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Long-term Treatment Efficacy and Safety Following Switch to Doravirine/ Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF): Week 144 Results of the DRIVE-SHIFT Trial

Princy Kumar[1]; Margaret Johnson[2]; Jean-Michel Molina[3]; Giuliano Rizzardini[4]; Pedro Cahn[5]; Markus Bickel[6]; Hong Wan[7]; Cristiana Morais[7]; Peter Sklar[7]; Wayne Greaves[7] for the DRIVE-SHIFT Study Group

[1]Georgetown University, Washington DC, USA; [2]Royal Free Hospital, London, UK; [3]University of Paris Diderot and Hôpital Saint-Louis, Paris, France; [4]Fatebenefratelli Sacco Hospital, Milan, Italy; [5]Fundación Huesped, Buenos Aires, Argentina; [6]Infektiologikum, Frankfurt, Germany; [7]Merck & Co., Inc., Kenilworth, NJ, USA

Background

- Viral suppression is a key treatment goal in people living with HIV
  - Virological failure is associated with a number of factors, including poor adherence, adverse drug effects, high pill burden/dosing frequency and viral drug resistance[1]
- Current treatment guidelines also recommend considering ART switch in treatment-experienced patients in order to simplify treatment regimens or to improve tolerability[1]
- Doravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV-1 in adults with no prior ART or as maintenance ART in treatment-experienced adults with virological suppression (HIV-1 RNA <50 copies/mL) on a stable ART regimen with no history of treatment failure and no known substitutions associated with resistance to doravirine[2,3]
  - Doravirine is administered either as 100 mg once-daily oral tablet in combination with other antiretroviral agents,[2] or as part of a once-daily fixed-dose combination tablet of doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg (DOR/3TC/TDF)[3]
- Doravirine demonstrated non-inferior efficacy and was associated with favourable safety and lipid profiles in two Phase 3 trials of doravirine in treatment-naïve people living with HIV-1 versus comparator regimens[4,5]
- The DRIVE-SHIFT trial evaluated switching from a stable antiretroviral regimen to once-daily DOR/3TC/TDF in adults with ≥6 months' virological suppression and no previous virological failure[6]
  - Week 48 data demonstrated non-inferior efficacy of switch to DOR/3TC/TDF in participants with virological suppression on ART versus remaining on baseline ART
  - DOR/3TC/TDF had a superior lipid profile versus baseline ritonavir-containing regimens and was generally well tolerated
- Here we report the long-term (up to 144 weeks) efficacy and safety of switch to maintenance DOR/3TC/TDF in the DRIVE-SHIFT trial

Methods

Trial design

- DRIVE-SHIFT (MK-1439A-024; NCT02397096) is a Phase 3, multi-centre, open-label, randomised, active-controlled, noninferiority trial in participants aged ≥18 years with HIV-1 across Europe, North America, Latin America and Asia[6]
  - Participants were required to have plasma HIV-1 RNA levels <40 copies/mL at screening with ≥6 months' continuous virological suppression on ART and no previous virological failure
  - Permitted baseline regimens consisted of two nucleoside reverse transcriptase inhibitors plus one of a ritonavir- or cobicistat-boosted protease inhibitor ([PI] atazanavir, darunavir or lopinavir), cobicistat-boosted elvitegravir, or an NNRTI (efavirenz, nevirapine or rilpivirine)
  - Participants were randomised (2:1) to switch to once-daily DOR/3TC/TDF on Day 1 (immediate switch group [ISG]) or Week 24 (delayed switch group [DSG])
- Participants who completed the Base Study through Week 48 could enter Study Extension 1, which continued through Week 144

Procedures and assessments

- The efficacy of DOR/3TC/TDF was evaluated through Week 144 with the following exploratory endpoints:
  - Proportion of participants with HIV-1 RNA ≥50 copies/mL and <50 copies/mL; plasma HIV-1 RNA quantification was performed at all visits in the Base Study and Study Extension 1 (FDA Snapshot approach for missing data)
  - Change from baseline in CD4+ T-cell count; determined at Day 1 and Weeks 12, 24, 36, 48, 96 and 144 (observed failure approach for missing data)
  - Development of protocol-defined virological failure (PDVF), defined as two consecutive measurements of HIV-1 RNA ≥50 copies/mL at least one week apart
- Development of viral resistance to the study drug was investigated in participants with confirmed PDVF, and for those who discontinued early for other reasons if plasma HIV-1 RNA was >400 copies/mL
  - Post-baseline genotypic viral resistance to doravirine 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
  - 2.5-fold change in IC_{50} versus wild-type virus was used as a broad assay-reproducibility threshold for potential phenotypic resistance to doravirine
- Safety evaluations included the change in fasting serum lipids, changes in weight and the incidence of adverse events (AEs)
  - Change in fasting lipids from the time of switch to 24 weeks post-switch and to Study Week 144 was summarised with mean change and 95% confidence intervals (CI); the last observation carried forward (LOCF) approach was used for missing data or data collected after changes in lipid-lowering therapy
  - Mean weight change and 95% CI by time since switch to DOR/3TC/TDF was calculated and adjusted for baseline variables associated with weight change, i.e., weight at time of switch, race (black or non-black), ethnicity (Hispanic or other), sex, age, baseline CD4+ T-cell count and baseline HIV-1 RNA
  - AEs (clinical and laboratory-related) were summarised with descriptive statistics

Statistical analyses

- Participants who completed the Base Study but did not continue to Study Extension 1 were excluded from efficacy analyses post Week 48
- All randomised participants who received at least one dose of DOR/3TC/TDF in the Base Study or Study Extension 1 were included in the safety analyses
- Demography, efficacy and safety data are summarised using descriptive statistics only

Results

Participants

- The analysis included 656 participants (ISG, 447; DSG, 209) who switched to DOR/3TC/TDF; baseline participant characteristics are summarised in Table 1
  - Nine ISG participants who completed the Base Study (Week 48 HIV-1 RNA <40 copies/mL) but did not enter Study Extension 1 were excluded from efficacy analyses post Week 48

Table 1. Baseline Characteristics of Participants who Switched to DOR/3TC/TDF

	DOR/3TC/TDF ISG (N=447)	DOR/3TC/TDF DSG (N=209)	DOR/3TC/TDF total (N=656)
Age (years), median (min, max)	43.0 (21, 71)	43.0 (22, 71)	43.0 (21, 71)
Male, n (%)	372 (83.2)	182 (87.1)	554 (84.5)
Race and ethnicity, n (%)			
Asian	17 (3.8)	6 (2.9)	23 (3.5)
Black or African American	56 (12.5)	30 (14.4)	86 (13.1)
Multiracial	24 (5.4)	11 (5.3)	35 (5.3)
Other	6 (1.3)	2 (1.0)	8 (1.2)
White	344 (77.0)	160 (76.6)	504 (76.8)
Hispanic or Latino	97 (21.7)	39 (18.7)	136 (20.7)
Region, n (%)			
Asia/Pacific	19 (4.3)	12 (5.7)	31 (4.7)
Europe	268 (60.0)	128 (61.2)	396 (60.4)
Latin America	49 (11.0)	23 (11.0)	72 (11.0)
North America	111 (24.8)	46 (22.0)	157 (23.9)
Baseline plasma HIV-1 RNA <50 copies/mL, n (%)	436 (97.5)	209 (100.0)	645 (98.3)
Baseline CD4+ T-cell count			
Median (min, max), cells/mm^3	633.0 (82, 1928) [N=439]	626.0 (140, 1687) [N=206]	629.0 (82, 1928) [N=645]
<200 cells/mm^3, n (%)	13 (2.9)	3 (1.4)	16 (2.4)
ART regimen prior to enrolment, n (%)			
Ritonavir- or cobicistat-boosted PI	316 (70.7)	146 (69.9)	462 (70.4)
Cobicistat-boosted elvitegravir	25 (5.6)	11 (5.3)	36 (5.5)
NNRTI	106 (23.7)	52 (24.9)	158 (24.1)
Duration of prior ART regimen			
Median (min, max), months	47.8 (6.9, 264.9)	50.5 (7.2, 181.1)	48.8 (6.9, 264.9)
≥1 year, n (%)	421 (94.2)	197 (94.3)	618 (94.2)

ART, antiretroviral therapy; DOR/3TC/TDF, doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg; DSG, delayed switch group; InSTI, integrase strand transfer inhibitors; ISG, immediate switch group; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Efficacy outcomes

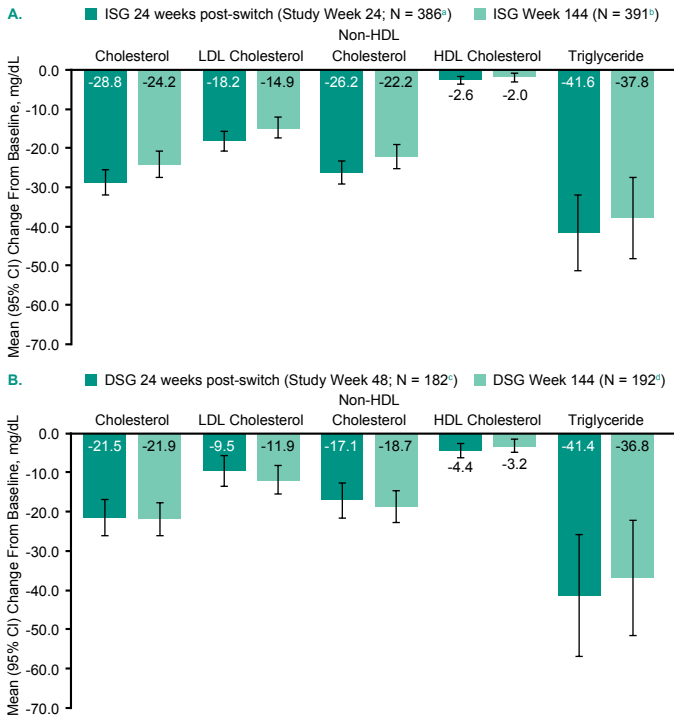
- At Week 144, 2.7% (12/438) of participants in ISG and 4.8% (10/209) in DSG had HIV-1 RNA ≥50 copies/mL (Table 2)
  - Compared with 1.6% (7/447) of participants in ISG and 2.9% (6/209) in DSG who had HIV-1 RNA ≥50 copies/mL at Week 48
- The mean increase from baseline in CD4+ T-cell count was 39.5 and 55.9 cells/mm^3 for ISG and DSG, respectively (Table 2)
- PDVF following switch occurred in 2.1% (9/438) and 3.3% (7/209) of participants for ISG and DSG, respectively (Table 2)
  - HIV-1 RNA >200 copies/mL was observed in 5/16 participants with PVDF
  - PDVF occurred post Week 48 in 9 participants (3 in ISG; 6 in DSG)
- Resistance testing criteria (HIV-1 RNA >400 copies/mL) were met in 4 participants with PDVF, and 3 participants without PDVF who discontinued DOR/3TC/TDF (Table 2)
- No genotypic or phenotypic resistance to DOR, 3TC or TDF was observed in participants who met the criteria for resistance testing

Table 2. Efficacy Summary at Week 144[a]

	DOR/3TC/TDF ISG (N=438)	DOR/3TC/TDF DSG (N=209)
HIV-1 RNA[b], n (%) [95% CI]		
≥50 copies/mL	12 (2.7) [1.4, 4.7]	10 (4.8) [2.3, 8.6]
<50 copies/mL	351 (80.1) [76.1, 83.8]	175 (83.7) [78.0, 88.5]
Change from baseline in CD4+ T-cell count (cells/mm^3)[c,d], mean (95% CI)	39.5 (17.8, 61.1)	55.9 (26.3, 85.4)
Protocol-defined virological failure (PDVF)[e], n (%)		
Overall study: Baseline to Week 144[c]	9 (2.1)	7 (3.3)
Extension only: Week 49 to Week 144	3 (0.7)	6 (2.9)
Resistance test results in participants with PDVF, n	2	2
DOR resistance	0	0
NRTI resistance	0	0
Resistance test results in participants who discontinued, n	3	0
DOR resistance	0	n/a
NRTI resistance	0	n/a

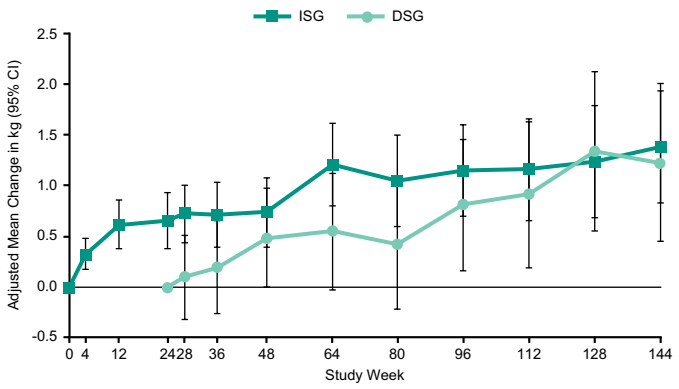
[a]Participants were switched to DOR/3TC/TDF at Week 0 (ISG) or Week 24 (DSG); [b]FDA Snapshot approach; [c]Baseline is Week 0 for ISG and Week 24 (post-switch baseline) for DSG; [d]Observed failure approach; [e]Defined as two consecutive measurements of HIV-1 RNA ≥50 copies/mL at least one week apart.
DOR/3TC/TDF, doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg; DSG, delayed switch group; FDA, Food and Drug Administration; ISG, immediate switch group; n/a, not applicable; PVDF, protocol-defined virological failure.

Figure 1. Change in Fasting Lipids After Switch to DOR/3TC/TDF at 24 Weeks Post-Switch and Study Week 144 in (A) ISG Participants and (B) DSG Participants



Participants were switched to DOR/3TC/TDF at Week 0 (ISG) or Week 24 (DSG). The LOCF approach is applied for missing data or data collected after modifying lipid-lowering therapy.
[a]LDL cholesterol, N = 371; [b]LDL cholesterol, N = 375; [c]LDL cholesterol, N = 174; [d]LDL cholesterol, N = 185.
CI, confidence interval; DOR/3TC/TDF, doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg; DSG, delayed switch group; HDL, high-density lipoprotein; ISG, immediate switch group; LDL, low-density lipoprotein; LOCF, last observation carried forward.

Figure 2. Weight Change After Switch to DOR/3TC/TDF[a]



Adjusted Weight Change (kg), Mean (95% CI)

Study Week	ISG	DSG
24	0.7 (0.4, 0.9)	n/a*
48	0.7 (0.4, 1.1)	0.5 (-0.0, 1.0)
96	1.1 (0.7, 1.6)	0.8 (0.2, 1.5)
144	1.4 (0.8, 1.9)	1.2 (0.4, 2.0)

*DSG switched to DOR/3TC/TDF at Week 24.
[a]Adjusted for weight at time of switch, race (Black or non-Black), ethnicity (Hispanic or other), sex, age, baseline CD4+ T-cell count and baseline HIV-1 RNA.
CI, confidence interval; DOR/3TC/TDF, doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg; DSG, delayed switch group; ISG, immediate switch group.

Safety outcomes

- Reductions in fasting lipids were observed 24 weeks post-switch and maintained through Study Week 144 (LOCF approach) (Figure 1)
- Adjusted weight change following switch was modest, with increases of 1.4 kg and 1.2 kg for ISG and DSG through Study Week 144, respectively (144 and 120 weeks post-switch, respectively) (Figure 2)
- Overall, 4.1% (n=27) participants discontinued due to an AE through Week 144, of whom 5 patients experienced onset of a drug-related AE during Study Extension 1 leading to discontinuation (headache [n=1]; hyperphosphaturia [n=1]; increased blood creatinine [n=1]; increased hepatic enzyme [n=1]; and osteoporosis [n=1])
- Adverse events through Week 144 are summarised in Table 3
  - Overall, 87.7% (575/656) of participants experienced ≥1 AE, and 22.3% (n=146) experienced a drug-related AE
  - Serious AEs were experienced by 10.7% (n=70) of participants, and there were no deaths reported following DOR/3TC/TDF treatment or within 14 days of final dose
- The most common AEs of any causality were nasopharyngitis (16.2% [n=106]), headache (12.3% [n=81]) and diarrhoea (9.1% [n=60]) (Table 3)

Table 3. Summary of AEs Through Week 144[a]

AEs,[b] n (%)	DOR/3TC/TDF (N=656)
≥1 AE	575 (87.7)
Drug-related AEs	146 (22.3)
Serious AEs	70 (10.7)
Serious drug-related AEs	6 (0.9)
Deaths	0 (0.0)
Treatment discontinuation due to an AE	27 (4.1)
Treatment discontinuation due to a drug-related AE	18 (2.7)
Treatment discontinuation due to a serious AE	9 (1.4)
Treatment discontinuation due to a serious drug-related AE[c]	4 (0.6)
Most common AEs (>5% incidence overall)	
Nasopharyngitis	106 (16.2)
Headache	81 (12.3)
Diarrhoea	60 (9.1)
Back pain	52 (7.9)
Upper respiratory tract infection	50 (7.6)
Influenza	41 (6.3)
Arthralgia	37 (5.6)
Alanine aminotransferase increased	36 (5.5)
Cough	35 (5.3)

[a]Participants were switched to DOR/3TC/TDF at Week 0 (ISG) or Week 24 (DSG); [b]Analysis includes AEs occurring or worsening after the first dose of DOR/3TC/TDF once daily through last dose of Study Extension 1 medication (or 14 days after the last dose of Study Extension 1 medication if not continuing into the Study Extension 2); [c]Serious drug-related AEs were depression (n=1), lipase increase (n=1), renal failure (n=1) and lipase and amylase increase (n=1).
AE, adverse event; DOR/3TC/TDF, doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg.

Conclusions

- Long-term virologic suppression was maintained in adults with HIV-1 who switched to DOR/3TC/TDF from a boosted PI, boosted elvitegravir or an NNRTI regimen
- Switching to DOR/3TC/TDF resulted in low rates of virologic failure with no evidence of resistance to doravirine
- Findings at Week 144 confirm previous data that show once-daily DOR/3TC/TDF is a generally well-tolerated option for maintaining viral suppression in adults considering a change in therapy
- DOR/3TC/TDF as switch therapy has a favourable lipid profile compared with baseline regimens and results in minimal weight gain

Disclosures

- Princy Kumar has received consulting fees from Gilead, Merck Sharp & Dohme Corp. and ViiV; Jean-Michel Molina has participated in advisory boards for Gilead, Merck Sharp & Dohme Corp. and ViiV; Giuliano Rizzardini has received consulting/advisor fees from AbbVie, Gilead, Merck Sharp & Dohme Corp. and ViiV, and has board membership with AbbVie, Gilead, Merck Sharp & Dohme Corp. and ViiV; Pedro Cahn has received research funds from Merck Sharp & Dohme Corp., Richmond and ViiV, and participated in advisory boards for Merck Sharp & Dohme Corp. and ViiV; Markus Bickel and Margaret Johnson have no conflicts of interest to declare; Hong Wan, Cristiana Morais, Peter Sklar and Wayne Greaves are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Kenilworth, NJ, USA.
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