Safety and efficacy of doravirine as first-line therapy in adults with HIV-1: week 192 results from the open-label extensions of the DRIVE-FORWARD and DRIVE-AHEAD phase 3 trials

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Summary

Background In two phase 3 trials for first-line therapy in adults with HIV-1, doravirine showed non-inferior efficacy, a favourable safety profile, and a superior lipid profile to darunavir and efavirenz through to 48 and 96 weeks. Here we report 192-week results from both studies.

Methods DRIVE-FORWARD and DRIVE-AHEAD are multicentre, double-blind, randomised, active comparator-controlled, phase 3 trials of first-line antiretroviral treatment in adults with HIV-1. Eligible participants (aged ≥18 years) were naive to antiretroviral therapy, had plasma HIV-1 RNA 1000 copies per mL or more at screening, had no known resistance to any of the trial drugs, and had creatinine clearance 50 mL per min or more. DRIVE-FORWARD was conducted at 125 sites in 15 countries and compared doravirine (100 mg) with ritonavir-boosted darunavir (ritonavir [100 mg] and darunavir [800 mg]), each administered orally once daily with two nucleoside or nucleotide reverse transcriptase inhibitors (tenofovir disoproxil fumarate [300 mg] and emtricitabine [200 mg] or abacavir sulfate [600 mg] and lamivudine [300 mg]). DRIVE-AHEAD was conducted at 126 sites in 23 countries and compared doravirine (100 mg), lamivudine (300 mg), and tenofovir disoproxil fumarate (300 mg) with that of efavirenz (600 mg), emtricitabine (200 mg), and tenofovir disoproxil fumarate (300 mg), all administered orally once daily. DRIVE-FORWARD enrolment was between Dec 1, 2014, and June 1, 2020, and DRIVE-AHEAD enrolment was between June 10, 2015, and Aug 10, 2020. After the 96-week double-blind phase, eligible participants could enter an open-label extension and either continue doravirine or switch from comparator to doravirine for an additional 96 weeks. Efficacy (HIV-1 RNA <50 copies per mL) and safety assessments (adverse events and changes in laboratory parameters) were pooled. The DRIVE-FORWARD and DRIVE-AHEAD trials were registered with ClinicalTrials.gov, NCT02275780 and NCT02403674.

Findings Of 1494 participants treated in the double-blind phase (1261 [84%] male and 233 [16%] female), 550 continued doravirine and 502 switched to doravirine in the extension. Using the FDA snapshot approach, HIV-1 RNA less than 50 copies per mL was maintained in 457 (83%) of 550 participants who continued doravirine and 404 (80%) of 502 participants who switched to doravirine. Protocol-defined virological failure and development of resistance were low, occurring mainly before week 96. Two (<1%) of 550 participants who continued doravirine reported serious drug-related adverse events, and three (1%) who continued doravirine and one (<1%) of 502 who switched to doravirine discontinued due to drug-related adverse events. Participants continuing or switching to doravirine showed generally favourable lipid profiles, little weight gain, and small decreases in estimated glomerular filtration rates, with no discontinuations due to increased creatinine or renal adverse events.

Interpretation Favourable efficacy and safety profiles for doravirine at week 96 were maintained through to week 192 in participants who continued or switched to doravirine, supporting use of doravirine for long-term first-line HIV-1 treatment and for virologically suppressed adults switching therapy.

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See Online for appendix

Introduction

Doravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) for treatment of HIV-1 in adults and adolescents.[1,2] Doravirine was rationally designed to address known disadvantages of approved NNRTIs, minimise neuropsychiatric and lipid effects, reduce resistance liabilities, and limit drug–drug interactions.[3] At clinically relevant concentrations, doravirine demonstrates potent in vitro activity against wild-type and common NNRTI-resistant HIV-1 variants, including

Research in context

Evidence before this study

Doravirine is a next-generation non-nucleoside reverse transcriptase inhibitor approved for the treatment of people with HIV-1 in combination with other antiretroviral agents, and it is included in the European AIDS Clinical Society guidelines as a recommended first-line therapy for adults and adolescents. We searched PubMed for publications from database inception to Jan 13, 2022, with no language restrictions, using the terms "MK-1439" or "doravirine", and identified ten phase 3 clinical trial publications, four phase 2 trial publications, and 13 phase 1 trial publications. Results of phase 1 trials showed that doravirine can be dosed once daily without food restrictions and has a low potential for drug–drug interactions, including with acid-reducing drugs. Phase 2 trials were conducted to investigate doravirine pharmacokinetics, efficacy, safety, and central nervous system effects for dose selection and for use as first-line therapy in adults with HIV-1. In two first-line therapy phase 3 trials (DRIVE-FORWARD and DRIVE-AHEAD), doravirine-based regimens showed non-inferior efficacy and superior lipid profiles through to 48 and 96 weeks compared with ritonavir-boosted darunavir and efavirenz-based regimens, respectively. In DRIVE-AHEAD, doravirine showed lower rates of neuropsychiatric adverse events through to 96 weeks compared with efavirenz. Weight gain in these phase 3 trials was minimal in all treatment groups and similar to the average yearly change in adults without HIV-1.

Added value of this study

Durability of virological response and long-term tolerability and safety are important attributes of treatment for people with HIV-1. The DRIVE-FORWARD and DRIVE-AHEAD trials investigated long-term efficacy and safety of doravirine through 96-week double-blind base studies and 96-week open-label extensions. We report results of these 192-week analyses, which showed that doravirine was effective in maintaining viral suppression with a low incidence of drug resistance in both the double-blind and extension phases of the trials. Doravirine-based regimens were well tolerated through to 192 weeks, showing little effect on lipid levels, bodyweight, and renal function (despite the inclusion of tenofovir in most regimens).

Implications of all the available evidence

Developing durable and safe treatment options with a low incidence of resistance is important given the need for lifelong therapy for people with HIV-1. These data at 192 weeks reinforce the favourable results after 96 weeks of treatment with doravirine as first-line therapy in adults, as well as for adults who switched to doravirine, supporting the use of doravirine for long-term HIV-1 treatment.

those bearing transmitted drug resistance-associated substitutions Lys103Asn, Tyr181Cys, Gly190Ala, Lys103Asn plus Tyr181Cys, and Glu138Lys.[4] Doravirine has a low potential for clinically meaningful drug–drug interactions and can be administered without food restrictions.[5,6] Doravirine is available as a single tablet that can be combined with other antiretroviral drugs and as a fixed-dose tablet that contains doravirine (100 mg), lamivudine (300 mg), and tenofovir disoproxil fumarate (300 mg) for once-daily use.[1,2] Current guidelines from the European AIDS Clinical Society include doravirine (in combination with tenofovir and lamivudine or emtricitabine) as a recommended first-line regimen for adults with HIV-1.[7]

Two phase 3 trials evaluated the safety and efficacy of doravirine as first-line treatment for people with HIV-1. The DRIVE-FORWARD trial compared doravirine with ritonavir-boosted darunavir, both given once daily in combination with two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs). Results through to week 96 of DRIVE-FORWARD showed non-inferior antiviral efficacy, similar safety, and a superior lipid profile of doravirine compared with ritonavir-boosted darunavir.[8,9] In the DRIVE-AHEAD trial, the fixed-dose combination of doravirine, lamivudine, and tenofovir disoproxil fumarate given once daily showed non-inferior efficacy and a superior lipid profile and fewer prespecified neuropsychiatric adverse events compared with the fixed dose combination of efavirenz, emtricitabine, and tenofovir disoproxil fumarate.[10,11] In both studies, weight gain over 96 weeks was low in all treatment groups and similar to the average yearly change in adults without HIV-1.[12,13]

Considering the need for lifelong treatment, it remains essential to evaluate the long-term safety and efficacy of HIV regimens. In both DRIVE-FORWARD and DRIVE-AHEAD, participants who completed 96 weeks of double-blind treatment in the base study were offered an additional 96 weeks of treatment with the doravirine-based regimen in an open-label extension. Herein, we present 192-week safety and efficacy results from both trials in participants who were randomly assigned to doravirine, as well as safety and efficacy results over the course of 96 weeks in participants who switched from boosted darunavir or efavirenz in the base studies to doravirine in the extensions.

Methods

Study design

DRIVE-FORWARD and DRIVE-AHEAD are multicentre, double-blind, randomised, active comparator-controlled, phase 3 trials of first-line antiretroviral treatment in adults with HIV-1 (appendix p 8). DRIVE-FORWARD (MK-1439-018; NCT02275780) was conducted at 125 sites in 15 countries to compare the safety and efficacy of oral doravirine (100 mg) with that of ritonavir-boosted darunavir (ritonavir [100 mg] and darunavir [800 mg]), each administered once daily with two investigator-selected NRTIs (tenofovir disoproxil fumarate [300 mg]

and emtricitabine [200 mg] or abacavir sulfate [600 mg] and lamivudine [300 mg]).[8,9] DRIVE-AHEAD (MK-1439A-021; NCT02403674) was conducted at 126 sites in 23 countries to compare the safety and efficacy of oral doravirine (100 mg), lamivudine (300 mg), and tenofovir disoproxil fumarate (300 mg) once daily with that of efavirenz (600 mg), emtricitabine (200 mg), and tenofovir disoproxil fumarate (300 mg) once daily.[10,11] DRIVE-FORWARD enrolment was between Dec 1, 2014, and June 1, 2020, and DRIVE-AHEAD enrolment was between June 10, 2015, and Aug 10, 2020. After the 96-week double-blind phase, participants who met eligibility criteria had the option to enter a 96-week open-label extension phase. In DRIVE-FORWARD, participants continued or switched to doravirine plus two NRTIs at week 96; changes in NRTIs between the base study and the study extension were made on a case-by-case basis, as needed, by agreement of the investigator and the sponsor; tenofovir alafenamide fumarate was permitted. In DRIVE-AHEAD, participants continued or switched to doravirine, lamivudine, and tenofovir disoproxil fumarate at week 96. Both trials were conducted in accordance with Good Clinical Practices and the study protocols were approved by an independent ethics committee at each study site.

Participants

Detailed eligibility criteria for participants in the DRIVE-FORWARD and DRIVE-AHEAD base studies have been described previously.[8–11] Eligible participants (aged ≥18 years) were naive to antiretroviral therapy, had plasma HIV-1 RNA 1000 copies per mL or more at screening, had no known resistance to any of the trial drugs, and had creatinine clearance 50 mL per min or more. For both trials, participants were eligible to enrol in the 96-week open-label extension if they completed the 96-week base study and, according to the investigator, derived benefit from study participation and treatment with doravirine was considered clinically appropriate. All participants provided written informed consent to enter the extension.

Randomisation and masking

The randomisation and masking procedures for the 96-week base studies were previously described.[8–11] All participants received open-label study medication in the 96-week extensions.

Procedures

Details of procedures performed during the 96-week base studies were previously described.[8–11] For both trials, extension visits occurred at weeks 100, 116, 132, 148, 164, 180, and 192. Plasma HIV-1 concentrations were measured by the central laboratory (Quest Diagnostics, Secaucus, NJ, USA) with the Abbott RealTime HIV-1 assay (Abbott Molecular, Des Plaines, IL, USA). $CD4^+$ T-cell counts were measured using flow cytometry at weeks 100, 148, and 192 by the central laboratory.

Protocol-defined virological failure (PDVF) was defined as either non-response (confirmed [two consecutive measures ≥1 week apart] HIV-1 RNA ≥200 copies per mL at week 24 or week 36 or ≥50 copies per mL at week 48) or rebound (confirmed HIV-1 RNA ≥50 copies per mL after initial response of <50 copies per mL at any time during the trial). Strict recommendations were implemented for study treatment discontinuation if participants met criteria for PDVF, regardless of adherence to study drug. Resistance testing was performed by Monogram Biosciences (San Francisco, CA, USA) for participants with confirmed PDVF or who discontinued early without PDVF; more than 400 copies per mL of HIV-1 RNA was required for resistance testing. Genotypic resistance to doravirine was defined by any of the following substitutions in reverse transcriptase: Ala98Gly; Leu100Ile; Lys101Glu or Lys101Pro; Lys103Asn or Lys103Ser; Val106Ala, Val106Ile, or Val106Met; Val108Ile; Glu138Ala, Glu138Gly, Glu138Lys, Glu138Gln, or Glu138Arg; Val179Leu; Tyr181Cys, Tyr181Ile, or Tyr181Val; Tyr188Cys, Tyr188His, or Tyr188Leu; Gly190Ala or Gly190Ser; His221Tyr; Pro225His; Phe227Cys, Phe227Leu, or Phe227Val; Met230Ile or Met230Leu; Leu234Ile; Pro236Leu; and Tyr318Phe. In the absence of a clinical cutoff, phenotypical viral resistance was defined by Monogram Biosciences on the basis of a 2·5-fold change in the half-maximal inhibitory concentration versus reference virus for a broad assay reproducibility threshold for potential phenotypical resistance to doravirine.

Safety was monitored by adverse event reporting, treatment-emergent abnormalities in laboratory test results, and physical examinations. Adverse events were assessed by the investigator for intensity (ie, mild, moderate, or severe), seriousness, and relationship to study therapy. Laboratory values were graded according to the Division of AIDS criteria.[14] Lipids (ie, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides) were measured after 8 h of fasting.

Statistical analysis

Calculations for sample size in each trial have been described previously.[8–11] Efficacy, resistance, and safety data (ie, adverse events and laboratory tests) from the DRIVE-FORWARD and DRIVE-AHEAD trials were pooled for analysis. The objectives were to pool the groups that continued a doravirine-based regimen from the base study throughout the extension from the DRIVE-FORWARD and DRIVE-AHEAD trials to study the long-term effects (192 weeks) of a doravirine-based regimen and to pool the groups that switched from a comparator regimen to a doravirine-based regimen to confirm drug effectiveness and safety after receiving 96 weeks of a doravirine-based regimen, regardless of the antiretroviral therapy administered in the base studies. Because the duration of treatment differed, there was no intention to compare these two pooled groups; therefore,

data were presented in a descriptive manner. Lipids, bodyweight, and estimated glomerular filtration rate (eGFR) were analysed separately by study. Results are presented for the following groups: (1) the doravirine cumulative group, which includes available data from day 1 to week 192 for all participants randomly assigned to doravirine; (2) the doravirine continued group, which includes available data from week 96 to week 192 for the subset of participants who were randomly assigned to doravirine in the double-blind phase and then continued to receive doravirine in the open-label extension; and (3) the doravirine switch group, which includes available data from week 96 to week 192 for participants randomly assigned to darunavir or efavirenz in the double-blind phase and switched to doravirine for the open-label extension.

Statistical methods used for analysis of data from the double-blind phase were previously described;[8–11] these methods were also used for the open-label extension. For efficacy assessments, the US Food and Drug Administration (FDA) snapshot approach and the observed failure approach were used. In the observed failure approach, baseline values were carried forward for virological failures and other missing values were excluded from analysis.

In addition to the efficacy and safety analyses prespecified in the protocols, the following post-hoc analyses were conducted. Median (IQR) bodyweight change was calculated from day 1 through to week 192 for all participants and from week 96 through to week 192 for participants who switched to doravirine in the extension. Median change in the eGFR from day 1 through to week 192 was calculated from serum creatinine values using the modification of diet in renal disease equation.[15] Predictors of PDVF were investigated using a generalised linear model. The generalised linear model used a binomial distribution, a log link, and the following covariates: baseline CD4⁺ T-cell counts and HIV-1 RNA copies per mL, HIV-1 subtype, sex, age group, overall drug adherence, and clinical trial. The likelihood ratio test was used to assess the overall effect of the covariates, and the profile likelihood function was used to compute the 95% CI of the parameter estimates. The DRIVE-FORWARD and DRIVE-AHEAD trials were registered with ClinicalTrials.gov, NCT02275780 and NCT02403674.

	Doravirine cumulative (n=747)	Doravirine continued (n=550)	Doravirine switch (n=502)
Sex			
Female	123 (16%)	93 (17%)	68 (14%)
Male	624 (84%)	457 (83%)	434 (86%)
Race			
Asian	66 (9%)	58 (11%)	53 (11%)
Black or African American	154 (21%)	100 (18%)	86 (17%)
Multiple	58 (8%)	45 (8%)	45 (9%)
Other*	13 (2%)	7 (1%)	8 (2%)
White	456 (61%)	340 (62%)	310 (62%)
Hispanic or Latino	219 (29%)	165 (30%)	144 (29%)
Mean age, years	34·2 (10·5)	34·6 (10·5)	34·0 (10·4)
Tenofovir disoproxil fumarate in regimen	697 (93%)	512 (93%)	472 (94%)
Mean CD4 count, cells per µL	434 (213)	437 (211)	415 (210)
CD4 count strata			
≤50 cells per µL	15 (2%)	9 (2%)	16 (3%)
>50 to ≤200 cells per µL	71 (10%)	45 (8%)	51 (10%)
>200 cells per µL	661 (88%)	496 (90%)	435 (87%)
Mean plasma HIV-1 RNA, log_{10} copies per mL	4·4 (0·7)	4·4 (0·7)	4·4 (0·7)
Plasma HIV-1 RNA strata			
≤100 000 copies per mL	591 (79%)	449 (82%)	407 (81%)
>100 000 copies per mL	156 (21%)	101 (18%)	94 (19%)
History of AIDS	82 (11%)	56 (10%)	56 (11%)
Hepatitis B or C†	22 (3%)	14 (3%)	18 (4%)
Viral subtype B	498 (67%)	359 (65%)	345 (69%)
HIV-1 RNA <50 copies per mL at week 96	NA	520 (95%)	471 (94%)
Median CD4 count at week 96	NA	659 (71–1985)	627 (85–2043)

Data are n (%), mean (SD), or median (range). NA=not applicable. *Other race includes American Indian, Alaska Native, Native Hawaiian, and other Pacific Islander. †Evidence of hepatitis B surface antigen or hepatitis C virus RNA.

Table 1: **Baseline demographic and clinical characteristics**

Role of the funding source

The funder had a role in study design, study management, data collection, data analysis, data interpretation, and writing of the report.

Results

Among 766 participants treated in the double-blind phase of DRIVE-FORWARD, 492 entered the extension, including 259 participants who continued doravirine and 233 who switched from ritonavir-boosted darunavir to doravirine, with 406 (83%) participants completing the 96-week extension. Among 728 participants treated in the double-blind phase of DRIVE-AHEAD, 560 entered the extension, including 291 participants who continued doravirine and 269 who switched from efavirenz to doravirine, with 435 (78%) participants completing the extension. In both trials, the main reason for discontinuation from the extension was withdrawal by the participant (appendix p 9).

Baseline demographics and prognostic characteristics for participants who were randomly assigned to doravirine (doravirine cumulative group; n=747), participants who continued doravirine in the extension (doravirine continued group; n=550), and participants who switched to doravirine in the extension (doravirine switch group; n=502) were generally similar between all groups in both trials and most representative of young White males (table 1). In both trials, most participants had CD4⁺ T-cell counts greater than 200 cells per µL and HIV-1 RNA less than or equal to 100 000 copies per mL at the time of random assignment (table 1).[8,10] Of the DRIVE-FORWARD participants who switched to doravirine plus

two NRTIs during the extension, 203 (87%) of 233 received tenofovir disoproxil fumarate plus emtricitabine (appendix p 3) and 30 (13%) received abacavir sulfate plus lamivudine.

Among the 747 participants in the doravirine cumulative group, efficacy analyses using the FDA snapshot approach showed virological suppression (HIV-1 RNA <50 copies per mL) at week 192 in 457 (61%) participants and HIV-1 RNA of 50 copies per mL or more in 121 (16%) participants. There were no virological data available for 169 (23%) participants. The most common reason for missing data was discontinuation for reasons not related to treatment (appendix p 4). When efficacy was assessed using the observed failure approach, which excludes participants with missing data, 457 (79%) of 578 participants in the doravirine cumulative group were virologically suppressed at week 192 (figure 1A). In this group, the mean change in CD4⁺ T-cell counts from day 1 to week 192 was 236 cells per µL (95% CI 217–256).

Among participants who entered the extension, HIV-1 RNA less than 50 copies per mL (FDA snapshot approach) was maintained at week 192 in 457 (83%) of 550 participants in the doravirine continued group and 404 (80%) of 502 participants in the doravirine switch group (appendix p 4). Using the observed failure approach, 457 (95%) of 480 participants in the doravirine continued group and 404 (90%) of 447 participants in the doravirine switch group had HIV-1 RNA less than 50 copies per mL at week 192 (figure 1B). CD4⁺ T-cell counts continued to increase from week 96 to week 192 with a mean change from baseline of 48 cells per µL (95% CI 31–65) for the doravirine continued group and 65 cells per µL (46–83) for the doravirine switch group. Efficacy outcomes for the doravirine continued group in DRIVE-FORWARD were similar to those in DRIVE-AHEAD; efficacy outcomes for the doravirine switch groups were also similar between the trials (appendix p 5).

By week 192, PDVF was observed in 83 (11%) of 747 participants in the doravirine cumulative group: 49 with HIV-1 RNA of 200 copies per mL or less and 34 with more than 200 copies per mL at the confirmation visit (data not shown). Most virological failures occurred in the base studies (n=68), with 41 occurring in the first 48 weeks (appendix p 6). During the extension, 15 (3%) of 550 participants in the doravirine continued group met criteria for PDVF: 12 with HIV-1 RNA of 200 copies per mL or less and three with more than 200 copies per mL. Among participants in the doravirine switch group, PDVF was observed in 26 (5%) of 502 participants: 16 with HIV-1 RNA of 200 copies per mL or less and ten with more than 200 copies per mL. In a post-hoc analysis, a baseline CD4⁺ T-cell count of 200 cells per µL or less and age younger than the median age of the group (median 32 years [95% CI 30–34]) were associated with increased risk of PDVF, whereas baseline viral load, HIV subtype, sex, and treatment adherence were not significant predictors of PDVF (appendix p 7). Overall drug adherence was near 100% among participants with and without PDVF based on participant self-reporting.

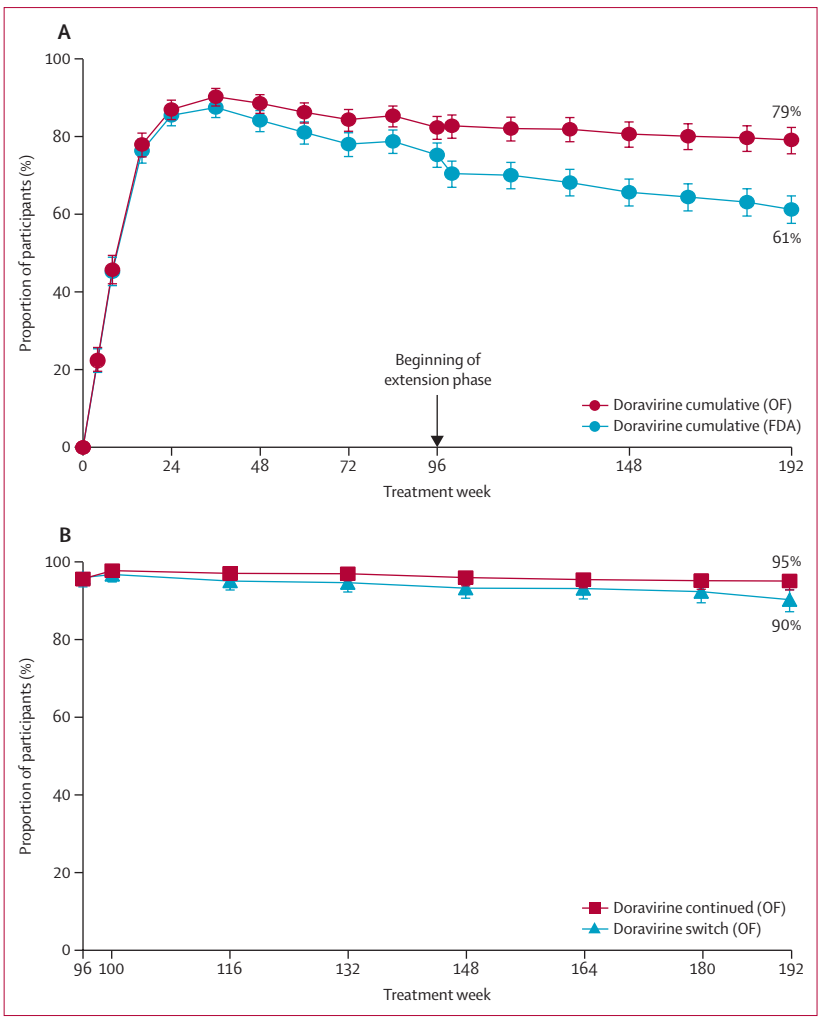

Figure 1: **Proportion of participants with HIV-1 RNA less than 50 copies per mL over time**
(A) All participants randomly assigned to doravirine. The first measurement in the extension was at week 100. (B) Participants who entered the open-label extension. Error bars show 95% CIs. FDA=US Food and Drug Administration snapshot approach. OF=observed failure approach.

51 (7%) of 747 participants from the doravirine cumulative group met criteria for resistance testing (34 with PDVF and 17 who discontinued early without PDVF). Genotypic resistance to doravirine was detected in ten (1%) participants during the base studies (nine within the first 48 weeks), eight with phenotypic resistance, and in two participants during the extension, one with phenotypic resistance. The three participants without phenotypic resistance had the following reverse transcriptase substitutions: Tyr318Tyr or Tyr318Phe (0·35-fold reduced susceptibility), Val106Ile (0·84-fold reduced susceptibility), and Ala98Gly plus Val106Val or Val106Ile (1·66-fold reduced susceptibility). Eight (1%) of 747 participants in the doravirine cumulative group developed genotypic resistance to NRTIs, all during the base studies (seven participants in the first 48 weeks; appendix p 6).

	Doravirine cumulative, day 1–week 192 (n=747)	Doravirine continued, week 96–192 (n=550)	Doravirine switch, week 96–192 (n=502)
One or more adverse events	668 (89%)	409 (74%)	378 (75%)
Serious adverse events	81 (11%)	36 (7%)	28 (6%)
Drug-related adverse events	258 (35%)	38 (7%)	37 (7%)
Serious drug-related adverse events	5 (1%)	2 (<1%)	0
Discontinued due to adverse events	24 (3%)	6 (1%)	4 (1%)
Due to drug-related adverse events	17 (2%)	3 (1%)	1 (<1%)
Due to serious adverse events	5 (1%)	3 (1%)	3 (1%)
Most common adverse events			
Diarrhoea	136 (18%)	27 (5%)	31 (6%)
Nasopharyngitis	129 (17%)	67 (12%)	50 (10%)
Headache	128 (17%)	28 (5%)	30 (6%)
Upper respiratory infection	115 (15%)	46 (8%)	31 (6%)
Nausea	87 (12%)	16 (3%)	11 (2%)
Cough	67 (9%)	25 (5%)	16 (3%)
Fatigue	63 (8%)	9 (2%)	10 (2%)
Dizziness	63 (8%)	7 (1%)	8 (2%)
Back pain	61 (8%)	19 (3%)	18 (4%)
Pharyngitis	57 (8%)	20 (4%)	20 (4%)
Syphilis	57 (8%)	22 (4%)	30 (6%)
Insomnia	55 (7%)	13 (2%)	14 (3%)
Influenza	51 (7%)	23 (4%)	17 (3%)
Bronchitis	49 (7%)	23 (4%)	18 (4%)
Gastroenteritis	45 (6%)	18 (3%)	13 (3%)
Arthralgia	42 (6%)	16 (3%)	11 (2%)
Vomiting	41 (5%)	8 (1%)	5 (1%)

Data are n (%).

Table 2: **Summary of clinical adverse events at week 192**

Nine (2%) participants from the doravirine switch group met criteria for resistance testing (six with PDVF and three who discontinued early without PDVF). Genotypic resistance to doravirine was detected in four (1%) participants; three (1%) with phenotypic resistance. The remaining participant carried the reverse transcriptase substitutions Val106Val or Val106Ala and Phe227Phe, Phe227Cys, Phe227Leu, or Phe227Arg (2·33-fold reduced susceptibility). Two (<1%) of 502 participants in the doravirine switch group developed NRTI genotypic resistance (appendix p 6).

Adverse events reported in 10% or more of participants in any group were diarrhoea, nasopharyngitis, headache, upper respiratory infection, and nausea (table 2). The proportions of participants who reported diarrhoea, headache, and nausea were generally lower during the extension than during the double-blind phase.[9,11] One participant in the doravirine cumulative group died during the first 48 weeks of DRIVE-FORWARD, as described previously; the death was considered not related to study treatment.[8] No deaths were reported during the extension of either trial.

Drug-related adverse events were reported by 258 (35%) of 747 participants in the doravirine cumulative group. During the extension (weeks 96–192), drug-related adverse events were reported by 38 (7%) of 550 participants in the doravirine continued group and 37 (7%) of 502 participants in the doravirine switch group (table 2). Drug-related adverse events led to treatment discontinuation in 17 (2%) of 747 participants in the doravirine cumulative group; most of these discontinuations occurred during the double-blind phase of the trials.[9,11] During the extension, four participants discontinued treatment due to a drug-related adverse event: three (1%) participants from the doravirine continued group discontinued due to angioedema, osteopenia, and insomnia, respectively, and one (<1%) participant from the doravirine switch group discontinued due to increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) that were not associated with viral hepatitis and were resolving by the day after the last dose of study treatment. For the five (1%) participants in the doravirine cumulative group who had serious drug-related adverse events, three participants were in the base studies,[9,11] and two participants were in the extension of DRIVE-FORWARD. Two (<1%) participants in the doravirine continued group had serious drug-related adverse events: one participant had angioedema (noted previously) that resolved after discontinuation and one participant had myocardial infarction, which was treated with stent placement and acetylsalicylic acid, ticagrelor, atorvastatin, candesartan, and bisoprolol. The doravirine-based regimen was continued (with tenofovir alafenamide replacing tenofovir disoproxil fumarate), and the participant was discharged 4 days later in a clinically stable condition.

Through to week 192, the most frequently reported laboratory changes meeting grade 3 and grade 4 criteria were increases in serum creatinine, AST, ALT, lipase, and creatine kinase (table 3). During the extension, grade 3 or 4 increases in ALT occurred in eight (1%) of 548 participants in the doravirine continued group and in eight (2%) of 496 participants in the doravirine switch group. For 11 of these participants, the increased ALT had resolved to grade 0 or 1 by the last on-treatment measurement. Four participants with increased ALT, all in the doravirine continued group, had a clinical diagnosis of viral hepatitis as an adverse event: two in DRIVE-AHEAD had hepatitis C (ALT grade 3 and grade 4; doravirine was discontinued in the participant with ALT grade 4) and two in DRIVE-FORWARD (one with hepatitis A and one with hepatitis C; both ALT grade 4).

Observed changes from baseline for fasting lipids at week 192 in the doravirine cumulative group were small (figure 2A). At week 192, the mean change in the total cholesterol to high-density lipoprotein ratio was –0·2 (95% CI –0·4 to 0·0) in the DRIVE-FORWARD trial and –0·2 (–0·3 to 0·0) in the DRIVE-AHEAD trial for the doravirine cumulative group. For participants who switched to doravirine, the previously reported mean increases in lipid levels from baseline (day 1) through to week 96 while receiving the comparator regimen

(darunavir or efavirenz) were followed by decreases in low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, total cholesterol, and triglycerides from week 96 to week 192 after switching to doravirine (figure 2B, C).

Median bodyweight gain from day 1 to week 192 for the doravirine cumulative group was 1·9 kg (IQR –1·1 to 6·2) in DRIVE-FORWARD and 2·0 kg (–1·7 to 5·7) in DRIVE-AHEAD (appendix p 10). Participants who continued doravirine in the extension had a median weight increase from week 96 to week 192 of 1·0 kg (–1·6 to 3·8) in DRIVE-FORWARD and 0·5 kg (–1·8 to 3·1) in DRIVE-AHEAD. Participants who switched to doravirine in the extension had a median weight gain of 1·5 kg (–1·0 to 4·4) in DRIVE-FORWARD and 2·0 kg (–0·6 to 5·0) in DRIVE-AHEAD between week 96 and week 192.

In DRIVE-FORWARD, eGFR showed a small and similar median decrease between day 1 and week 96 in both treatment groups and remained stable through to week 192 with continued doravirine (median change –11·3 mL per min per 1·73 m² [IQR –19·1 to –3·2]) or switch to doravirine (median change –12·5 mL per min per 1·73 m² [–21·4 to –3·4]; figure 3A). A similar pattern was observed in participants assigned to doravirine plus lamivudine and tenofovir disoproxil fumarate in DRIVE-AHEAD (median change in eGFR –10·5 mL per min per 1·73 m² at week 192 [–19·7 to –1·6]; figure 3B). However, in participants assigned to efavirenz, emtricitabine, and tenofovir disoproxil fumarate, eGFR was stable from day 1 to week 96 and decreased after the switch to doravirine, lamivudine, and tenofovir fumarate (median change –9·3 mL per min per 1·73 m² [–18·6 to –1·9]; at week 192).

Among participants in DRIVE-FORWARD assigned to doravirine plus two NRTIs, the median change in eGFR at week 192 was not substantially different between NRTIs: –11·4 mL per min per 1·73 m² for doravirine plus tenofovir disoproxil fumarate and emtricitabine and –9·0 mL per min per 1·73 m² for doravirine plus abacavir sulfate and lamivudine (appendix p 11). Among participants in DRIVE-FORWARD who switched to doravirine in the extension, the median change in eGFR at week 192 was –13·1 mL per min per 1·73 m² for doravirine plus tenofovir disoproxil fumarate and emtricitabine and –6·1 mL per min per 1·73 m² for doravirine plus abacavir sulfate and lamivudine.

The incidence of a grade 3 or 4 increase in serum creatinine was low: 17 (3%) of 548 participants in the doravirine continued group and one (<1%) of 496 participants in the doravirine switch group. In 11 of these participants, the creatinine level was within normal limits at the last on-treatment measurement, and no participant discontinued doravirine due to increased creatinine.

	Doravirine cumulative, day 1–week 192 (n=747)	Doravirine continued, week 96–192 (n=550)	Doravirine switch, week 96–192 (n=502)
Fasting LDL cholesterol, mg/dL			
Grade 3: ≥190	7/663 (1%)	6/486 (1%)	4/456 (1%)
Fasting triglyceride, mg/dL			
Grade 3: >500–1000	9/669 (1%)	5/494 (1%)	1/457 (<1%)
Grade 4: >1000	0/669	0/494	1/457 (<1%)
Creatinine, mg/dL			
Grade 3: >1·8 to <3·5 × ULN or increase of 1·5 to <2·0 × above baseline	32/743 (4%)	15/548 (3%)	1/496 (<1%)
Grade 4: ≥3·5 × ULN or increase of ≥2·0 × above baseline	5/743 (1%)	2/548 (<1%)	0/496
AST, IU/L			
Grade 3: 5·0 to <10·0 × ULN	14/743 (2%)	7/548 (1%)	5/496 (1%)
Grade 4: ≥10·0 × ULN	3/743 (<1%)	1/548 (<1%)	0/496
ALT, IU/L			
Grade 3: 5·0 to <10·0 × ULN	12/743 (2%)	5/548 (1%)	7/496 (1%)
Grade 4: ≥10·0 × ULN	5/743 (1%)	3/548 (1%)	1/496 (<1%)
Lipase, IU/L			
Grade 3: 3·0 to <5·0 × ULN	20/743 (3%)	9/548 (2%)	5/496 (1%)
Grade 4: ≥5·0 × ULN	9/743 (1%)	3/548 (1%)	3/496 (1%)
Creatine kinase, IU/L			
Grade 3: 10·0 to <20·0 × ULN	28/743 (4%)	8/548 (1%)	11/496 (2%)
Grade 4: ≥20·0 × ULN	20/743 (3%)	9/548 (2%)	5/496 (1%)

Data are n/N (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. LDL=low-density lipoprotein. ULN=upper limit of normal. *Participants were counted once per test in the highest grade reported. Only participants with a worsened grade relative to baseline are included. The most common findings were defined as those occurring in ≥1% of participants in at least one study group.

Table 3: **Most common grade 3 and 4 laboratory findings through to week 192***

Discussion

This pooled analysis of data from the DRIVE-FORWARD and DRIVE-AHEAD studies showed that doravirine maintained efficacy and safety through to 192 weeks as first-line therapy for adults with HIV-1, extending previously published findings that showed the high level of efficacy and safety of doravirine in the same trials at weeks 48 and 96.[8–11] To our knowledge, this is the first report showing the 4-year durability of doravirine for first-line therapy in people with HIV. In addition, doravirine maintained viral suppression in adults who switched from a boosted darunavir-based or efavirenz-based regimen and showed low emergence of resistance. These results are consistent with those reported in the DRIVE-SHIFT trial, in which adults with HIV-1 who were virologically suppressed at baseline on a protocol-specified antiretroviral regimen maintained viral suppression after switching to doravirine, lamivudine, and tenofovir disoproxil fumarate.[16,17] Furthermore, the results of these studies show that a doravirine-based regimen is generally well tolerated as first-line or switch therapy.

At week 192, 83% of participants who continued doravirine in the extension had fewer than 50 copies per mL of HIV-1 RNA (FDA snapshot approach), supporting the durability of doravirine in maintaining viral suppression. In addition, 80% of participants in the doravirine switch group maintained viral suppression at week 192. The

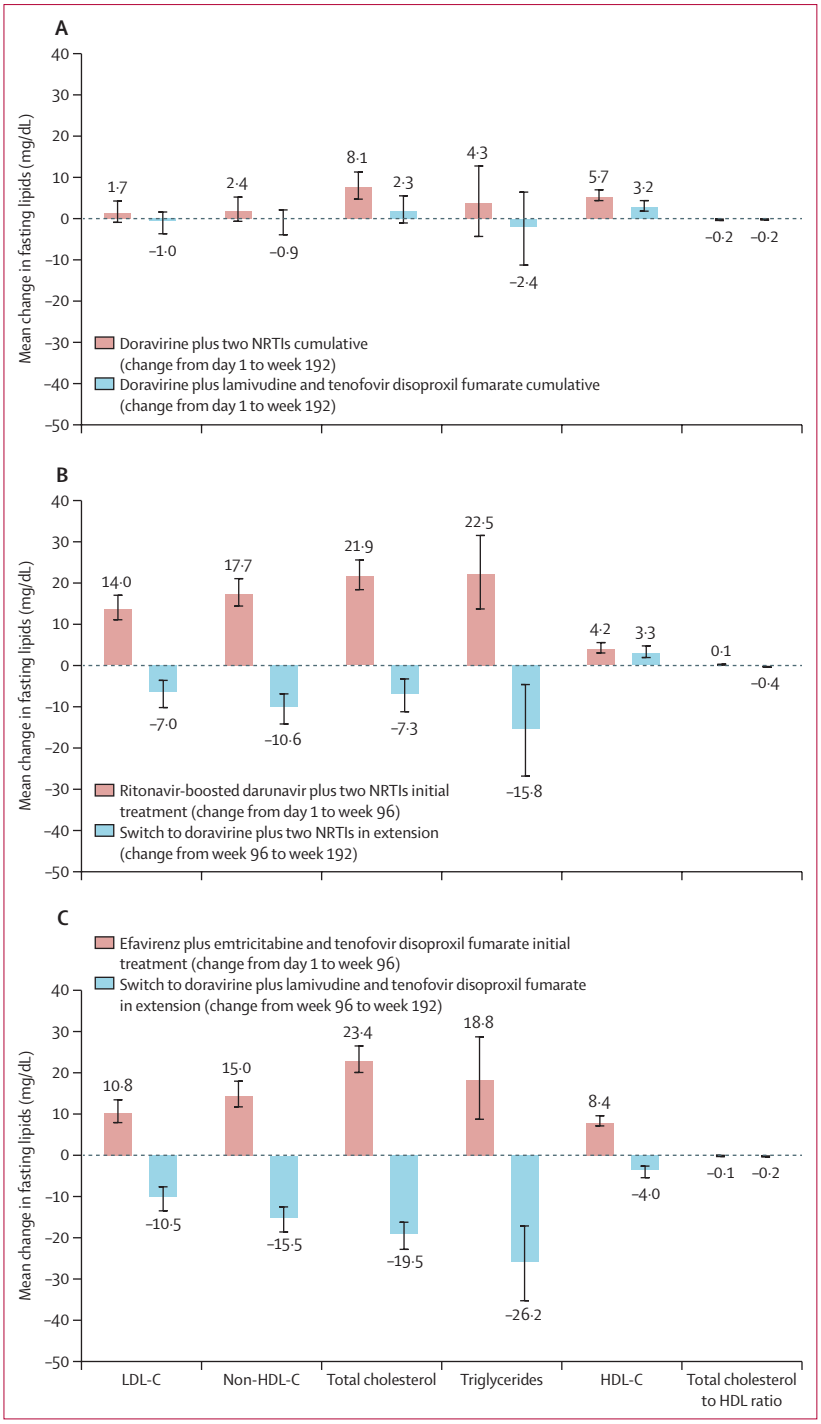

Figure 2: **Mean change in fasting lipids**
(A) Participants randomly assigned to doravirine (change from day 1 to week 192). (B) Participants randomly assigned to darunavir (change from day 1 to week 96) and switched to doravirine (change from week 96 to week 192) in DRIVE-FORWARD. (C) Participants randomly assigned to efavirenz (change from day 1 to week 96) and switched to doravirine (change from week 96 to week 192) in DRIVE-AHEAD. Error bars on all three charts show 95% CIs. HDL-C=high-density lipoprotein cholesterol. LDL-C=low-density lipoprotein cholesterol. non-HDL-C=non-high-density lipoprotein cholesterol. NRTI=nucleoside (or nucleotide) reverse transcriptase inhibitor.

lower efficacy observed in the doravirine cumulative group was mainly due to missing data, which were counted as failure by the FDA snapshot approach. By the observed failure approach (which excludes participants with data missing for non-efficacy reasons), 79% of participants in the doravirine cumulative group were virologically suppressed at week 192. High efficacy was also observed during the study extension using this approach: viral suppression was maintained at week 192 in 95% of participants in the doravirine continued group and 90% of participants in the doravirine switch group. These data suggest that doravirine is similar to other antiretroviral drugs in its durability in maintaining viral suppression even up to 192 weeks.[18–23] Furthermore, the increase in CD4$^+$ T-cell counts that was observed in the base studies[9,11] was maintained through to week 192.

Criteria for PDVF were stringent and required treatment discontinuation if 50 copies per mL or more of HIV-1 RNA was confirmed by a consecutive measurement. Nevertheless, PDVF observed during both trials was low and the majority of PDVF in the doravirine cumulative group occurred in the first 96 weeks (68 [9%] of 747).[9,11] Among participants in the doravirine switch group, PDVF was very low (26 [5%] of 502). Our post-hoc analysis showed baseline CD4$^+$ T-cell count and age were associated with increased risk of PDVF. These results were consistent with previous findings that a CD4$^+$ T-cell count of less than 200 cells per µL is a known predictor for lower virologic response.[24] The previously observed increased risk of PDVF among younger participants might be due to lower drug adherence. Although overall self-reported drug adherence was nearly 100% among participants with or without PDVF, this indirect method has the potential for overestimation.[25]

Development of resistance to doravirine during both trials was low, 12 (2%) of 747 participants in the doravirine cumulative group, with most occurring in the first 48 weeks. Doravirine resistance was also infrequent during the trial extensions, developing in only six (1%) of 1052 participants. Similarly, resistance-associated mutations to NRTIs co-administered with doravirine were identified in only two participants in the doravirine switch group. Together, these data suggest that doravirine was efficacious as long-term therapy, and extended doravirine use as first-line therapy for people with HIV did not lead to later development of viral resistance. These data also provide support for the benefit of doravirine as a switch therapy in people with HIV who are virologically suppressed.

During the base studies, doravirine showed a favourable safety profile compared with efavirenz-based or ritonavir-boosted darunavir-based regimens.[8–11] During the open-label extensions, only 7% of participants in the doravirine continued group reported drug-related adverse events, compared with 32% in the doravirine treatment groups in the base studies;[9,11] this was not unexpected because participants were continuing a regimen they had been

following for almost 2 years. However, the low rate of drug-related adverse events in the doravirine switch group (7%) was surprising because participants who switch regimens often report more adverse events than those who continue their previous regimen.[16] Furthermore, very few participants discontinued doravirine due to drug-related adverse events, demonstrating the tolerability of doravirine through to 192 weeks. Overall, these data validate the favourable safety profile of doravirine as long-term therapy.

People with HIV commonly have dyslipidaemia, which is sometimes associated with antiretroviral therapy and becomes a greater concern with increasing age[11,26,27] because dyslipidaemia can increase the risk of cardiovascular disease among people with HIV.[26] As previously reported, doravirine-based regimens led to minimal changes in fasting lipids during the first 96 weeks of treatment in DRIVE-FORWARD and DRIVE-AHEAD, whereas fasting lipids at week 96 increased in participants who received the comparator regimens.[9,11] During the extension studies, lipid parameters changed minimally in participants who continued doravirine from the base studies, whereas fasting low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, total cholesterol, and triglycerides decreased substantially in participants who switched to doravirine. These results highlight the benefit of doravirine in terms of the lipid profile, whether doravirine is used as first-line treatment or for adults switching regimens.

Weight gain can lead to substantial medical complications for people with HIV. As initial therapy, regimens containing dolutegravir, bictegravir, or tenofovir alafenamide are associated with greater weight gain (mean >4 kg at week 96) than other antiretroviral regimens.[28] Among participants receiving doravirine, minimal weight gain (approximately 2 kg) was observed in the DRIVE-FORWARD and DRIVE-AHEAD cumulative groups at week 192. Tenofovir disoproxil fumarate is associated with weight loss,[29] and the combination with doravirine in these trials might have attenuated any weight gain beyond what is expected in the general population. Similarly, low weight gain was observed between weeks 96 and 192 among the participants who switched to a doravirine-based regimen; these gains might partially be due to the removal of the weight-suppressing effects of efavirenz[30] and the gastrointestinal effects of ritonavir-boosted darunavir.[31] These weight findings and the favourable lipid profiles suggest an overall neutral cardiovascular risk profile of doravirine.

Because reduction in kidney function is commonly observed in people with HIV on therapy, it is important to understand the long-term effects of a doravirine-based regimen on kidney function, especially given its combination with tenofovir in the fixed-dose formulation.[32] Decreases in eGFR observed in DRIVE-FORWARD and DRIVE-AHEAD were relatively small and similar to reductions observed with bictegravir, emtricitabine, and tenofovir alafenamide and dolutegravir-based regimens

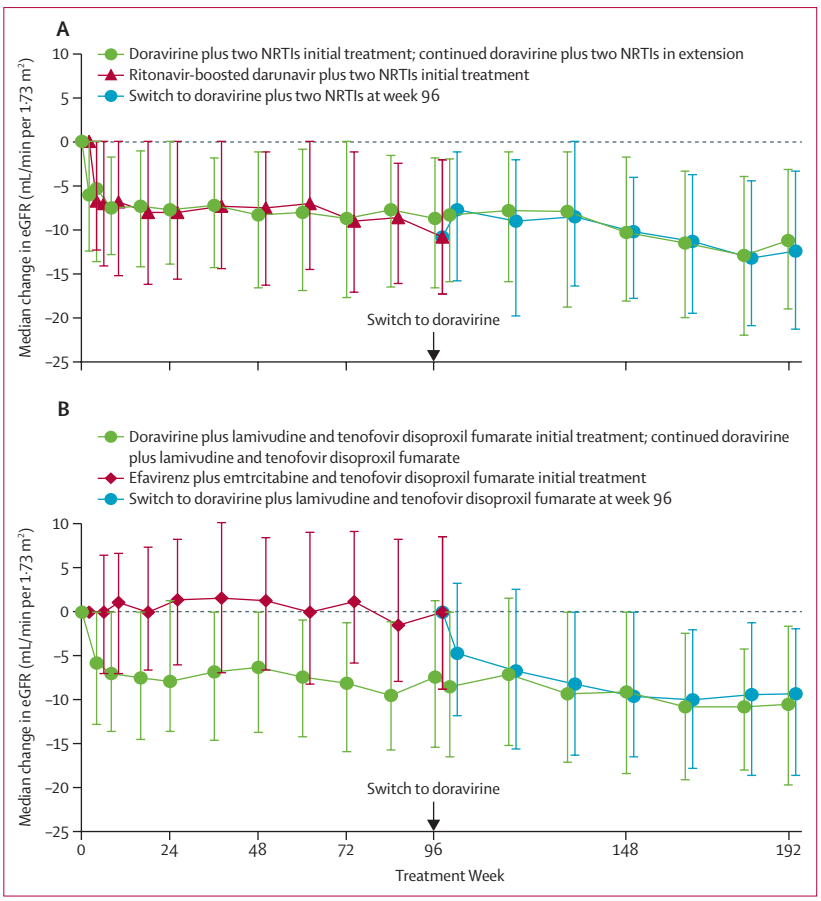

Figure 3: **Median change in eGFR from day 1 through to week 192**
(A) Median change in eGFR for DRIVE-FORWARD participants randomly assigned to doravirine plus two NRTIs who continued their doravirine-based regimen in the extension, and participants randomly assigned to ritonavir-boosted darunavir plus two NRTIs who switched to doravirine plus two NRTIs at week 96. (B) Median change in eGFR for DRIVE-AHEAD participants randomly assigned to doravirine, lamivudine, and tenofovir disoproxil fumarate who continued their doravirine-based regimen in the extension, and participants randomly assigned to efavirenz, emtricitabine, and tenofovir disoproxil fumarate who switched to doravirine, lamivudine, and tenofovir disoproxil fumarate at week 96. Data were offset to avoid overlap. Error bars on both charts show IQRs. eGFR=estimated glomerular filtration rate. NRTI=nucleoside (or nucleotide) reverse transcriptase inhibitor.

for people with HIV.[23] Clinical outcomes potentially related to decreased eGFR were not observed in the current studies; in the extension, the incidence of adverse events that were due to renal abnormalities was low, and zero participants discontinued due to a drug-related renal adverse event. The rapid decrease in eGFR followed by stabilisation over time suggests a mechanism that involves renal transporters, and further investigations of the mechanism of eGFR changes with doravirine are ongoing.

A major strength of the current study is the long-term assessment of doravirine as first-line therapy in people with HIV and as a durable regimen for those who switch to a doravirine-based regimen from another antiretroviral regimen. The use of pooled data from two separate trials allows robust analyses to support the 192-week durability of doravirine, building on the evidence base from the first 96 weeks of the studies. Pooling the switch groups from two trials is a limitation since participants were randomly

assigned to different comparator regimens in the base studies. Other limitations of this study were that most participants were male and of a younger age group, and minority racial and ethnic groups were under-represented, thus limiting the generalisability of the results.

After 192 weeks of treatment, doravirine maintained favourable efficacy and safety profiles in participants who were initially randomly assigned to doravirine and in those who switched to doravirine. These results support the long-term efficacy, safety, durability, and overall therapeutic benefit of doravirine-based regimens.

Contributors

HT, PS, and SK designed the study. CO, J-MM, PC, JL, and KS enrolled the participants and collected the data. HW, VT, and ZJX performed the statistical analyses. RL, ZJX, and CO had direct access to and verified the underlying data reported in this manuscript. All authors contributed substantially to the interpretation of the results and drafting of the manuscript, including critically reviewing or revising the manuscript for important intellectual content. All authors had full access to the study data and had final responsibility for the decision to submit for publication.

Declaration of interests

SK, HC, HW, VT, ZJX, EA-A, PS, HT, and RL are current or former employees of Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA, and may own stock or options in Merck & Co, Rahway, NJ, USA. CO has received grant funding from Gilead Sciences, Merck & Co, ViiV Healthcare, Janssen Pharmaceuticals, and AstraZeneca, and has served on advisory boards for Gilead Sciences, Merck & Co, ViiV Healthcare, and Janssen Pharmaceuticals. J-MM has received grant funding from Gilead Sciences, and has served on advisory boards for Aelix, Gilead Sciences, Merck & Co, and ViiV Healthcare. PC has received grant funding from ViiV Healthcare and Merck & Co; has received consulting fees from ViiV Healthcare; has received payment or honoraria from ViiV Healthcare, Gilead Sciences, and Janssen Pharmaceuticals; and has served on an advisory board for Moderna. KS and JL declare no competing interests.

Data sharing

The data sharing policy, including restrictions, of Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA is available at: http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to dataaccess@merck.com.

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