Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial

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Summary

Background Doravirine is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) with a pharmacokinetic profile supporting once-daily dosing, and potent in-vitro activity against the most common NNRTI-resistant HIV-1 variants. We compared doravirine with ritonavir-boosted darunavir, when both were given with two nucleoside reverse transcriptase inhibitors (NRTIs), in adults with previously untreated HIV-1 infection.

Methods In this randomised, controlled, double-blind, multicentre, non-inferiority trial, adults with HIV-1 infection were screened and enrolled at 125 clinical centres in 15 countries. Eligible participants (aged ≥18 years) were naive to antiretroviral therapy with plasma HIV-1 RNA of at least 1000 copies per mL at screening. Participants who had previously been treated for a viral infection other than HIV-1, those taking immunosuppressive drugs, and individuals with active acute hepatitis were excluded. Participants were randomly assigned (1:1) via an interactive voice and web response system to receive oral doravirine 100 mg or darunavir 800 mg plus ritonavir 100 mg once daily, with two investigator-selected NRTIs (tenofovir and emtricitabine or abacavir and lamivudine) for up to 96 weeks. Randomisation was stratified by HIV-1 RNA measurements at screening (≤100 000 *vs* >100 000 copies per mL) and the NRTI pair. Study participants, funding institution staff, investigators, and study site personnel were masked to treatment group assignment. The primary efficacy endpoint was the proportion of participants achieving HIV-1 RNA of less than 50 copies per mL at week 48 defined by the US Food and Drug Administration snapshot algorithm, with non-inferiority established if the lower bound of the two-sided 95% CI for the treatment difference (doravirine minus darunavir) was greater than –10 percentage points. All participants who received at least one dose of study drug were included in the primary efficacy and safety analyses. This trial is active, but not recruiting, and is registered with ClinicalTrials.gov, number NCT02275780.

Findings Between Dec 1, 2014, and Oct 20, 2015, 1027 participants were screened for eligibility, of whom 769 participants were randomly assigned to treatment (385 with doravirine and 384 with ritonavir-boosted darunavir). 56 participants discontinued treatment in the doravirine group compared with 71 in the darunavir group, mostly due to loss to follow-up. 383 participants who received doravirine and 383 who received darunavir were included in the primary efficacy analyses. At week 48, 321 (84%) participants in the doravirine group and 306 (80%) in the darunavir group achieved plasma HIV-1 RNA of less than 50 copies per mL (difference 3·9%, 95% CI –1·6 to 9·4), indicating non-inferiority of the doravirine regimen. The most common study drug-related adverse events were diarrhoea (21 [5%] of 383 participants in the doravirine group and 49 [13%] of 383 participants in the darunavir group), nausea (25 [7%] *vs* 29 [8%]), and headache (23 [6%] *vs* ten [3%]). 18 participants (six [2%] of 383 participants in the doravirine group *vs* 12 [3%] of 383 participants in the darunavir group) discontinued treatment due to adverse events, which were considered drug-related in four (1%) participants in the doravirine group and 8 (2%) participants in the darunavir group. Serious adverse events occurred in 19 (5%) of 383 participants in the doravirine group and 23 (6%) of 383 in the darunavir roup, and were considered study-drug related in one (<1%) participant of each group.

Interpretation In treatment-naive adults with HIV-1 infection, doravirine combined with two NRTIs might offer a valuable treatment option for adults with previously untreated HIV-1 infection.

Funding Merck & Co.

Lancet HIV 2018

Published Online
March 25, 2018
http://dx.doi.org/10.1016/S2352-3018(18)30021-3

See Online/Comment
http://dx.doi.org/10.1016/S2352-3018(18)30037-7

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Introduction

Although non-nucleoside reverse transcriptase inhibitors (NNRTIs) are important components of combination antiretroviral therapy for previously untreated HIV-1 infection, all available drugs in this class have disadvantages. Efavirenz is the preferred third drug for

Research in context

Evidence before this study

We searched PubMed from inception to March 31, 2017, for clinical trials that mentioned doravirine or MK-1439 and found two previous clinical trials in adults with HIV-1. In a short-term monotherapy study in treatment-naive men with HIV-1 infection, doravirine 25 mg or 200 mg once daily for 7 days had robust antiviral activity, without evidence of viral resistance, and was generally well tolerated. In a phase 2, dose-ranging study in treatment-naive adults, doravirine 100 mg once daily administered with tenofovir disoproxil fumarate and emtricitabine was efficacious and well tolerated, with significantly fewer neuropsychiatric adverse events than efavirenz. To date, no studies have compared doravirine with a protease inhibitor for the treatment of HIV-1 infection.

Added value of this study

To the best of our knowledge, this is the first randomised, controlled, phase 3 trial of the safety and efficacy of doravirine 100 mg for HIV-1 infection. We found that in treatment-naive adults with HIV-1 infection, the antiretroviral efficacy of doravirine was non-inferior to that of ritonavir-boosted darunavir when given with two nucleoside reverse transcriptase inhibitors (NRTIs), as assessed by the proportion of participants who had plasma HIV-1 RNA of less than 50 copies per mL at week 48. Antiretroviral responses were similar in the doravirine and ritonavir-boosted darunavir groups regardless of baseline factors (eg, HIV-1 RNA >100 000 copies per mL and CD4 counts of <200 cells per µL). One participant developed resistance to doravirine and was discontinued by the investigator for non-compliance. Doravirine was generally well tolerated up to 48 weeks of treatment.

Implications of all the available evidence

The safety and efficacy profiles of doravirine observed in this study support and supplement the findings of previous studies and suggest that doravirine 100 mg once daily, given in combination with two NRTIs, might offer a valuable treatment option for adults with previously untreated HIV-1 infection.

use in combination with tenofovir and emtricitabine in WHO guidelines, but in other guidelines (US Department of Health and Human Services, European AIDS Clinical Society [EACS], and British HIV Association [BHIVA] guidelines) it is included only as an alternative regimen because of CNS intolerance[1] and possible association with suicidality.[2] Rash is another common side-effect of efavirenz,[3] and lipid abnormalities seem to be more common with efavirenz than with other NNRTIs.[4] Rilpivirine has low antiviral efficacy in patients with high viral load[5,6] and therefore is not recommended for individuals with baseline HIV-1 RNA of more than 100 000 copies per mL or CD4 counts of less than 200 cells per µL because of the increased risk of virological failure.[7] Additionally, rilpivirine requires dosing with food and should not be given with proton-pump inhibitors, which results in substantial lowering of rilpivirine plasma concentrations.[7] Nevirapine is associated with serious dermatological and hepatic toxicity and should not be prescribed in men with CD4 counts of more than 400 cells per µL or in women with counts greater than 250 cells per µL.[8] Etravirine is not approved for first-line treatment and requires twice-daily dosing.[9] New NNRTI drugs without these limitations are needed.

Doravirine is a novel NNRTI with potent antiviral activity against wild-type HIV-1 (half maximal inhibitory concentration [IC_{50}] 12 nM in the presence of 100% normal human serum) and variants with the most frequently transmitted NNRTI-resistance mutations (ie, Lys103Asn, Tyr181Cys, and Gly190Ala).[10,11] The in-vitro resistance profile of doravirine is distinct from other NNRTIs,[12] and mutant viruses selected by efavirenz or rilpivirine, including those with reverse transcriptase Glu138Lys or Lys101Glu mutations, remain susceptible to doravirine.[10,12] Doravirine is a substrate for cytochrome P450 3A-mediated metabolism but is not thought to have drug interactions via major drug-metabolising enzymes or transporters.[13] No clinically meaningful interactions were observed in healthy volunteers when doravirine was given with tenofovir disoproxil fumarate, atorvastatin, oral contraceptives, or pantoprazole.[14–17] In other phase 1 studies,[18–20] the bioavailability of doravirine was not affected by food intake, age, sex, or moderate hepatic impairment.

In a short-term monotherapy study,[21] doravirine 25 mg or 200 mg once daily for 7 days had antiviral activity and was generally well tolerated in treatment-naive men with HIV. In a phase 2 study[22,23] of treatment-naive adults, doravirine 100 mg once daily given with tenofovir disoproxil fumarate and emtricitabine was efficacious and well tolerated, with significantly fewer neuropsychiatric adverse events than efavirenz. On the basis of these promising results, we did a randomised, controlled, double-blind, phase 3, non-inferiority trial comparing doravirine with ritonavir-boosted darunavir, both given with two nucleoside reverse transcriptase inhibitors (NRTIs), in adults with previously untreated HIV-1 infection.

Methods

Study design and participants

DRIVE-FORWARD is a randomised, controlled, double-blind, parallel-group, non-inferiority phase 3 trial, which was done at 125 clinical centres in 15 countries (Argentina, Australia, Austria, Canada, Chile, Denmark,

France, Germany, Italy, Romania, Russia, South Africa, Spain, UK, USA; appendix p 2). Study investigators enrolled adults (aged ≥18 years) with HIV-1 infection who were naive to antiretroviral therapy, with plasma HIV-1 RNA at screening of at least 1000 copies per mL, alkaline phosphatase concentrations three times the upper limit of normal or less, aminotransferase concentrations five times the upper limit of normal or less, a creatinine clearance rate of 50 mL/min or higher at the time of screening, and no documented or known resistance to any of the study regimen components (defined broadly according to the presence of exclusionary mutations; appendix p 3). Exclusion criteria are listed in the appendix. The study protocol was approved by an independent ethics committee at each study site, and written informed consent was obtained from all participants.

Randomisation and masking

The study investigators randomly assigned participants (1:1), using an interactive voice and web response system, to receive either doravirine or ritonavir-boosted darunavir, with a fixed-dose combination of tenofovir and emtricitabine or abacavir and lamivudine. To conceal treatment assignment, participants also received placebos that matched the other treatment; thus, all participants received four tablets daily. A computer-generated randomised allocation sequence for treatment assignment was created by the funder, and randomisation was stratified by plasma HIV-1 RNA count (≤100 000 or >100 000 copies per mL) at screening and by the NRTI component, which was selected by the investigator. Participants, investigators, study site personnel, and funding institution staff were masked to treatment group assignment.

Procedures

Participants received oral doravirine (100 mg), or darunavir (800 mg) and ritonavir (100 mg), in combination with either tenofovir (300 mg) and emtricitabine (200 mg) or abacavir (600 mg) and lamivudine (300 mg), once a day for up to 96 weeks.

Study visits were scheduled at week 2, 4, 8, 16, 24, 36 and 48. Blood samples for HIV-1 RNA testing were collected at all study visits with the exception of the week 2 safety check. Plasma viral loads were measured by the central laboratory (Quest Diagnostics, Secaucus, NJ, USA) with the Abbott RealTime HIV-1 Assay (Abbott Molecular, Des Plaines, IL, USA), which has a lower limit of quantification of 40 copies per mL. Virological failure was defined as non-response (confirmed HIV-1 RNA of ≥200 copies per mL at week 24 or week 36, or confirmed HIV-1 RNA of ≥50 copies per mL at week 48) or rebound (confirmed HIV-1 RNA of ≥50 copies per mL after initial response [ie, <50 copies per mL] at any time during the study). Confirmatory HIV-1 RNA samples were collected 1–4 weeks after the original sample. Study treatment was discontinued if participants met criteria for protocol-defined virological failure (PDVF), regardless of compliance to study therapy.

Genotypic testing of viral reverse transcriptase and protease sequences and tests for phenotypic resistance were done in participants with PDVF and those who discontinued the trial for any reason. Testing required samples with HIV-1 RNA of more than 400 copies per mL and was done by Monogram Biosciences (San Fransisco, CA, USA) with samples from virological failure confirmation visits or, if not available, from early discontinuation visits. Genotypic resistance to doravirine after baseline was defined by the presence of any of the following mutations in the reverse transcriptase gene: Leu100Ile, Lys101Glu, Val106Ala, Val106Ile, Val106Met, Val108Ile, Glu138Lys, Tyr188Leu, Gly190Ala, Gly190Ser, His221Tyr, Pro225His, Phe227Cys, Phe227Leu, Phe227Val, Met230Ile, Met230Leu, Leu234Ile, Pro236Leu, or Tyr318Phe. Genotypic resistance to darunavir and the NRTIs used in this trial after baseline was also assessed by Monogram Biosciences. Phenotypic viral resistance was defined on the basis of the difference between the IC_{50} values for participants' virus and wild-type virus. Because the threshold for phenotypic resistance to doravirine has not been defined, an IC_{50} value 2·5 times higher than that for the wild-type virus was used as a broad assay-reproducibility cutoff for potential phenotypic resistance to doravirine, which is commonly done for antiretrovirals in development.

CD4 cell counts (absolute and percentage) were determined at screening, day 1, and weeks 8, 24, and 48 by the central laboratory using flow cytometry. At each study visit, vital signs were measured, adverse events were monitored, and blood samples were collected for laboratory safety tests. All adverse events reported by the participant or observed by the investigator were assessed for maximum intensity, seriousness, association with study drugs, and association with immune reconstitution syndrome. All protocol-required laboratory values were graded according to the Division of AIDS Criteria.[24]

Outcomes

The primary efficacy endpoint was the proportion of participants who had plasma HIV-1 RNA of less than 50 copies per mL at week 48 as defined by the US Food and Drug Administration (FDA) snapshot algorithm.[25] Secondary endpoints were HIV-1 RNA of less than 40 copies per mL and change from baseline in CD4 T-cell count. Exploratory endpoints were HIV-1 RNA of less than 200 copies per mL, time to loss of virological response, PDVF, and the development of viral resistance to the study medications. Safety outcomes were change from baseline in LDL-cholesterol and non-HDL-cholesterol, incidence of adverse events, time to discontinuation because of adverse events, and predefined limits of change in laboratory parameters.

Statistical analysis

Assuming a true response rate of 80% at week 48, a sample size of 340 participants per treatment group

See Online for appendix

would achieve 90% power to detect non-inferiority at a one-sided α of 0·025. Non-inferiority was established if the lower bound of the two-sided 95% CI for the treatment difference (doravirine minus darunavir) was greater than –10 percentage points.

The efficacy analyses used the full analysis set, defined as all randomly assigned participants who received at least one dose of study treatment with participants included in the treatment group to which they were randomly assigned. Assessment of the primary efficacy endpoint used the FDA snapshot approach, which treats all missing data as treatment failures regardless of the reason, including early discontinuation of study therapy. Participants who changed background NRTI therapy after week 2 with HIV-1 RNA of 50 copies per mL or higher at the time of switch were counted as treatment failures at subsequent visits. The difference between treatment groups in the proportion of participants achieving HIV-1 RNA of less than 50 copies per mL and the associated 95% CIs were calculated by the stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of the sample size per arm for each stratum. The secondary and exploratory virological endpoints were analysed using the same method as the primary endpoint. SAS software (version 9.3 or 9.4; SAS Institute, Cary, NC, USA) was used for all analyses.

To assess the consistency of treatment benefit, summary statistics (with 95% CI) and estimates of the between-treatment difference (with a nominal 95% CI) were calculated for the primary endpoint within subgroups based on baseline HIV-1 RNA, assigned NRTI pair, and baseline CD4 cell count. These calculations used the observed failure approach for missing data (ie, participants who discontinued treatment because of poor efficacy were considered to have had treatment failure thereafter). No statistical analyses of treatment effects were done within or between subgroups. The change from baseline in CD4 cell count was summarised by treatment group with the observed failure approach; baseline values were carried forward for participants who discontinued because of poor efficacy, and participants with missing values for other reasons were excluded. The difference between treatments was estimated with the associated 95% CI on the basis of the *t* distribution. The safety analyses used the all-participants as-treated population, defined as all randomly assigned participants who received at least one dose of study treatment with participants included in the treatment group for the regimen they received. The proportions of participants with any adverse event, drug-related or serious adverse events, and discontinuation because of an adverse event were summarised with between-treatment differences and 95% CIs calculated with the Miettinen and Nurminen method.[26] Time to discontinuation because of adverse events was estimated with Kaplan-Meier product-limit estimates.

The change from baseline in fasting lipids was analysed with ANCOVA models adjusted by baseline fasting lipid concentrations and treatment group. The treatment difference and 95% CI were calculated for all lipid parameters; p values for the between-treatment comparison were calculated for LDL-cholesterol and non-HDL-cholesterol only to test the hypothesis that doravirine is superior to ritonavir-boosted darunavir. For participants with missing lipid data, the last lipid observation after randomisation was carried forward. For participants who changed lipid-lowering therapy during the study, the last lipid observation before the change was carried forward for later timepoints.

We did two planned interim analyses. The first analysis assessed the overall neuropsychiatric adverse event profile for doravirine versus ritonavir-boosted darunavir, and was done after 200 participants had completed 8 weeks of treatment. Neuropsychiatric adverse events in the following subcategories were examined: dizziness, sleep disorders or disturbances, altered sensorium, depression and suicide or self-injury, and psychosis and psychotic disorders. This analysis was not expected to lead to study termination for safety reasons and was considered an administrative review of the data; no adjustment for type I error was necessary. The second interim analysis was done when 340 participants had completed 24 weeks of treatment or discontinued treatment before week 24. The study could be stopped if the conditional power needed to demonstrate non-inferiority in the final analysis at week 48 was less than 20% based on the proportion of participants who had plasma HIV-1 RNA of less than 50 copies per mL at week 24. No adjustment for type I error was required.

An external data monitoring committee (DMC) monitored ongoing safety data and provided recommendations to ensure the safety of study participants and the integrity of the trial. Voting members of the DMC included clinicians and an external statistician experienced in HIV-1 infection, and an unblinded trial statistician who helped prepare the analyses for the DMC served as a non-voting member. The DMC reviewed the interim efficacy data and recommended that the trial continue without amendment to the protocol.

This trial is active, but not recruiting, and is registered with ClinicalTrials.gov, number NCT02275780.

Role of the funding source

The funder of the study had a role in study design, study management, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Between Dec 1, 2014, and Oct 20, 2015, 1027 individuals were screened for participation in this study, and 769 were randomly assigned to treatment: 385 to the doravirine

group and 384 to the darunavir group (figure 1). Of the 252 participants who did not meet eligibility criteria, 124 (49%) were excluded because they had one or more mutations associated with decreased susceptibility to any study drug, and 48 (19%) were excluded because they had screening plasma HIV-1 RNA of less than 1000 copies per mL or treatment for HIV-1 infection was not recommended on the basis of physician assessment. Of the 769 participants who were randomly assigned, 383 participants in the doravirine group and 383 participants in the darunavir received at least one dose of study drug and were included in the week 48 analyses. The last follow-up visit included in this publication was on Sept 29, 2016. Overall, 127 (17%) of 766 participants had discontinued study treatment by week 48 (56 [15%] of 383 participants in the doravirine group; 71 [19%] of 383 participants in the darunavir group). In both groups, the most common reason for early discontinuation was loss to follow-up (17 [4%] of 383 participants in the doravirine group; 19 [5%] of 383 participants in the darunavir group).

The median age of the treated population was 33 years (IQR 27–42) and 760 (99%) participants were aged younger than 65 years. The treated population included 645 (84%) men and 121 (16%) women, of whom 560 (73%) were white, 73 (10%) had previously been diagnosed with AIDS (as reported by the investigator), and 538 (70%) had subtype B HIV-1 infection (table 1). At baseline, 22% of the doravirine group and 19% of the ritonavir-boosted darunavir group had plasma HIV-1 RNA of more than 100 000 copies per mL, with 17 (4%) and 12 (3%), respectively, exceeding 500 000 copies per mL.

At week 48, 321 (84%) of 383 participants in the doravirine group and 306 (80%) of 383 participants in the darunavir group had plasma HIV-1 RNA of less than 50 copies per mL (difference 3·9%, 95% CI –1·6 to 9·4; table 2, figure 2), showing non-inferiority of doravirine to darunavir. Similar results were obtained in the per-protocol analysis (appendix p 4). The full characterisation of virological outcomes at week 48 defined by the FDA snapshot algorithm was similar between the treatment groups (table 2). The proportion of participants with HIV-1 RNA of less than 50 copies per mL at each timepoint was similar between the treatment groups, with both groups reaching a plateau at week 24 (figure 2). Among the participants with HIV-1 RNA of 100 000 copies per mL or higher at baseline, 64 (81%) of 79 participants in the doravirine group and 55 (76%) of 72 participants in the darunavir group had plasma HIV-1 RNA of less than 50 copies per mL at week 48 (difference 3·0%, 95% CI –11·2 to 17·1; appendix p 5). In the small subgroup of participants with HIV-1 RNA of more than 500 000 copies per mL at baseline, 14 (82%) of 17 particpants in the doravrine group and six (50%) of 12 participants in the darunavir group had plasma HIV-1 RNA of less than 50 copies per mL at week 48 (difference 30·9%, 95% CI –4·1 to 65·9). Among participants with low CD4 count (<200 cells per µL) at baseline, 34 (83%) of 41 in the doravirine group and 44 (72%) of 61 in the darunavir group had HIV-1 RNA of less than 50 copies per mL at week 48 (difference 9·4% [95% CI –7·4 to 26·2]).

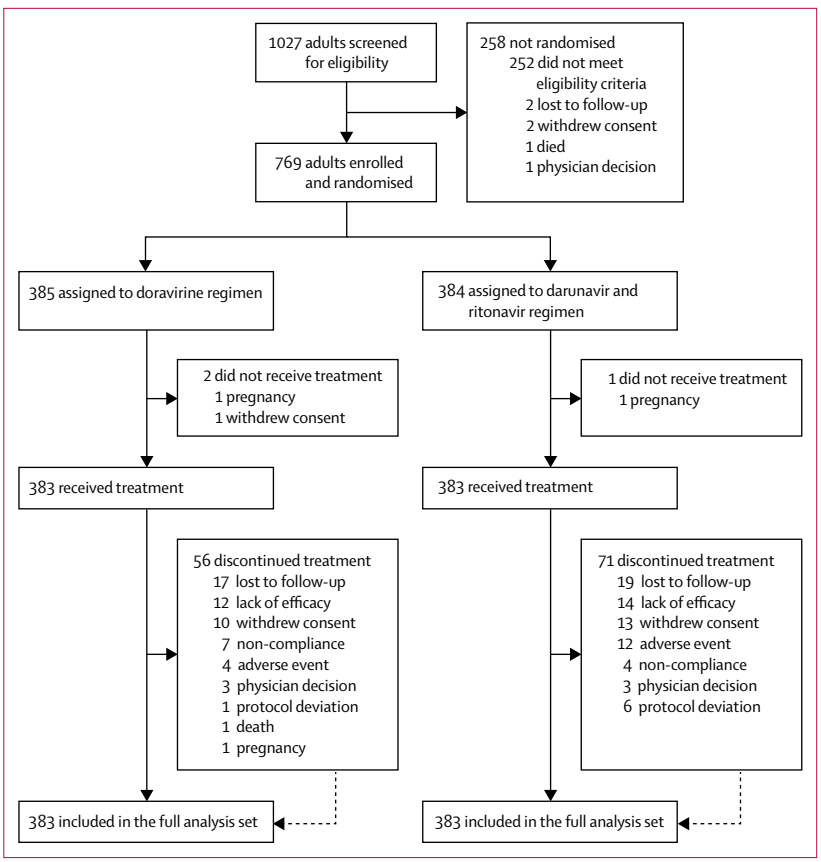

Figure 1: **Trial profile**

Results for the secondary virological endpoints were consistent with those for the primary endpoint (appendix p 4). Using the observed failure approach, at week 48, 321 (88%) of 364 participants in the doravirine group and 306 (86%) of 355 participants in the darunavir group achieved HIV-1 RNA of less than 50 copies per mL. At week 48, the mean change from baseline in CD4 cell counts was 193 per µL (95% CI 172 to 214) in the doravirine group and 186 per µL (168 to 204) in the darunavir group (mean difference 7·1 per µL, 95% CI –20·8 to 35·0).

19 (5%) of 383 participants in the doravirine group and 24 (6%) of 383 participants in the darunavir group had PDVF at week 48, which was because of virological rebound after an initial response in most cases: 17 (89%) of 19 participants in the doravirine group and 19 (79%) of 24 participants in the darunavir group. At the virological failure confirmation visit, 12 (63%) of 19 participants in the doravirine group and 14 (58%) of 24 participants in the darunavir group had plasma HIV-1 RNA of less than 200 copies per mL. Among the

participants with virological rebound, nine (53%) of 17 participants in the doravirine group and ten (53%) of 19 participants in the darunavir and ritonavir group had HIV-1 RNA of less than 100 copies per mL.

Resistance testing was done in 15 of 43 participants with PDVF at week 48 (seven participants in the doravirine group; eight in the darunavir group; appendix p 7). Of the remaining 28 participants with PDVF, 24 were not tested because they had HIV-1 RNA of less than 400 copies per mL (11 participants in the doravirine group; 13 in the darunavir group), two participants in the darunavir group had samples collected after the data cutoff, and two did not have samples collected because of site error (one participant in both groups). In the doravirine group, no genotypic mutations associated with resistance to doravirine were identified and no phenotypic resistance to doravirine was observed. In the darunavir group, polymorphic mutations in the viral protease gene were identified in three participants (with no decrease in phenotypic susceptibility to darunavir; appendix p 6). No primary genotypic resistance mutations or phenotypic resistance to emtricitabine, tenofovir, abacavir, or lamivudine were detected in any participant of either treatment group.

93 participants discontinued study treatment early for reasons other than PDVF, 40 (10%) of 383 participants in the doravirine group and 53 (14%) of 383 participants in the darunavir group; two (1%) participants in the doravirine group and three (1%) in the darunavir group had samples with sufficient HIV-1 RNA for resistance testing (>400 copies per mL) at the time of discontinuation (appendix p 6). One participant in the doravirine group, who discontinued treatment because of non-compliance at week 24, developed resistance to doravirine (reverse transcriptase Val106Ile, His221Tyr, and Phe227Cys mutations and IC_{50} 97 times higher than wild-type virus IC_{50}) and emtricitabine (reverse transcriptase Met184Val mutation). This participant did not meet the criteria for

	Doravirine regimen (n=383)	Darunavir and ritonavir regimen (n=383)
Sex		
Men	319 (83%)	326 (85%)
Women	64 (17%)	57 (15%)
Race		
White	280 (73%)	280 (73%)
Black	86 (22%)	88 (23%)
Asian	7 (2%)	7 (2%)
Other*	10 (3%)	7 (2%)
Ethnic origin		
Hispanic or Latino	93 (24%)	86 (22%)
Region		
Europe	170 (44%)	179 (47%)
North America	140 (37%)	146 (38%)
South America	38 (10%)	33 (9%)
Africa	23 (6%)	22 (6%)
Asia-Pacific	12 (3%)	3 (1%)
Median age, years	33·0 (27–41)	34·0 (27–43)
Median CD4 count (cells per μL)	410 (299–550)	393 (257–547)
CD4 count (cells per μL)		
≤200	42 (11%)	67 (17%)
>200	341 (89%)	316 (83%)
Median HIV-1 RNA log_{10} copies per mL	4·4 (4·0–4·9)	4·4 (4·0–4·8)
HIV-1 RNA concentration†		
≤100 000 copies per mL	300 (78%)	308 (80%)
>100 000 copies per mL	83 (22%)	74 (19%)
Previous AIDS diagnosis	36 (9%)	37 (10%)
NRTI component†		
Tenofovir and emtricitabine	333 (87%)	335 (87%)
Abacavir and lamivudine	50 (13%)	48 (13%)
Hepatitis B or C positive‡	11 (3%)	18 (5%)
HIV viral subtype		
Subtype B	266 (69%)	272 (71%)
Subtype non-B	117 (31%)	111 (29%)

Data are n (%) or median (IQR). Doravirine and ritonavir-boosted darunavir treatment were given with a fixed-dose combination of tenofovir and emtricitabine or abacavir and lamivudine. NRTI=nucleoside reverse transcriptase inhibitor. *Other includes multiracial, American Indian, Alaska Native, Native Hawaiian, and Pacific Islanders. †Stratification factor for randomisation. ‡Presence of hepatitis B surface antigen or presence of hepatitis C virus RNA was assessed by PCR quantitative tests.

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

	Doravirine regimen (n=383)	Darunavir and ritonavir regimen (n=383)
HIV-1 RNA <50 copies per mL	321 (84%)	306 (80%)
HIV-1 RNA ≥50 copies per mL	43 (11%)	50 (13%)
HIV-1 RNA ≥50 copies per mL in week 48 window	12 (3%)	14 (4%)
Changed background therapy	0	1 (<1%)
Treatment discontinued before week 48 due to lack of efficacy	8 (2%)	11 (3%)
Treatment discontinued before week 48 for other reasons with last available HIV-1 RNA ≥50 copies per mL	23 (6%)	24 (6%)
No virological data available in the week 48 window	19 (5%)	27 (7%)
Discontinued study because of adverse event or death*	5 (1%)	11 (3%)
Discontinued study for other reasons†	11 (3%)	15 (4%)
On study but missing data in the week 48 window	3 (1%)	1 (<1%)

Data are n (%). Doravirine and ritonavir-boosted darunavir regimens were given with fixed-dose combinations of tenofovir and emtricitabine or abacavir and lamivudine. *Participants who discontinued treatment because of adverse event or death at any timepoint between day 1 and the end of the week 48 window if this resulted in no virological data on treatment during the specified window. †Other reasons include loss to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol violation, and participant decision.

Table 2: **Virological outcomes at week 48 window (days 295–378)**

PDVF because no confirmation sample was collected. Another participant in the doravirine group, who discontinued treatment due to rash at week 2, was identified as phenotypically resistant (IC_{50} 2·8 times higher than wild-type virus). However, no resistance mutations to doravirine or other NNRTIs were identified, and the IC_{50} increase was minimal when compared with the 2·2 times increase in IC_{50} identified in this participant at baseline.

Clinical adverse events were reported by 307 (80%) of 383 participants in the doravirine group and 300 (78%) of 383 participants in the darunavir group (table 3) and were considered related to study therapy in 117 (31%) participants and 123 (32%) participants, respectively. The most common drug-related adverse events were diarrhoea (21 [5%] of 383 participants in the doravirine group and 49 [13%] of 383 participants in the darunavir group), nausea (25 [7%] *vs* 29 [8%]), and headache (23 [6%] *vs* ten [3%]). These events were also the most commonly reported adverse events overall, regardless of association with study medication. With the exception of the higher incidence of diarrhoea in the darunavir group than the doravirine group, no clinically relevant differences were identified between treatment groups in the incidence of specific drug-related adverse events. The incidence of skin rash and neuropsychiatric events was similar between the treatment groups (table 3). Most cases of rash were mild (21 participants in the doravirine group; 27 participants in the darunavir group). Three participants discontinued treatment because of rash: two in the doravirine group (one moderate and one severe) and one (moderate) in the darunavir group. None of the neuropsychiatric events resulted in treatment discontinuation, and suicidal behaviour was not reported in either group.

19 (5%) of 383 participants in the doravirine group and 23 (6%) of 383 participants in the darunavir group had serious adverse events, but these were considered drug-related in only one participant (<1%) in each group: one participant in the doravirine group had nausea and vomiting that resolved after 4 days without dose interruption or modification, and one participant in the darunavir group had peripheral oedema and was withdrawn from the study, but recovered after 1·2 months. One participant (aged 41 years) in the doravirine group with history of tuberculosis, seizures, hypersensitivity, and hypertension, died after about 7 months in the study of unknown causes, which were not thought to be related to study therapy. On day 222 (the last reported dose), the patient reported dizziness and subsequently collapsed and died in his home. At the time of death, mild muscle spasms, mild cough, and mild diarrhoea were ongoing, but no other deterioration of health was reported before death.

Six (2%) of 383 participants in the doravirine group and 12 (3%) of 383 participants in the darunavir group discontinued the study due to adverse events, which were considered drug-related in four (1%) participants in the doravirine group (nausea [n=1], abdominal pain and nausea [n=1], and rash [n=2]) and eight (2%) participants in the darunavir and ritonavir group (abdominal pain and hiatus hernia [n=1]; abdominal pain, flatulence, and nausea [n=1]; diarrhoea [n=1]; increased alanine transaminase and aspartate transaminase [n=1];

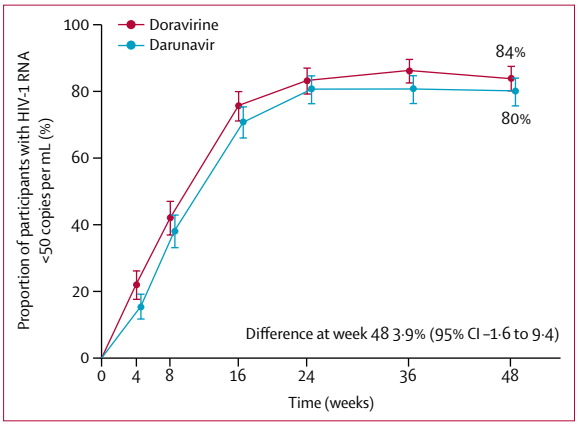

Figure 2: **Proportion of participants with HIV-1 RNA of less than 50 copies per mL by visit**
Plasma viral loads were defined by use of the US Food and Drug Administration snapshot algorithm (ie, participants who did not complete treatment are considered to have treatment failure). Error bars show 95% CI.

	Doravirine regimen (n=383)		Darunavir and ritonavir regimen (n=383)	
	All cause	Treatment-related	All cause	Treatment-related
Any adverse event	307 (80%)	117 (31%)	300 (78%)	123 (32%)
Serious adverse event	19 (5%)	1 (<1%)	23 (6%)	1 (<1%)
Discontinued due to adverse event*	6 (2%)	4 (1%)	12 (3%)	8 (2%)
Most common adverse events†				
Upper abdominal pain	19 (5%)	9 (2%)	10 (3%)	2 (1%)
Diarrhoea	54 (14%)	21 (5%)	86 (22%)	49 (13%)
Nausea	41 (11%)	25 (7%)	46 (12%)	29 (8%)
Fatigue	31 (8%)	18 (5%)	20 (5%)	8 (2%)
Nasopharyngitis	30 (8%)	0	39 (10%)	0
Upper respiratory infection	36 (9%)	0	23 (6%)	0
Back pain	21 (5%)	0	8 (2%)	0
Dizziness	19 (5%)	11 (3%)	15 (4%)	7 (2%)
Headache	53 (14%)	23 (6%)	41 (11%)	10 (3%)
Cough	19 (5%)	1 (<1%)	6 (2%)	0
Events of clinical interest				
Rash‡	28 (7%)	8 (2%)	32 (8%)	12 (3%)
Neuropsychiatric§	44 (11%)	22 (6%)	50 (13%)	19 (5%)

Data are n (%). Both regimens were administered with a fixed-dose combination of tenofovir and emtricitabine or abacavir and lamivudine. *The number of participants who discontinued in the doravirine group includes one participant who died and one who discontinued after week 48. †Incidence of 5% or more in either treatment group. ‡Two participants in the doravirine group and one participant in the darunavir group discontinued study treatment due to rash. §Neuropsychiatric events include disturbances in attention, dizziness, somnolence, abnormal dreams, confusion, depressed mood, depression, insomnia, major depression, nightmares, and psychotic disorder. No participants discontinued study treatment due to neuropsychiatric adverse events.

Table 3: **Summary of adverse events**

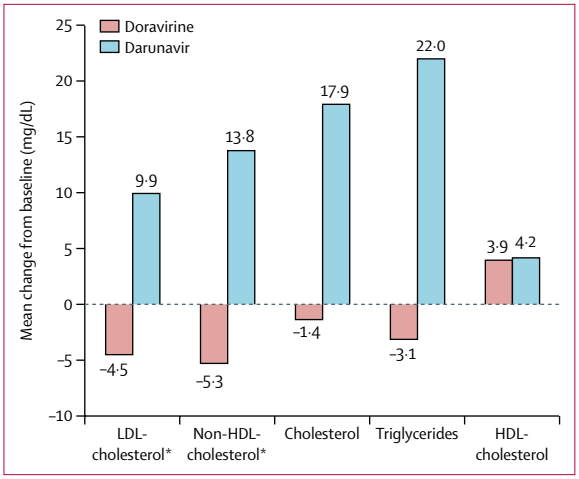

Figure 3: **Change from baseline in fasting lipid concentrations at week 48**
Statistical analyses were not prespecified for cholesterol, triglyceride, or HDL-cholesterol. *p<0·0001 for between-group comparison.

increased alanine transaminase, increased aspartate aminotransferase, and creatine phosphokinase [n=1]; peripheral oedema [n=1]; pyrexia [n=1]; and rash [n=1]). The Kaplan-Meier product-limit estimates revealed a smaller risk of discontinuation as a result of adverse events in the doravirine group than the darunavir group (appendix p 7).

The incidence of grade 3 or 4 laboratory abnormalities were similar between the regimens (appendix p 8), with the exception of increases in LDL-cholesterol concentration (grade 3), which occurred in one (<1%) participant in the doravirine group compared with nine (3%) participants in the darunavir group (difference −2·5%, 95% CI −5·0 to −0·8). The mean change in LDL-cholesterol from baseline to week 48 was −4·5 mg/dL (SD 20·6) in the doravirine group versus 9·9 mg/dL (27·3) in the darunavir group (mean difference −14·6 mg/dL, 95% CI −18·2 to −11·1; p<0·0001, figure 3). The mean change in non-HDL-cholesterol was similar (mean difference −19·3 mg/dL, −23·3 to −15·4; p<0·0001, figure 3). Total cholesterol and triglyceride concentrations decreased slightly in the doravirine group and increased in the darunavir group, whereas HDL-cholesterol increased slightly in both groups (figure 3). Six (2%) of 383 participants in the doravirine group and four (1%) of 383 in the darunavir and group started lipid-lowering therapy during the first 48 weeks of the study.

A grade 3 increase in serum creatinine occurred in five (1%) of 383 participants in the doravirine group and ten (3%) of 383 in the darunavir group (appendix p 9). The mean change from baseline in serum creatinine over time ranged from 0·04 mg/dL (SD 0·07) to 0·07 mg/dL (0·09) in the doravirine group and from 0·05 mg/dL (0·09) to 0·06 mg/dL (0·10) in the darunavir group (appendix p 9). None of the study participants discontinued therapy due to suspected tenofovir-related renal disease.

Discussion

In this randomised, double-blind, multicentre, phase 3, non-inferiority trial doravirine was compared with darunavir, both in combination with two NRTIs, for the treatment of antiretroviral-naive adults with HIV-1. At week 48, the efficacy of doravirine was non-inferior to that of darunavir, with 84% of participants in the doravirine group and 80% of participants in the darunavir group achieving plasma HIV-1 RNA counts of less than 50 copies per mL. The efficacy of doravirine was similar to that of ritonavir-boosted darunavir in participants with baseline HIV-1 RNA of more than 100 000 copies per mL or with baseline CD4 counts of less than 200 cells per µL. The change in CD4 cell counts from baseline to week 48 was also similar in the two treatment groups.

The proportion of participants with HIV-1 RNA of less than 50 copies per mL in the doravirine group (84%) was similar to that observed for the NNRTIs rilpivirine and efavirenz in ECHO (83% and 83%)[5] and THRIVE (86% and 82%).[27] However, the proportion of participants with a virological response in the darunavir group (80%) was lower than reported in ARTEMIS (84%)[28] and FLAMINGO (83%).[29] This result might be associated with the proportion of participants who discontinued treatment with ritonavir-boosted darunavir for reasons other than poor efficacy (57 [15%] of 383 participants), which decreases the observed response rate found with the FDA snapshot algorithm.

Another possible reason for lower efficacy is the definition of PDVF used in this trial: specifically, discontinuation from the trial was required for participants with confirmed plasma HIV-1 RNA of more than 50 copies per mL after suppression to less than 50 copies per mL at any time during the trial. Other clinical trials have allowed participants to remain on study treatment despite meeting PDVF criteria or have used a higher, clinically relevant threshold for PDVF (ie, 200 copies per mL).[29,30] Most participants who met PDVF criteria in our study had HIV-1 RNA of less than 200 copies per mL and most participants with virological rebound had HIV-1 RNA of less than 100 copies per mL. If these participants had been allowed to continue in the trial, viral loads might have been suppressed again to less than 50 copies per mL in some participants. Notably, efficacy results for the darunavir group determined with the observed failure approach (86%) were more similar to results of other trials[28,29] of darunavir in treatment-naive participants with HIV-1 infection.

The efficacy observed across subgroups indicates that doravirine has similar efficacy to an approved preferred protease inhibitor that is part of the current recommended standard of care in EACS and BHIVA treatment guidelines. Although lower efficacy was observed in participants with high baseline HIV-1 RNA measurements or low pretreatment CD4 cell count in both treatment groups, these findings are consistent with previous reports[31,32] for other antiretroviral drugs, and were less

pronounced for the doravirine group than for the darunavir group. In both treatment groups, efficacy was similar regardless of the NRTI component, which was tenofovir and emtricitabine in 668 (87%) of 769 participants.

The proportion of participants with PDVF was low: 5% in the doravirine group and 6% in the darunavir group. Among individuals with PDVF who had successful genotype and phenotype testing, no primary genotypic resistance mutations or phenotypic resistance to any study drug was identified in either treatment group. Of 127 participants who discontinued early, one individual in the doravirine group developed both genotypic and phenotypic resistance to doravirine and emtricitabine. Thus, the overall proportion of participants who developed resistance to doravirine was 0·3% (one of 383), which is lower than reported for other NNRTIs in recent trials (eg, 1·0–2·3% for efavirenz after 48 weeks).[33,34] However, additional data are needed to confirm these findings because resistance was assessed in only a few participants with low viral loads. Additionally, cross-resistance to other NNRTIs requires investigation.

Doravirine was generally well tolerated, with few discontinuations because of adverse events (2%) and only one drug-related serious adverse event (1%). We found no clinically relevant differences in incidence of specific adverse events between treatment groups, with the exception of a higher incidence of diarrhoea in the darunavir group (22% *vs* 14%), which is consistent with the known safety profile of ritonavir-boosted darunavir. The effect of doravirine on fasting lipid concentrations was superior to that of ritonavir-boosted darunavir, as shown by significant between-treatment differences for the mean change from baseline in LDL-cholesterol and non-HDL-cholesterol concentrations.

The incidences of rash and neuropsychiatric adverse events in the doravirine group were similar to those in the darunavir group, and most of these events were of mild intensity. Only two participants discontinued treatment with doravirine because of rash, and no participants in the trial discontinued due to a neuropsychiatric adverse event. Compared with other NNRTIs, the incidences of rash and neuropsychiatric events in this study were similar to those observed with rilpivirine and lower than those observed with efavirenz in the ECHO and THRIVE studies.[5,27] In a direct comparison with efavirenz, the proportion of participants with neuropsychiatric events was significantly lower in the doravirine group at week 8 (22% *vs* 44%)[22] and week 24 (27% *vs* 46%).[23] Preliminary results from the ongoing DRIVE-AHEAD[35] study show a superior neuropsychiatric profile for the fixed combination of doravirine, lamivudine, and tenofovir disoproxil fumarate compared with efavirenz, emtricitabine, and tenofovir.

The ritonavir-boosted darunavir regimen was chosen as the comparator in this study because it is among the recommended first-line drugs in multiple HIV treatment guidelines. Because darunavir and ritonavir are not coformulated, study participants were required to take four pills daily to conceal treatment assignments. This led to challenges for recruitment and retention and might have contributed to the higher rate of loss to follow-up and participant withdrawal than in other trials. Although the resistance profile of doravirine seems encouraging since only one participant developed genotypic and phenotypic resistance to doravirine, more clinical data for doravirine are needed. Ongoing and future studies will provide further insight into the resistance profile of doravirine. Another limitation of this study is the low number of women (121 [16%]) and participants aged older than 65 years (1%) enrolled in the trial.

In summary, we found that the antiretroviral efficacy of doravirine was non-inferior to that of ritonavir-boosted darunavir, as assessed by the proportion of participants achieving HIV-1 RNA less than 50 copies per mL at week 48. The antiviral response rates were similar in both treatment groups regardless of baseline factors, such as HIV-1 RNA of more than 100 000 copies per mL and CD4 counts of less than 200 cells per µL. Resistance to doravirine developed in one participant, who was discontinued from the trial by the investigator because of non-compliance. Doravirine was generally well tolerated during 48 weeks of treatment and had a favourable safety and lipid profile compared with darunavir and ritonavir. For people with HIV, doravirine presents another treatment option, with broad efficacy that is similar to two well established antiretroviral drugs (darunavir and efavirenz), a unique resistance profile, excellent tolerability, a superior neuropsychiatric profile compared with efavirenz, and a superior lipid profile compared with ritonavir-boosted darunavir.

Contributors

J-MM, KS, PES, and PC contributed to the study concept and design. J-MM, PC, JL, and ED were primary investigators for the study. M-TL provided the viral resistance data. XX and AR provided the statistical plan and did the statistical analysis. LL, SK, PS, B-YN, and CH designed the study and provided study management and clinical oversight. All authors interpreted the data, provided input to the report reviewed the manuscript, and approved the final version.

Declaration of interests

J-MM reports grants from Merck and Gilead, speaker fees from Gilead, and has served on advisory boards for Merck, Gilead, Janssen, Bristol-Myers Squibb, ViiV Healthcare, and Teva. KS reports grants awarded to her institution, Thomas Jefferson University, from Gilead Sciences and has served on advisory boards for Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare. PES has served as a consultant or scientific advisory board member for AbbVie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, ViiV Healthcare, Merck, and Janssen; and reports grants from Bristol-Myers Squibb, Gilead, Merck, and GlaxoSmithKline, and ViiV healthcare. PC reports grants from Merck, Abbvie, and ViiV healthcare and personal fees from Merck and ViiV healthcare. ED has served as an advisory board member and speaker for Gilead Science and Janssen Pharmaceutical. M-TL, XX, AR, LL, SK, PS, B-YN, GJH, and CH are employees of Merck & Co and might own stock or stock options in the company. JL declares no competing interests.

Acknowledgments

This study was funded by Merck & Co who provided financial support and investigational drug supplies for the study. We thank the study participants and their families and caregivers for participating in this trial. We also thank the investigators and their staff and the following

employees of Merck & Co for their contributions: Kim Strohmaier for medical writing, Carol Zecca for editorial assistance, and Danielle Mancaruso for graphics support.

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