	13 (5.8)
Hispanic or Latino ethnicity	99 (22.1)	45 (20.2)
Region, n (%)		
Asia/Pacific	19 (4.3)	12 (5.4)
Europe	268 (60.0)	137 (61.4)
Latin America	49 (11.0)	24 (10.8)
North America	111 (24.8)	50 (22.4)
CD4+ T-Cell count		
Median (range), cells/mm^3	633 (82–1928)	625 (140–1687)
<200 cells/mm^3, n (%)	13 (2.9)	4 (1.8)
≥200 cells/mm^3, n (%)	426 (95.3)	216 (96.9)
Previous ART regimen, n (%)		
Boosted PI	316 (70.7)	156 (70.0)
Darunavir	166 (37.1)	82 (36.8)
Atazanavir	96 (21.5)	43 (19.3)
Lopinavir	54 (12.1)	31 (13.9)
Cobicistat-boosted elvitegravir	25 (5.6)	12 (5.4)
NNRTI	106 (23.7)	55 (24.7)
Efavirenz	78 (17.4)	36 (16.1)
Nevirapine	17 (3.8)	12 (5.4)
Rilpivirine	11 (2.5)	7 (3.1)
Coadministered NRTIs, n (%)		
TDF/FTC	330 (73.8)	154 (69.1)
TAF/FTC	22 (4.9)	11 (4.9)
TDF/3TC	10 (2.2)	10 (4.5)
ABC/3TC	61 (13.6)	28 (12.6)
ZDV/3TC	23 (5.1)	19 (8.5)
Duration of previous regimen		
Median (range), mo	48.4 (7–265)	50.5 (7–181)
≥12 months, n (%)	421 (94.2)	211 (94.6)
RT K103N, Y181C, and/or G190A†	11 (2.5)	13 (5.8)
History of AIDS, n (%)	80 (17.9)	35 (15.7)
Hepatitis B and/or C,‡ n (%)	14 (3.1)	9 (4.0)

*Other races include multiracial, American Indian, and Alaska Native.

†NNRTI mutations on pre-ART genotype in participants on a boosted PI or elvitegravir regimen; number of participants with specific mutations by the treatment group (ISG, DSG): K103N (7, 11), Y181C (2, 0), G190A (1, 1), K103N/Y181C (0, 1), Y181C/G190A (1, 0).

‡Evidence of hepatitis B surface antigen or hepatitis C virus RNA.

Across subgroups defined by demographics and baseline clinical characteristics, the antiretroviral efficacy of DOR/3TC/TDF at week 24 was comparable to that of the baseline regimen at week 24 (Fig. 3), consistent with the overall results. Virologic response rates in the DOR/3TC/TDF ISG were high regardless of the previous regimen: 93.0%, 100%, and 94.3%, respectively, in participants switched from boosted PIs, boosted elvitegravir, or NNRTIs. The efficacy of DOR/3TC/TDF at week 48 was also comparable to the baseline regimen at week 24 across demographics and baseline clinical characteristics (see Supplemental Digital Content, http://links.lww.com/QAI/B313).

Eleven participants in the DOR/3TC/TDF ISG had NNRTI resistance mutations at baseline: 10 (90.9%) were virologically suppressed at week 48, and 1 discontinued on day 29 (due to protocol deviation) with HIV-1 RNA <50 copies/mL. Thirteen participants in the Baseline Regimen DSG had NNRTI resistance mutations at baseline; 12 of these participants switched to DOR/3TC/TDF at week 24: 11 (91.7%) were virologically suppressed at week 48, and 1 discontinued on day 262 (due to noncompliance) with HIV-1 RNA <50 copies/mL on day 195 (last available measurement).

The proportion of participants with HIV-1 RNA ≥50 copies/mL was 1.8% in both treatment groups at week 24 (Figs. 2) and 1.6% in the DOR/3TC/TDF ISG at week 48 (the primary comparison time point), supporting the noninferiority of switching to DOR/3TC/TDF [difference −0.2 (−2.5 to 2.1) vs the baseline regimen at week 24]. The mean change from baseline in CD4+ T-cell count was minimal: +5 cells/mm^3 in the DOR/3TC/TDF ISG and +18 cells/mm^3 in the Baseline Regimen DSG at week 24, and +14 cells/mm^3 in the DOR/3TC/TDF ISG at week 48.

Eight participants met criteria for PDVF: 6 in the DOR/3TC/TDF ISG, 1 in the Baseline Regimen DSG, and 1 in the DSG after switching to DOR/3TC/TDF; none of these participants had RT K103N, Y181C, and/or G190A mutations at baseline. Three participants with PDVF (2 in the DOR/3TC/TDF ISG and 1 in the Baseline Regimen DSG) had samples with HIV-1 RNA >400 copies/mL available for resistance testing. Neither ISG participant developed genotypic or phenotypic resistance to DOR, 3TC, or TDF. The DSG participant (who was receiving ritonavir-boosted DRV, FTC, and TDF) showed genotypic and phenotypic resistance to 3TC and FTC (conferred through RT M184M/I) at week 12. Viral drug resistance testing was also performed for 3 participants (1 in the DOR/3TC/TDF ISG and 2 in the Baseline Regimen DSG) who discontinued early without PDVF. None of these participants developed genotypic or phenotypic resistance to any component of the study therapy.

Safety and Tolerability

During weeks 0–24, AEs were reported by 68.9% of the DOR/3TC/TDF ISG and 52.5% of the Baseline Regimen DSG. In both groups, the majority of participants with AEs rated the maximum intensity as mild (64.3% and 59.0%, respectively). The most frequently reported AEs were nasopharyngitis and headache (Table 2). AEs that were considered drug-related were reported during weeks 0–24 in 19.5% of the DOR/3TC/TDF ISG and 2.2% of the Baseline Regimen DSG; none of the specific drug-related AEs occurred in ≥2% of either group. Among participants in the DSG who switched to DOR/3TC/TDF at week 24, the AE profile during weeks 24–48 was similar to that reported for the DOR/3TC/TDF ISG during weeks 0–24 (Table 2).

Rates of serious AEs were low in both treatment groups during weeks 0–24 and during weeks 24–48 (Table 2). A total
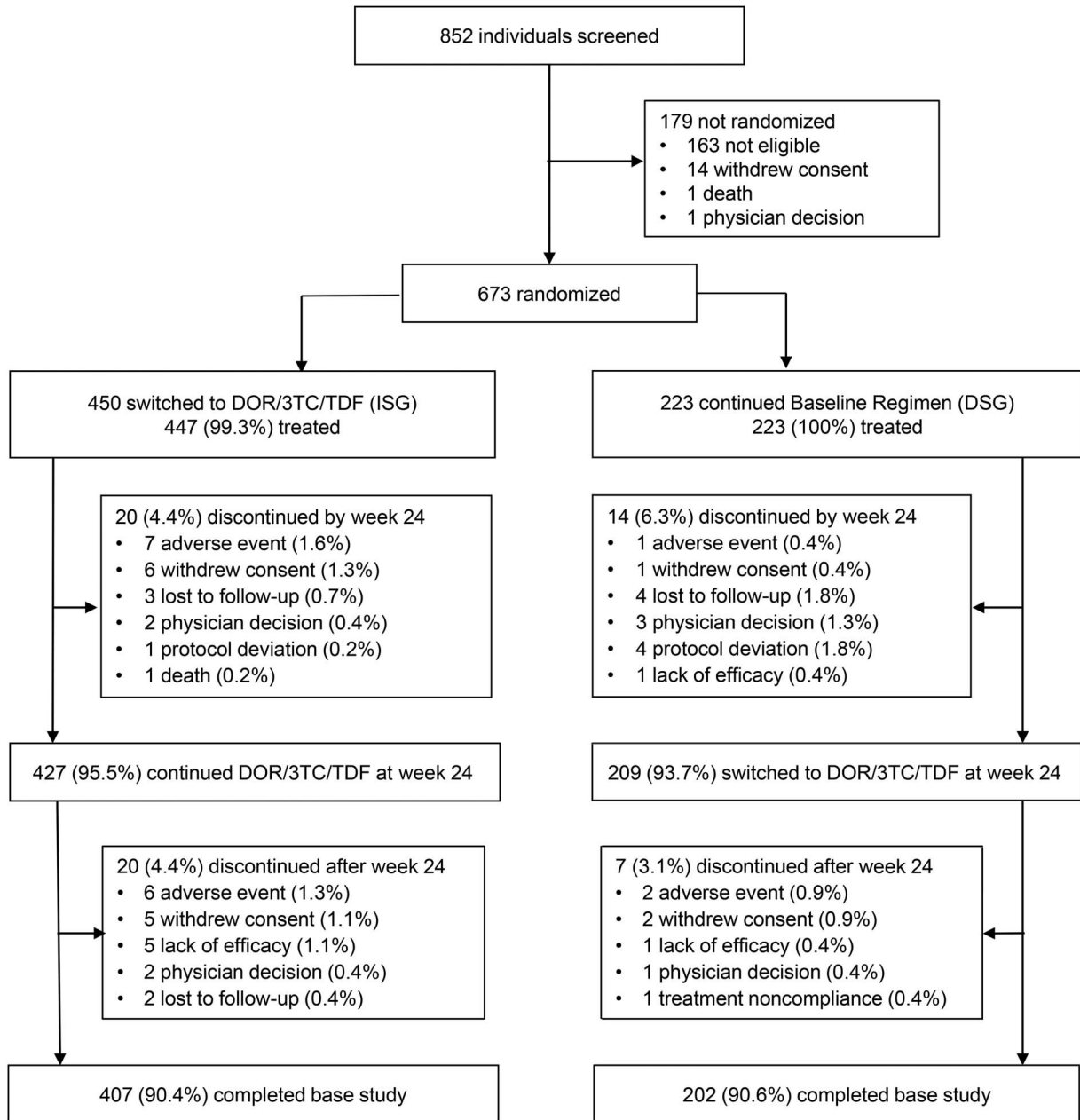
FIGURE 1. Trial profile. DOR/3TC/TDF, doravirine/lamivudine/tenofovir disoproxil fumarate. Baseline Regimen = 2 NRTIs with a boosted PI, boosted elvitegravir, or an NNRTI. Percentages are based on the number of participants randomized (450 to ISG and 223 to DSG).

of 5 participants had serious AEs that were considered related to DOR/3TC/TDF: depression, increased lipase (grade 4), concurrent elevations in alanine aminotransferase (ALT) (grade 3) and aspartate aminotransferase (AST) (grade 2), concurrent elevations in amylase and lipase (both grade 4), and renal failure. The elevated ALT and AST resolved with no change in therapy. In the other 4 participants, the study drug was discontinued and the serious AEs resolved, except for increased lipase in 1 participant (see Supplemental Digital Content, http://links.lww.com/QAI/B313). No deaths were reported during the study among randomized participants.

Rates of treatment discontinuation due to AEs were low in both treatment groups during weeks 0–24 and during weeks 24–48 (Table 2). These events were considered related to DOR/3TC/TDF in 13 participants. The most common AEs causing discontinuation were increased transaminase levels (ALT, AST, or both; 4 participants) and increased lipase (3 participants, none with pancreatitis). Most AEs that led to discontinuation of DOR/3TC/TDF had resolved or were resolving at the last study contact (see Supplemental Digital Content, http://links.lww.com/QAI/B313).
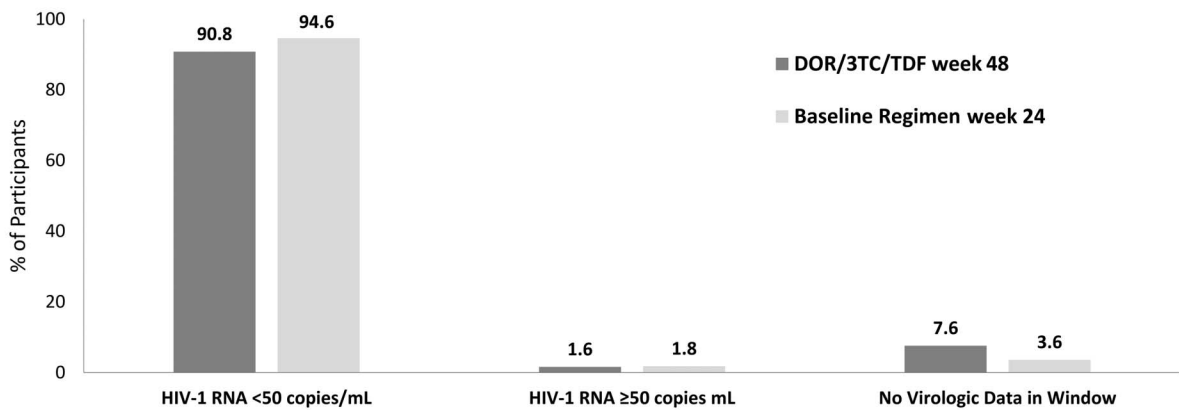
DOR/3TC/TDF week 24 vs Baseline Regimen week 24
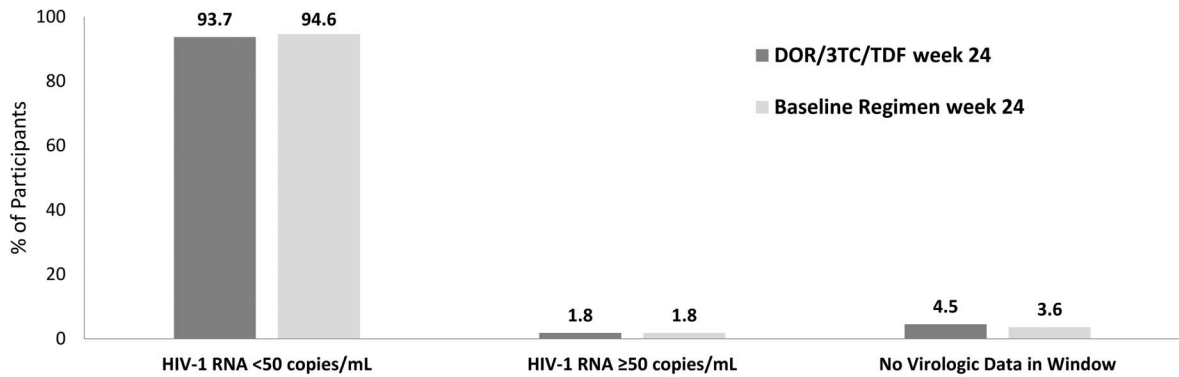
Difference (95% CI):	-0.9% (-4.7, 3.0)†	-0.0% (-2.3, 2.3)‡

† DOR/3TC/TDF is noninferior (not adjusted for multiplicity) to the Baseline Regimen if the lower bound of the 95% CI is above -8 percentage points.
‡ DOR/3TC/TDF is noninferior (not adjusted for multiplicity) to the Baseline Regimen if the upper bound of the 95% CI is below 4 percentage points.

DOR/3TC/TDF week 48 vs Baseline Regimen week 24

Difference (95% CI):	-3.8% (-7.9, 0.3)†	-0.2% (-2.5, 2.1)‡

† DOR/3TC/TDF is noninferior to the Baseline Regimen if the lower bound of the 95% CI is above -8 percentage points.
‡ DOR/3TC/TDF is noninferior (not adjusted for multiplicity) to the Baseline Regimen if the upper bound of the 95% CI is below 4 percentage points.

FIGURE 2. Virologic outcomes (the FDA Snapshot approach). DOR/3TC/TDF, doravirine/lamivudine/tenofovir disoproxil fumarate. Baseline Regimen = 2 NRTIs with a boosted PI, boosted elvitegravir, or an NNRTI.

In participants whose baseline regimen included a ritonavir-boosted PI, the mean change in fasting LDL-C and non-HDL-C from baseline to week 24 was significantly different ($P < 0.0001$) between the treatment groups (Fig. 4). Fasting cholesterol and fasting triglyceride levels were also substantially reduced among participants in the DOR/3TC/TDF ISG (Fig. 4). The mean change in the total cholesterol:HDL-C ratio was −0.44 in the DOR/3TC/TDF ISG and −0.57 in the Baseline Regimen DSG. Lipid-lowering therapy was started or changed (agent or dose) during the first 24 weeks of the study in 1.3% of participants receiving DOR/3TC/TDF and 2.7% receiving the baseline regimen.

The incidence of grade 3 or 4 laboratory abnormalities through week 24 was generally similar between the treatment groups (Table 2). Five participants in the Baseline Regimen

DSG experienced a grade 3 increase in bilirubin; all 5 were receiving ritonavir-boosted atazanavir. The laboratory profile for the DSG after switching to DOR/3TC/TDF was similar to that for the ISG during weeks 0–24. No participants in either treatment group had laboratory values that met the criteria for potential drug-induced liver injury (ALT or AST ≥3 × ULN plus bilirubin ≥2 × ULN and alkaline phosphatase <2 × ULN).

DISCUSSION

This randomized, open-label, phase 3 trial demonstrated the efficacy and safety of switching from a stable antiretroviral regimen to a single-tablet, fixed-dose regimen of DOR/3TC/TDF in virologically suppressed adults with HIV-

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	DOR/3TC/TDF n/N	DOR/3TC/TDF %	Baseline Regimen n/N	Baseline Regimen %	Difference in Percent Response, % (95% CI)
All participants	419/447	93.7	211/223	94.6	
Baseline CD4+ T-cell count					
< 200 cells/mm^3	12/13	92.3	3/4	75.0	
≥ 200 cells/mm^3	400/426	93.9	205/216	94.9	
Baseline ART regimen					
Boosted PI	294/316	93.0	147/156	94.2	
Boosted elvitegravir	25/25	100	11/12	91.7	
NNRTI	100/106	94.3	53/55	96.4	
Duration of previous regimen					
< 12 months	23/26	88.5	12/12	100	
≥ 12 months	396/421	94.1	199/211	94.3	
History of NNRTI mutations					
K103N, Y181C, or G190A	10/11	90.9	13/13	100	
HBV or HCV Coinfection					
Positive	12/14	85.7	9/9	100	
Negative	407/433	94.0	202/214	94.4	

Scale: -50 -30 -10 10 30 50
Favors Baseline Regimen ← → Favors DOR/3TC/TDF

B
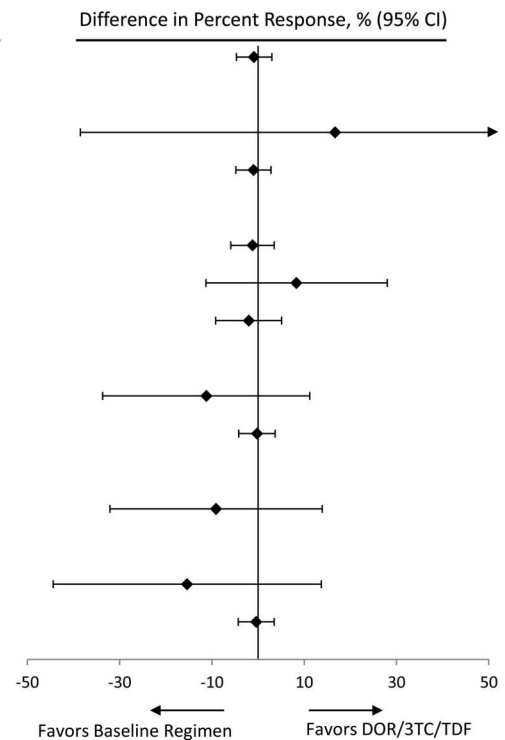
	DOR/3TC/TDF n/N	DOR/3TC/TDF %	Baseline Regimen n/N	Baseline Regimen %	Difference in Percent Response, % (95% CI)
All participants	419/447	93.7	211/223	94.6	
Age					
≤ Median (43y)	210/230	91.3	110/118	93.2	
> Median (43y)	209/217	96.3	101/105	96.2	
Gender					
Male	348/372	93.5	182/194	93.8	
Female	71/75	94.7	29/29	100	
Race/Ethnicity					
Asian	16/17	94.1	7/8	87.5	
Black	51/56	91.1	31/34	91.2	
White	323/344	93.9	160/168	95.2	
Hispanic/Latino	92/99	92.9	41/45	91.1	
Region					
Asia/Pacific	18/19	94.7	12/12	100	
Europe	253/268	94.4	130/137	94.9	
Latin America	45/49	91.8	23/24	95.8	
North America	103/111	92.8	46/50	92.0	

Scale: -50 -30 -10 10 30 50
Favors Baseline Regimen ← → Favors DOR/3TC/TDF
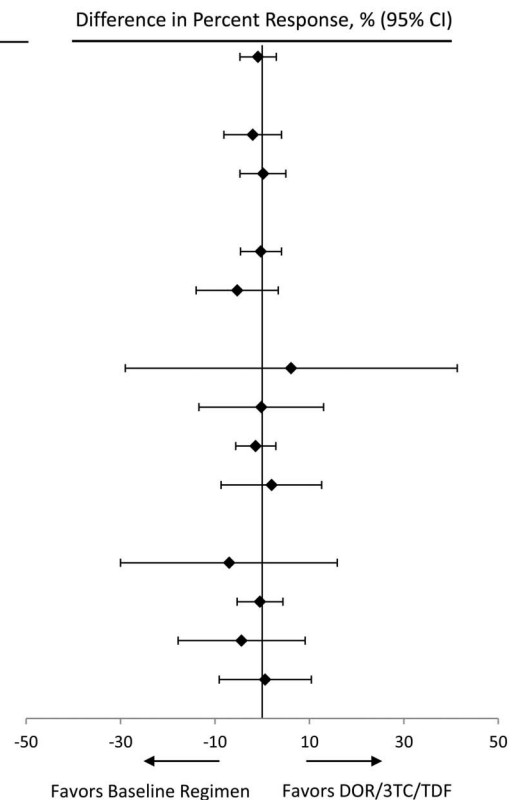
FIGURE 3. Proportion of participants with HIV-1 RNA <50 copies/mL at week 24 (the FDA Snapshot approach) by prognostic factors (A) and demographic factors (B).

TABLE 2. AEs and Laboratory Abnormalities

No. (%) of participants with:	ISG Week 0–24 DOR/3TC/TDF (N = 447)	DSG Week 0–24 Baseline Regimen (N = 223)	DSG Week 24–48 DOR/3TC/TDF (N = 209)	ISG Week 24–48 DOR/3TC/TDF (N = 427)
Any AE	308 (68.9)	117 (52.5)	126 (60.3)	253 (59.3)
Drug-related* AE	87 (19.5)	5 (2.2)	29 (13.9)	24 (5.6)
Serious AE	13 (2.9)	8 (3.6)	4 (1.9)	10 (2.3)
Serious drug-related AE	2 (0.4)	0 (0.0)	1 (0.5)	2 (0.5)
AE resulting in discontinuation†	11 (2.5)	1 (0.4)	4 (1.9)	6 (1.4)
Drug-related AE resulting in discontinuation†	7 (1.6)	0 (0.0)	4 (1.9)	4 (0.9)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most common AEs (incidence ≥5% in any group)				
Nasopharyngitis	33 (7.4)	12 (5.4)	9 (4.3)	19 (4.4)
Headache	29 (6.5)	5 (2.2)	14 (6.7)	12 (2.8)
Most common drug-related AEs (incidence ≥2% in any group)				
Headache	7 (1.6)	1 (0.4)	5 (2.4)	0 (0.0)
Most common grade 3 or 4 laboratory abnormalities, (incidence ≥1% in any group)				
LDL cholesterol mg/dL, grade 3	0/372 (0.0)	3/184 (1.6)	0/176 (0.0)	1/357 (0.3)
Total cholesterol mg/dL, grade 3	0/391 (0.0)	2/197 (1.0)	0/184 (0.0)	0/377 (0.0)
Triglycerides mg/dL, grade 3	1/391 (0.3)	2/197 (1.0)	1/184 (0.5)	1/377 (0.3)
Glucose mg/dL, grade 3	1/395 (0.3)	2/197 (1.0)	0/184 (0.0)	0/378 (0.0)
Total bilirubin mg/dL, grade 3	0/444 (0.0)	5/221 (2.3)	0/208 (0.0)	0/424 (0.0)
Alanine aminotransferase IU/L, grade 4	0/444 (0.0)	0/221 (0.0)	2/208 (1.0)	0/424 (0.0)
Lipase IU/L, grade 3	4/444 (0.9)	1/221 (0.5)	2/208 (1.0)	5/424 (1.2)
Creatine kinase IU/L, grade 3	3/444 (0.7)	3/221 (1.4)	0/208 (0.0)	0/424 (0.0)

The DSG continued their baseline regimen until time of switch to DOR/3TC/TDF (week 24). Baseline Regimen = ritonavir or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or NNRTI, each administered with 2 NRTIs.

*Determined by the investigator to be related to study therapy.

†Two participants in the ISG are counted in weeks 0–24 and in weeks 24–48 because their discontinuation was the result of AEs that occurred in both periods (see Supplemental Digital Content, http://links.lww.com/QAI/B313).

1 infection. Participants who received DOR/3TC/TDF for up to 48 weeks showed high rates of virologic suppression with low rates of virologic failure and discontinuation related to AEs. An open-label study design was chosen to reduce dosing complexity and to allow for evaluation of the acceptability of a single-tablet regimen. Because participants had been virologically suppressed for at least 6 months before enrollment, a treatment duration of 48 weeks after switching was considered important for evaluating the safety and tolerability of DOR/3TC/TDF and its durability in maintaining viral suppression. Because participants randomized to continue their baseline regimen might not be willing to wait 48 weeks before switching, this group was designated to switch at week 24. Thus, the primary efficacy analysis compared week 48 for DOR/3TC/TDF with week 24 for the baseline regimen. A secondary comparison was performed at week 24 for both treatment groups to assess the virologic response at the same duration of follow-up for both regimens.

Based on the proportion of participants with HIV-1 RNA <50 copies/mL at week 24, switching to DOR/3TC/TDF was comparable with continuation of the baseline regimen (93.7% vs 94.6%). After an additional 24 weeks, virologic suppression was maintained in 90.8% of participants receiving DOR/3TC/TDF, demonstrating the noninferior efficacy of DOR/3TC/TDF at week 48 compared with the baseline regimen at week 24. The difference in response rates for the primary comparison was mainly due to missing data for nonvirologic reasons (7.6% vs 3.6%), including discontinuations due to AEs. This imbalance reflects, in part, the opportunity for additional events to occur in the DOR/3TC/TDF ISG because of the longer evaluation period (48 weeks).

After this trial began, the recommended primary endpoint in FDA guidance for HIV switch trials[18] was changed to HIV-1 RNA ≥50 copies/mL, which was a secondary endpoint in this trial. Switching to DOR/3TC/TDF was comparable with continuation of the baseline regimen with respect to this endpoint: 1.8% of both groups had HIV-1 RNA ≥50 copies/mL at week 24, as did 1.6% of the DOR/3TC/TDF ISG at week 48.

The results for both virologic suppression and virologic rebound in this trial are similar to the week 48 results of other open-label switch trials, such as the STRIIVING study of
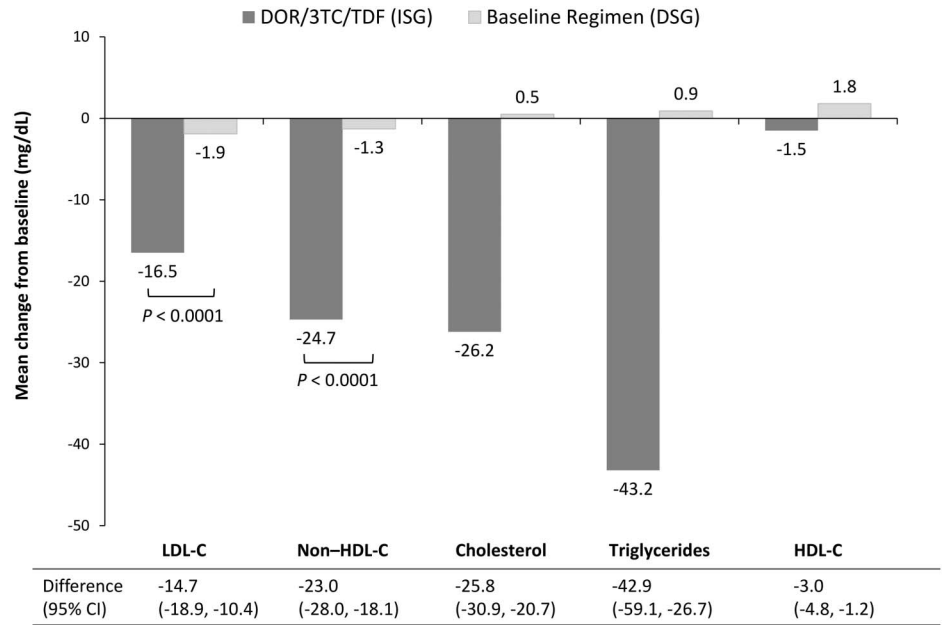
FIGURE 4. Mean change from baseline in fasting lipid levels at week 24, in participants receiving a ritonavir-boosted PI regimen at study entry. DOR/3TC/TDF, doravirine/lamivudine/tenofovir disoproxil fumarate. ISG (N = 266). DSG (N = 133). Baseline Regimen = ritonavir-boosted PI with 2 NRTIs.

	LDL-C	Non–HDL-C	Cholesterol	Triglycerides	HDL-C
Difference (95% CI)	-14.7 (-18.9, -10.4)	-23.0 (-28.0, -18.1)	-25.8 (-30.9, -20.7)	-42.9 (-59.1, -26.7)	-3.0 (-4.8, -1.2)

abacavir/dolutegravir/lamivudine (83% with HIV-1 RNA <50 copies/mL, <1% with HIV-1 RNA ≥50 copies/mL),[19] the EMERALD study of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (94.9% and 2.5%, respectively),[20] and the GS-US-380-1878 study of bictegravir/emtricitabine/tenofovir alafenamide (92% and 2%, respectively).[21]

Very few participants (7/676) met the criteria for PDVF after switching to DOR/3TC/TDF, and no viral resistance to DOR was identified in the participants whose samples could be tested. At study entry, 24 participants had virus with NNRTI resistance mutations K103N, Y181C, and/or G190A; of the 23 who switched to DOR/3TC/TDF, 21 remained suppressed through week 48 and 2 discontinued early for other reasons but were suppressed at their last study visit. These clinical findings are consistent with the in vitro activity of doravirine.

Switching to DOR/3TC/TDF demonstrated a superior lipid profile compared with continuation of a ritonavir-boosted PI-based regimen, with a statistically significant difference between the treatment groups for both LDL-C and non-HDL-C at week 24 ($P < 0.0001$). Previous studies have shown that DOR is lipid neutral in treatment-naive adults,[15,16] whereas boosted PIs are associated with increased lipid levels.[22] This trial shows that switching from a boosted PI to DOR/3TC/TDF improves lipid profiles.

DOR/3TC/TDF was generally well tolerated for up to 48 weeks, with no deaths and low rates of serious AEs and discontinuation due to AEs. Compared with participants who continued their baseline regimen, participants who switched to DOR/3TC/TDF had higher rates of any AE (68.9% vs 52.5%) and of treatment-related AEs (19.5% vs 2.2%) at week 24. The higher AE rates in the DOR/3TC/TDF group are not unexpected because these participants switched to a new treatment regimen, whereas participants in the Baseline Regimen group continued on the same therapy they had received for at least 6 months before entering this trial. In addition, because the participants were not blinded to whether they received the new regimen, ascertainment bias may have contributed to the difference in AE rates. Other antiretroviral switch studies have also found that participants who switched to a new regimen reported more drug-related AEs than those who continued their previous regimen, particularly when the trial was not blinded.[19–21,23]

Despite the high incidence of AEs reported, only 2% of participants (13/656) discontinued DOR/3TC/TDF because of AEs that were considered treatment related. Overall, the safety profile of DOR/3TC/TDF in treatment-experienced participants who switched to this regimen was consistent with the safety profile observed in the treatment-naive trials, DRIVE-FORWARD and DRIVE-AHEAD,[15,16] although the rate of drug-related AEs in the current trial (19.5%) was lower than in treatment-naive participants (31%).

In summary, switching to DOR/3TC/TDF was non-inferior to continuation of the previous regimen in virologically suppressed adults with HIV-1, with high rates of virologic suppression and low rates of virologic rebound. No resistance to DOR developed in either treatment group. DOR/3TC/TDF demonstrated a favorable safety profile over 48 weeks of treatment, and switching to DOR/3TC/TDF was associated with a favorable lipid profile compared with a boosted-PI regimen. These results show that switching to once-daily DOR/3TC/TDF is an effective and generally well-tolerated option for maintaining viral suppression in patients considering a change in therapy.

ACKNOWLEDGMENTS

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