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ORIGINAL ARTICLE

Efficacy, Safety, and Tolerability of Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate Fixed-Dose Combination Tablets in Adolescents Living With HIV: Results Through Week 96 from IMPAACT 2014

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Background. IMPAACT 2014 study is a phase I/II, multicenter, open-label, nonrandomized study of doravirine (DOR) co-formulated with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) as fixed-dose combination (DOR FDC) in adolescents with HIV-1. We report the efficacy, safety, and tolerability of DOR FDC through 96 weeks.

Methods. Participants were adolescents aged 12 to <18 years who weighed at least 45 kg and who were either antiretroviral (ARV)-naïve or virologically suppressed without documented resistance mutations to DOR/3TC/TDF. The efficacy endpoint was the proportion of participants with HIV-1 RNA <40 copies/mL assessed at weeks 48 and 96 using the observed failure approach. Safety and tolerability outcomes were incidence of adverse events (AEs) and treatment discontinuations.

Results. A total of 45 adolescents, median age 15 (range, 12–17) years, 58% females, were enrolled and 2 (4.4%) participants were ARV naïve. Of the 45 participants, 42 (93.3%) completed the study and 41 (91.1%) completed the study treatment. At week 48, 41/42 (97.6%; 95% confidence interval [CI], 87.4–99.9) and week 96, 37/40 (92.5%; 95% CI, 79.6–98.4) participants had achieved or maintained HIV-1 RNA <40 copies/mL. There were no treatment-related discontinuations due to AEs and no drug-related AEs ≥grade 3 or deaths.

Conclusions. We found once-daily dosing of DOR FDC to be safe and well tolerated for maintaining viral suppression through 96 weeks in adolescents living with HIV-1.

Key words: adolescents; doravirine; HIV-1; MK-1439A.

INTRODUCTION

Effective combination antiretroviral (ARV) treatment of HIV infection has allowed children and adolescents with perinatal HIV worldwide to grow up [1]. There remains a need for ARV regimens that are effective, well-tolerated, and with a low pill burden to support adherence to life-long treatment. In addition, the availability of multiple regimens that fit these criteria is essential for adolescents, as virologic failure is relatively common in this age group [2–4]. ARV regimens can be associated with toxicities including neuropsychiatric toxicities with efavirenz, gastrointestinal toxicities with protease inhibitors (PIs), weight gain with integrase strand transfer inhibitors (INSTIs), and dyslipidemia with multiple ARV classes [5]. The long-term efficacy of the non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, which has been used as a preferred first-line agent for the treatment of HIV-1 since the late 1990s, has been hindered by its low genetic barrier to resistance and neuropsychiatric adverse event (AE) profile. In part to address these concerns, second-generation NNRTIs, etravirine, and rilpivirine were developed and approved in 2008 and 2011, respectively [6]. Doravirine (DOR) is a novel NNRTI that has shown excellent efficacy and safety in adults, can be given once daily [7, 8] and is active against both wild-type HIV and commonly identified NNRTI-resistant variants [9]. Moreover, DOR

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is associated with a lower incidence of neuropsychiatric side effects relative to efavirenz [10, 11], no food restrictions when compared to rilpivirine [10], and fewer drug–drug interactions than many other ARVs [12–14]. Positive effects on cardiovascular risk and lipid profile have also been documented [15, 16].

A once-daily DOR-containing regimen may be an attractive option for children and adolescents, especially as a fixed-dose single-tablet regimen. The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) 2014 study investigated the safety, tolerability, and pharmacokinetics of the adult DOR tablet (100 mg DOR) and adult DOR/lamivudine/tenofovir disoproxil fumarate (100/300/300 mg, DOR/3TC/TDF, MK-1439A) fixed-dose combination tablet (DOR FDC) in adolescents aged 12 to <18 years with HIV-1. Previously, we reported that the target plasma exposure was achieved with a single dose 100 mg DOR and DOR FDC was found to be well-tolerated and demonstrated good virologic efficacy through 24 weeks [17]. This report presents the efficacy, safety, and tolerability of DOR FDC through 96 weeks.

METHODS

Study Design and Participants

IMPAACT 2014 is a phase I/II open-label, nonrandomized, multicenter study of DOR and DOR FDC in children and adolescents with HIV-1. Participants were enrolled into one of two cohorts. Cohort 1 investigated the pharmacokinetics (PK) of a 100 mg dose of DOR in adolescents with HIV-1 and Cohort 2 evaluated the efficacy, safety, tolerability, and sparse PK of the DOR FDC following once-daily administration. There were 55 participants enrolled in the study: 10 participants into Cohort 1 and 45 into Cohort 2. Results of the Cohort 1 intensive PK analysis, and the efficacy, safety, tolerability, and sparse PK through week 24 for Cohort 2 were previously reported [17]. In Cohort 2, we enrolled adolescents aged 12 to <18 years of age who weighed at least 45 kg and were either ARV-naïve or virologically suppressed without prior documented resistance mutations to any component of DOR/3TC/TDF. To meet criteria for virologic suppression, participants must have had one or more HIV RNA results below the lower level of quantitation (BLLQ) within 6 months prior to enrollment, all HIV RNA measurements BLLQ within 3 months of enrollment, and an HIV RNA <40 copies/mL at screening [18]. The study was conducted at IMPAACT Network sites following approvals from local institutional review boards and in-country ethics committees. Parents/legal guardians provided informed consent and all youth provided assent for participation before initiation of study procedures.

Participants discontinued their ARVs at study entry if they were on a previous regimen. Both the ARV-naïve and ARV-experienced participants were initiated on DOR FDC at study entry, with a planned treatment duration of 96 weeks. All participants had sparse PK evaluations for DOR at week 48 and after week 24 had study visits at 36, 48, 64, 80, and 96 weeks. The week 96 visit window was extended an additional 16 weeks via a letter of amendment, for a total of up to 24 weeks beyond the target date, to assure participant access to DOR FDC after study completion.

Study Evaluations

Safety laboratory tests (chemistries, complete blood count), pregnancy tests, and HIV-1 RNA were obtained at each study visit. Urinalysis, CD4 cell count, and lipid profiles were collected at several visits. Plasma HIV-1 RNA concentrations were determined by the Realtime HIV-1 (Abbott Molecular, Des Plaines, IL). Plasma samples were assayed for genotypic resistance at baseline for ARV-naïve participants and all participants in the case of virologic failure. Phenotypic resistance (Monogram Biosciences, San Francisco, CA) was also assessed if a participant experienced virologic failure. Adherence was determined using a self-report questionnaire at each visit starting at week 4. DOR plasma concentrations were quantified by liquid chromatography-tandem mass spectrometry with the lower limit of quantification of 1 ng/mL (developed and validated by Syneos Health Clinique, Quebec, QC, Canada).

Study Monitoring

AEs were graded according to the Division of AIDS Table for Grading Severity of Pediatric and AEs (corrected version 2.1, July 2017) [19]. Grade ≥3 AEs, serious AEs (SAE), malignancies, immune reconstitution inflammatory syndrome events, and pregnancies were reported in an expedited manner to the IMPAACT 2014 study team and to the study sponsor, National Institute of Allergy and Infectious Diseases, Division of AIDS. Virologic failure was defined as two consecutive plasma HIV-1 RNA test results ≥200 copies/mL at any time after the date of enrollment for those who entered the study with viral suppression, or at or after week 24 for participants who were ARV naïve at entry. Participants with confirmed virologic failure could remain on the study drug if the reason for failure was a remediable cause such as nonadherence and there were no resistance mutations to the study agents determined by genotypic resistance testing.

Statistical Analyses

Safety and tolerability outcomes were evaluated from all AEs, regardless of severity grade, and grade 3 or higher treatment-related AEs at weeks 48 and 96 and included all participants who were exposed to the study drug. For participants who discontinued the study drug prior to reaching week 96, safety data were restricted through four weeks after last dose date. Descriptive statistics were used to summarize the participant characteristics and tolerability. Unless otherwise stated, median and range were used to summarize continuous variables and proportion and 95% confidence intervals (CIs) were used for categorical variables.

Virologic efficacy analyses were based on the plasma HIV-1 RNA levels <40 copies/mL and <200 copies/mL, assessed at week 48 and 96 using the observed failure approach, in which missing values are considered as failures for participants missing data due to discontinuation of study drug, virologic failure or non-treatment-related reasons with last available RNA ≥40/200 copies/mL; otherwise participants with missing values are excluded. Supplementary analyses used the FDA snapshot algorithm [20]. Based on this algorithm, participants were classified as virologic failures if they had missing HIV-1 RNA data throughout the windows surrounding the week 48 and 96 visits, discontinued, or switched from the study drug to another regimen prior to the time points of interest. The proportion of participants with plasma HIV-1 RNA <40 copies/mL and <200 copies/mL, bounded by 95% CIs, are presented. Immunologic response measured by mean changes in CD4 count and percent from baseline to weeks 48 and 96 are presented with 95% CIs, both in the aggregate and broken down by ARV treatment status at entry.

RESULTS

Study Population

Between September 23, 2019, and February 26, 2020, 45 adolescents were enrolled into Cohort 2. The last participant study visit was on May 25, 2022; the last data update was September 16, 2022. Of the 45 participants, 42 (93.3%) completed the study and 41 (91.1%) completed study treatment at week 96. Three participants prematurely discontinued study treatment and follow-up, two due to pregnancy and one due to nonadherence to study treatment. An additional participant discontinued study treatment at week 80 due to an AE that was not related to the study drug; this participant remained on the study (Supplementary Figure 1).

Participant baseline characteristics are summarized in Table 1. Twenty-six (57.8%) participants were female and 35 (77.8%) were from the Asia-Pacific region. At baseline, the median age was 15 (range, 12–17) years and the median weight was 51.6 (range, 45.1–79.8) kg. Two (4.4%) participants were ARV naïve. The median duration of prior ARV treatment for the 43 virologically suppressed participants was 2.8 (range, 0.3–14.9) years. Of the 43 virologically suppressed participants, most were on NNRTI-based regimens (32/43; 74.4%) prior to study entry, while 10 (23.3%) were on PI-based and 1 (2.3%) was on an INSTI-based regimen. For all Cohort 2 participants, the median baseline CD4 cell count was 713 (range, 84–1397) cells/mm^3; and CD4 percentage was 34.2% (range, 5.7–50.0) and the median HIV-1 RNA was 1.6 (range, 1.6–5.9) $\log_{10}$ copies/mL.

Table 1. Baseline Characteristics of Study Participants

	Treatment-naïve (N = 2)	Virologically Suppressed (N = 43)	Total (N = 45)
Characteristics	n (%)	n (%)	n (%)
Sex			
Male	1 (50.0)	18 (41.9)	19 (42.2)
Female	1 (50.0)	25 (58.1)	26 (57.8)
Ethnicity			
Hispanic or Latino	0 (0)	1 (2.3)	1 (2.2)
Not Hispanic or Latino	2 (100.0)	42 (97.7)	44 (97.8)
Geography			
Africa	0 (0)	9 (20.9)	9 (20.0)
Asia/Pacific	2 (100.0)	33 (76.7)	35 (77.8)
North America	0 (0)	1 (2.3)	1 (2.2)
Class of Prior ART			
NRTI	0 (0)	43 (100.0)	43 (95.6)
NNRTI	0 (0)	32 (74.4)	32 (71.1)
INSTI	0 (0)	1 (2.3)	1 (2.2)
PI	0 (0)	10 (23.3)	10 (22.2)
Not applicable	2 (100.0)	0 (0)	2 (4.4)
Variables	Median (min, max)	Median (min, max)	Median (min, max)
Duration of prior ART (years)	-	2.8 (0.3, 14.9)	2.8 (0.3, 14.9)
Age (years)	15.5 (14, 17)	15 (12, 17)	15 (12, 17)
Weight at baseline (kg)	59.3 (53.3, 65.2)	51.5 (45.1, 79.8)	51.6 (45.1, 79.8)
CD4 cell count (cells/mm^3)	99 (84, 114)	715 (315, 1397)	713 (84, 1397)
CD4 percent (%)	7.6 (5.7, 9.5)	34.4 (18.9, 50.0)	34.2 (5.7, 50.0)
HIV-1 RNA[a] ($\log_{10}$ copies/mL)	5.8 (5.7, 5.9)	1.6 (1.6, 1.6)	1.6 (1.6, 5.9)

Abbreviations: N, number of participants in each group; n (%), number (percent) of participants in each subcategory; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor.

[a]Since the assay's lower limit of quantification is 40 copies/mL, all participants with HIV-1 RNA value of <40 copies/mL are imputed as having 39 copies/mL.

Table 2. Efficacy Analysis at Weeks 48 and 96 According to Prior ARV Treatment Experience

	Treatment-naive (N = 2)		Virologically Suppressed (N = 43)		Total (N = 45)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Week 48						
FDA snapshot approach						
Proportion of participants with HIV-1 RNA < 40 copies/mL	1/2	50.0 (1.3, 98.7)	40/43	93.0 (80.9, 98.5)	41/45	91.1 (78.8, 97.5)
Proportion of participants with HIV-1 RNA < 200 copies/mL	1/2	50.0 (1.3, 98.7)	42/43	97.7 (87.7, 99.9)	43/45	95.6 (84.9, 99.5)
Observed failure approach						
Proportion of participants with HIV-1 RNA < 40 copies/mL	1/2	50.0 (1.3, 98.7)	40/40	100.0 (91.2, 100.0)	41/42	97.6 (87.4, 99.9)
Proportion of participants with HIV-1 RNA < 200 copies/mL	1/2	50.0 (1.3, 98.7)	42/42	100.0 (91.6, 100.0)	43/44	97.7 (88.0, 99.9)
Week 96						
FDA snapshot approach						
	1/2	50.0 (1.3, 98.7)	36/43	83.7 (69.3, 93.2)	37/45	82.2 (67.9, 92.0)
Proportion of participants with HIV-1 RNA < 200 copies/mL	1/2	50.0 (1.3, 98.7)	38/43	88.4 (74.9, 96.1)	39/45	86.7 (73.2, 94.9)
Observed failure approach						
Proportion of participants with HIV-1 RNA < 40 copies/mL	1/2	50.0 (1.3, 98.7)	36/38	94.7 (82.3, 99.4)	37/40	92.5 (79.6, 98.4)
Proportion of participants with HIV-1 RNA < 200 copies/mL	1/2	50.0 (1.3, 98.7)	38/40	95.0 (83.1, 99.4)	39/42	92.9 (80.5, 98.5)

	Mean [n]	(95% CI)	Mean [n]	(95% CI)	Mean [n]	(95% CI)
Week 48						
Change from baseline in $\log_{10}$ plasma HIV-1 RNA	−2.1 [2]	(−5.8, 26.1)	-	-	-	-
Change from baseline in CD4 cell count (cells/mm^3)	175.0 [2]	(−99.0, 937.4)	75.5 [41]	(6.7, 144.3)	80.1 [43]	(14.2, 146.0)
Change from baseline in CD4 percent	9.1 [2]	(−7.6, 29.4)	−0.9 [41]	(−2.1, 0.3)	−0.4 [43]	(−1.7, 0.9)
Week 96						
Change from baseline in $\log_{10}$ plasma HIV-1 RNA	−4.3 [1]	-	-	-	-	-
Change from baseline in CD4 cell count (cells/mm^3)	455.0 [1]		31.4 [37]	(−40.7, 103.4)	42.5 [38]	(−31.1, 116.1)
Change from baseline in CD4 percent	19.9 [1]		−1.0 [37]	(−2.7, 0.7)	−0.5 [38]	(−2.5, 1.5)

Abbreviations: N, number of participants in each group; n, number of participants in each subcategory.
Due to low specimen volume, some participants' plasma samples were diluted by a factor of 5 before being tested. This dilution increased the assay's limit of quantification (LoQ) from 40 to 200 copies/mL. In the analysis of proportion of patients with HIV-1 RNA < 40 copies/mL, such records were treated as missing values. Samples for two participants at Week 48 and Week 96 were diluted (by a factor of 5 each). For binary endpoints: n/N with % (95% CI) was reported for each group, where 95% CI is the exact 95% confidence interval. For continuous endpoints: mean changes with the 95% confidence intervals were reported. The 95% CIs were calculated based on t-distribution.

Virologic Efficacy

According to the FDA Snapshot Algorithm, 41/45 participants (91.1%; 95% CI [78.8, 97.5]) and 37/45 participants (82.2%; 95% CI [67.9, 92.0]) achieved or maintained HIV-1 RNA < 40 copies/mL at weeks 48 and 96, respectively, and 43/45 participants (95.6%; 95% CI [84.9, 99.5]) and 39/45 participants (86.7%; 95% CI [73.2, 94.9]) achieved or maintained HIV-1 RNA < 200 copies/mL at weeks 48 and 96, respectively. Based on the observed failure approach, 41/42 participants (97.6%; 95% CI [87.4, 99.9]) and 37/40 participants (92.5%; 95% CI [79.6, 98.4]) achieved or maintained HIV-1 RNA < 40 copies/mL, at weeks 48 and 96, respectively, and 43/44 participants (97.7%; 95% CI [88.0, 99.9]) and 39/42 participants (92.9%; 95% CI [80.5, 98.5]) had achieved or maintained HIV-1 RNA < 200 copies/mL at weeks 48 and 96, respectively; two participants withdrew from the study due to pregnancy prior to week 96 (viral load at last study visits were <40 copies/mL), one was discontinued from study drug due to an unrelated AE (viral load at last study visit was also <40 copies/mL) and for two the result was provided as <200 copies/mL only as the sample required dilution 1:5 secondary to low volume. For the one ARV-naïve participant who maintained viral suppression at week 96, the change from baseline in $\log_{10}$ plasma HIV-1 RNA at week 96 was −4.3 (Table 2).

Virological Failure

Two participants experienced virologic failure. One of the treatment-naïve participants experienced virologic failure at week 24 due to nonadherence; this participant was allowed to remain in the study as no DOR FDC resistance-associated mutations were identified at that time. Viremia was documented at week 64, again due to nonadherence, and at that time the participant had developed two resistance-associated mutations for DOR: P225H and V106A. One participant with virologic suppression at entry experienced virologic failure at week 96; no DOR FDC resistance-associated mutations were identified at time of failure.

Immunologic Response

Among the 43 participants who had CD4 data at baseline and at week 48, mean (95% CI) change from baseline to week 48 in CD4 counts was 80.1 (14.2, 146.0) cells/mm^3 and the mean (95% CI) change in CD4 percentage was −0.4% (−1.7, 0.9). Mean

(95% CI) change from baseline to week 48 in CD4 counts was 175.0 (−99.0, 937.4) cells/mm^3 for ART-naïve participants and 75.5 (6.7, 144.3) cells/mm^3 for ART-experienced participants. Mean (95% CI) change from baseline to week 48 in CD4 percentage was 9.1% (−7.6, 29.4) for ART-naïve participants and −0.9% (−2.1, 0.3) for ART-experienced participants (Table 2).

Among the 38 participants who had CD4 data at baseline and at Week 96, mean (95% CI) change from baseline to week 96 in CD4 count and percentage was 42.5 (−31.1, 116.1) cells/mm^3 and −0.5% (−2.5, 1.5), respectively. Change from baseline to week 96 was 455.0 cells/mm^3 for the ART-naïve participant and mean (95% CI) change was 31.4 (−40.7, 103.4) cells/mm^3 for ART-experienced participants. Change in CD4 percentage was 19.9% for the ART-naïve participant and mean change was −1.0% (−2.7, 0.7) for ART-experienced participants (Table 2).

Safety and Tolerability

Through the week 96 study visit, drug-related AEs were reported in four participants (8.9%) including a clinical symptom (grade 1 dizziness) and three abnormal laboratory values (grade 2 hyperbilirubinemia, grade 1 decreased neutrophil count, and grade 1 hypoglycemia). All these AEs were transient. All adolescents remained in the same body mass index (BMI) category; over the 96 weeks, the mean BMI change was 1.6 kg/m^2. One participant (2.2%) had grade 4 increased ALT which was determined not to be related to study drug, as another cause (active hepatitis C infection) was identified. The event led to permanent treatment discontinuation at week 80, but the participant remained on study until completed at week 96. Two participants (4.4%) experienced SAEs, both determined not to be related to study treatment. One participant had a grade 3 scrotal abscess and the other participant had grade 3 gastroenteritis and grade 2 lip injury.

Change in Clinical Parameters

Serum creatinine increased more than 30% from baseline in 5/45 (11.1%) with an accompanying greater than 30% decrease in estimated glomerular filtration rate (eGFR) from baseline in 4/45 (8.9%). However, all creatinine and eGFR values remained in the normal range throughout week 96. DOR FDC had a favorable lipid profile: mean change from baseline for total HDL, and LDL cholesterol at week 96 were −29.2, −16.2, and −9.9 mg/dL, respectively (Tables 3 and 4).

Pharmacokinetics

At week 48, the geometric mean (%CV) steady-state DOR predose and 0.5–2 hours pose-dose were 795 (237.5) nM, and 1310 (281.0) nM, respectively, exceeding the lower bound for efficacy (>560 nM) based on Phase 3 adult studies [21] (Supplementary Table1).

DISCUSSION

The DOR/3TC/TDF FDC tablet was effective, safe, and well-tolerated in this adolescent population. In this study, the virologic suppression rates to <40 copies/mL were 97.6% and 92.5% at 48 and 96 weeks, respectively, as defined by the observed failure approach. An increase in mean CD4 count from baseline was observed in both treatment-naïve and virologically suppressed groups. No drug-related AEs led to treatment discontinuation over the 96-week follow-up and there were no deaths.

Similar to the results in adults who were virologically suppressed and switched to DOR FDC [22, 23], we found that the majority of participants maintained virological suppression (<40 copies/mL); only one previously virologically suppressed participant experienced virologic failure at week 96, but no viral resistance to DOR was identified. These findings support once-daily DOR FDC as an option for maintaining viral suppression in adolescents considering a change in therapy. The treatment-naïve participant who experienced virologic failure due to nonadherence developed two resistance-associated mutations for DOR: P225H and V106A. This is consistent with reports from trials in adults where in almost all cases of virologic failure while on DOR treatment, V106A/M substitutions were selected first, with important secondary substitutions found at positions H221, P225, and/or F227 [24, 25]. However, a low rate of DOR resistance-associated mutations has been found (<2%) in clinical trials primarily attributed to poor adherence [26, 27]

Table 3. Summary of Adverse Events Through Week 96

Adverse Events	Total (N = 45) n (%)	95% CI
≥1 AEs	45 (100)	(92.1, 100)
≥1 drug-related AEs[a]	4 (8.9)	(2.5, 21.2)
Permanent discontinuation due to an AE[b]	1 (2.2)	(0.1, 11.8)
Permanent discontinuation due to a drug-related AE	0	(0, 7.9)
≥1 serious AEs[c]	2 (4.4)	(0.5, 15.1)
≥1 drug-related serious AEs	0	(0, 7.9)
Deaths	0	(0, 7.9)
≥Grade 3 AEs[d]	11 (24.4)	(12.9, 39.5)
≥Grade 3 drug-related AEs	0	(0, 7.9)
Most common AEs (>5% incidence overall)[e]		
Increase serum creatinine	5 (11.1)	
Decrease estimated glomerular filtration rate	4 (8.9)	

Abbreviations: AE, adverse events; CI, confident interval; SD, standard deviation.

[a]A treatment-naïve participant had grade 1 dizziness, resolved without discontinuation.

[b]A participant had grade 4 increase ALT and active hepatitis C infection.

[c]One had grade 3 gastroenteritis and grade 2 lip injury, another had grade 3 scrotal abscess.

[d]Grade ≥ 3 AEs included diarrhea (n = 1), gastroenteritis (n = 1), scrotal abscess (n = 1), increased ALT (n = 2), increased AST (n = 1), increased serum creatinine (n = 5), increased blood pressure (n = 2), decreased eGFR (n = 4), and hypertension (n = 2). Some participants had > 1 events.

[e]All occurred in virologic-suppressed group.

Table 4. Summary of Clinical Parameters for Participants at Baseline, Change From Baseline to Week 96

Measurements	Study Week	n	Baseline Mean	Mean Change (95% CI)	SD
Height (cm)	Baseline	45	160.5		
	Week 96	42	160.6	3.1 (2.0, 4.1)	3.3
Weight (kg)	Baseline	45	53.8		
	Week 96	42	53.7	6.5 (4.5, 8.5)	6.5
Body mass index (kg/m^2)	Baseline	45	20.9		
	Week 96	42	20.8	1.6 (0.9, 2.3)	2.2
Creatinine (mg/dL)	Baseline	45	0.6		
	Week 96	42	0.7	0.1 (0.0, 0.1)	0.1
eGFR[a]	Baseline	45	158.8		
	Week 96	42	159.1	−17.7 (−26.9, −8.5)	29.6
Cholesterol (mg/dL)	Baseline	45	168.7		
	Week 96	37	169.5	−29.2 (−40.3, −18.0)	33.4
HDL cholesterol (mg/dL)	Baseline	45	57.8		
	Week 96	38	59.3	−16.2 (−20.2, −12.1)	12.3
LDL cholesterol (mg/dL)	Baseline	45	89.2		
	Week 96	36	89.5	−9.9 (−18.5, −1.4)	25.2

Abbreviations: CI, confident interval; SD, standard deviation.
[a]eGFR, estimated glomerular filtration rate, from creatinine adjusted for BSA (mL/min/1.73 m^2) using Modified Schwartz equation.

The safety profile of DOR FDC was documented in previous adult studies [8, 12, 16, 21, 22, 26, 27], and the 24-week results of this study [17]. We continued to see a favorable safety and tolerability profile in our adolescent participants for up to 96 weeks: no deaths, no drug-related SAEs, and no discontinuations due to drug-related AEs. Three of the four drug-related AEs were abnormal lab values which were determined as not clinically significant. In contrast to previous adult studies reporting clinical AEs in more than 10% of study participants [26, 27], few were seen in our study (dizziness, n = 1). We did not perform fasting lipids in all adolescents. However, we observed a decrease in mean total cholesterol, HDL, and LDL cholesterol from baseline to week 96. These findings are consistent with the favorable DOR effect on the lipid profile as previously reported in adult studies [7, 8, 22, 23, 26]. Additionally, all participants remained in the same BMI category; the mean change of BMI was 1.6 kg/m^2 over 96 weeks. Similarly, minimal weight gain was observed in both treatment-naïve and virologically suppressed adults after initiation of a DOR regimen [23, 27].

A concern could be raised about the effects of treatment on renal function. The most common AEs seen in our study participants were increased serum creatinine from baseline in 11.1% and decreased estimated glomerular filtration from baseline in 8.9%. While this could be associated with TDF which is a component in the FDC that has known renal effects, alternatively the increase in creatinine could be related to the expected increase in muscle mass in these adolescents who continued to grow during the 2 years of the study. It is noted as well that all creatinine and eGFR values remained within normal limits throughout the study. The percent of participants with creatinine increases was higher than what was seen in the study of DOR/3TC/TDF in adults through 96 weeks that reported increased creatinine (>1.3 times upper limit of normal or increase of >0.3 mg/dL from baseline) in 3–4% [26, 27]. Many adolescents in our study had perinatally acquired HIV and had been exposed to several medications for many years prior to the study entry, therefore they might be more vulnerable to renal dysfunction. Monitoring of renal function is recommended for those receiving TDF-including regimens to detect accelerated decline and offer other treatment options in a timely manner [28].

Pre-dose DOR levels at week 48 were slightly lower than typical steady-state trough DOR levels demonstrated in adults [21], suggesting more rapid clearance. However, the levels remained above the lower bound for efficacy based on adult studies and well above the IC_{50} for wild-type virus [21, 29]. As most participants maintained virologic suppression, DOR exposure at the current dose appears to be efficacious and safe for adolescents.

DOR was rationally designed to address limitations associated with former approved NNRTIs that have been used as the first-line agents for the treatment of HIV-1. In recent years, integrase strand transfer inhibitors (INSTIs) have replaced NNRTIs as preferred first-line agents in international guidelines [30, 31]. This is due to high potency and inherent barriers to drug resistance [32]. Direct comparison between DOR and INSTI-based regimens for virologic efficacy and adverse outcomes are limited. Indirect evidence is available from a recent systematic review of the efficacy and safety of DOR-based ART regimens in adults. In this review, DOR was shown to provide good virological suppression, however, the odds-ratios between DOR-based and INSTI-based regimens were ≥1, indicating INSTI-based regimens had a higher proportion of patients achieving virological suppression [33]. Trials in adults have consistently shown improvements in lipid levels and minimal

weight gain associated with DOR-based ART [26, 27, 34, 35] which suggests superiority over INSTI-based regimens for these safety outcomes. Thus, DOR might be considered as an alternative treatment option to an INSTI-based regimen particularly when elevated lipids or weight gain are a concern. Although the participants in Cohort 2 of this trial were limited to those with weights ≥45 kg, the FDA recently approved DOR for use in adolescents ≥35 kg based on the results of this trial and additional pharmacokinetic modeling data [36], thus making a switch from a dolutegravir fixed-dose combination tablet to DOR FDC practical for most adolescents.

There are some limitations to this study. First, only two participants were treatment-naïve which limits generalizability of the results in that group. In addition, one of two treatment-naïve participants was not adherent to study drug and experienced virologic failure that likely falsely lowered estimated virologic efficacy in this subset. Another limitation is a selection bias as only virologically suppressed adolescents were enrolled into the treatment-experienced group. The participants had good adherence at baseline which likely contributed to the favorable outcome but limits the study's generalizability in adolescents with imperfect adherence.

In conclusion, DOR FDC offers excellent efficacy, safety, and tolerability for treatment of HIV-1 in adolescents. DOR FDC is an option for virologic-suppressed adolescents who require a long-term ARV treatment regimen. Further study is needed to confirm the efficacy among treatment-naïve adolescents.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

Notes

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Potential conflicts of interest. H. W., P. J., R. L. (now retired), H. T. (now retired), and H. C. are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA [license holder Pifeltro® and Delstrigo®] and hold stock in Merck & Co., Inc., Rahway, NJ, USA; H. T. was involved in study design and implementation; H. W. assisted with the data analysis; R. L. assisted with interpretation of results and P. J. and H. C. assisted with project administration and supervision. The remaining authors have no conflicts of interest to declare.

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