Switch to fixed-dose doravirine (100 mg) with islatravir (0·75 mg) once daily in virologically suppressed adults with HIV-1 on bictegravir, emtricitabine, and tenofovir alafenamide: 48-week results of a phase 3, randomised, controlled, double-blind, non-inferiority trial

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Summary

Background Doravirine and islatravir is an investigational, once-daily regimen with high antiviral potency, favourable safety and tolerability, and a low propensity for resistance. We investigated a switch from bictegravir, emtricitabine, and tenofovir alafenamide to doravirine (100 mg) and islatravir (0·75 mg) in virologically suppressed adults with HIV-1.

Methods We conducted a phase 3, multicentre, randomised, active-controlled, double-blind, double-dummy, non-inferiority trial at 89 research, community, and hospital-based clinics in 11 countries. Adults aged 18 years or older with fewer than 50 HIV-1 RNA copies per mL for at least 3 months on bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) and no history of previous virological failure on any past or current regimen were randomly assigned (1:1) by a computer-generated randomisation allocation schedule, with block randomisation based on a block size of four, to switch to doravirine (100 mg) and islatravir (0·75 mg) or continue bictegravir, emtricitabine, and tenofovir alafenamide orally once daily, with matching placebos taken by all participants. Participants, investigators, study staff, and sponsor personnel involved in study drug administration or clinical evaluation of participants were masked to treatment assignment until week 48. Participants were instructed at each visit to take one tablet from each of the two bottles received, one of study drug and one of placebo, once daily, and participants were assessed at baseline and weeks 4, 12, 24, 36, and 48. The primary endpoint was the proportion of participants with greater than or equal to 50 HIV-1 RNA copies per mL at week 48 in the full analysis set (ie, all participants who received at least one dose of study drug; US Food and Drug Administration snapshot; prespecified non-inferiority margin 4%). The study is ongoing, with all remaining participants in post-treatment follow-up, and is registered with ClinicalTrials.gov, NCT04223791.

Findings We screened 726 individuals for eligibility between Feb 18 and Sept 3, 2020, of whom 643 (88·6%) participants were randomly assigned to a treatment group (183 [28·5%] women and 460 [71·5%] men). 322 participants were switched to doravirine (100 mg) and islatravir (0·75 mg) and 321 continued bictegravir, emtricitabine, and tenofovir alafenamide (two participants [one with a protocol deviation and one who withdrew] assigned to bictegravir, emtricitabine, and tenofovir alafenamide did not receive treatment). The last follow-up visit for the week 48 analysis occurred on Aug 26, 2021. At week 48, two (0·6%) of 322 participants in the doravirine and islatravir group compared with one (0·3%) of 319 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group had greater than or equal to 50 HIV-1 RNA copies per mL (difference 0·3%, 95% CI –1·2 to 2·0). The per-protocol analysis showed consistent results. 25 (7·8%) participants in the doravirine and islatravir group had headache compared with 23 [7·2%] participants in the bictegravir, emtricitabine, and tenofovir alafenamide group; 101 (31·4%) compared with 98 (30·7%) had infections; and eight (2·5%) participants in each group discontinued therapy due to adverse events. 32 (9·9%) participants had treatment-related adverse events in the islatravir and doravirine group comapred with 38 (11·9%) in the bictegravir, emtricitabine, and tenofovir alafenamide group. In the islatravir and doravirine group, CD4 cell counts (mean change –19·7 cells per µL) and total lymphocyte counts (mean change $-0·20\times10^9$/L) were decreased at 48 weeks.

Interpretation Switching to daily doravirine (100 mg) and islatravir (0·75 mg) was non-inferior to bictegravir, emtricitabine, and tenofovir alafenamide at week 48. However, decreases in CD4 cell and total lymphocyte counts do not support the further development of once-daily doravirine (100 mg) and islatravir (0·75 mg).

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Introduction

Antiretroviral therapy (ART) has improved outcomes in people with HIV, with life expectancy now nearly equal to that for people without HIV if ART is started before advanced immunodeficiency has occurred.[1] Nonetheless, people with HIV develop premature age-related and HIV-related comorbidities,[1,2] making them particularly susceptible to drug interactions and the adverse effects of ART, such as changes in weight, lipids, organ function, bone density, or a combination. Consequently, a need exists for novel regimens that are highly potent and maintain viral suppression with minimal long-term toxicity and few drug interactions.[2–5] One approach to address this need is to minimise overall antiretroviral drug exposure with two-drug regimens.[2–4]

The combination of doravirine and islatravir is being investigated as a two-drug, fixed-dose, combination tablet given orally once daily for the treatment of HIV-1. Doravirine, an approved non-nucleoside reverse transcriptase inhibitor, has an improved overall drug profile compared with other non-nucleoside reverse transcriptase inhibitors. Doravirine was efficacious and well tolerated in clinical trials, with activity against common variants that are resistant to non-nucleoside reverse transcriptase inhibitors. Doravirine-based regimens have a favourable lipid profile, neuropsychiatric adverse effects occur less often, and drug–drug interactions are less likely than with other non-nucleoside reverse transcriptase inhibitor-based regimens.[6]

Islatravir is a highly potent investigational nucleoside analogue inhibitor of HIV reverse transcriptase.[7,8] Islatravir has multiple mechanisms of action, including translocation inhibition and delayed chain termination, with a high barrier to the development of resistance and potent in-vitro antiviral activity with clinical exposures that cover clinically relevant variants that are resistant to

Research in context

Evidence before this study

We searched the US National Library of Medicine PubMed database using the terms "doravirine" and "islatravir" with language restricted to English for research articles published between database inception and May 30, 2023, restricted to clinical trials that reported on the concurrent administration of doravirine and islatravir in humans. Four publications were identified with these search terms. A phase 1 study in healthy adults reported that there was no pharmacokinetic interaction between oral doravirine (100 mg) coadministered with oral islatravir (2·25 mg) once daily for 5 days. In a phase 2b study in adults with HIV-1 who were initiating antiretroviral therapy for the first time, the majority of participants reached HIV-1 RNA concentrations below 50 copies per mL at 24 weeks with the combination of doravirine (100 mg), islatravir (0·25 mg, 0·75 mg, or 2·25 mg), and lamivudine (300 mg) once daily. Participants continued on doravirine (100 mg) and islatravir (0·25 mg, 0·75 mg, or 2·25 mg) once daily (without lamivudine) for approximately another 24 weeks. High rates of viral suppression were maintained, and the regimens were well tolerated regardless of islatravir dose at 48 weeks. Participants then transitioned to doravirine (100 mg) with islatravir (0·75 mg) once daily, and sustained efficacy and safety were shown at weeks 96 and 144.

Added value of this study

Doravirine and islatravir is an investigational two-drug regimen that does not contain an integrase strand transfer inhibitor (INSTI). We conducted the first phase 3, randomised, double-blind trial (NCT04223791) that compared switching to oral doravirine (100 mg) and islatravir (0·75 mg) once daily versus continuing oral bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg), a first-line, three-drug, once-daily INSTI-based regimen, in virologically suppressed adults with HIV-1. Doravirine and islatravir was non-inferior to continuing bictegravir, emtricitabine, and tenofovir alafenamide for the primary endpoint of greater than or equal to 50 copies per mL of plasma HIV-1 RNA at 48 weeks (two participants in the doravirine and islatravir group *vs* one participant in the bictegravir, emtricitabine, and tenofovir alafenamide group). One participant who received doravirine and islatravir was noted to have confirmed viraemia (≥200 HIV-1 RNA copies per mL 2–4 weeks apart) at week 12, with undetectable islatravir plasma concentrations and no genotypic or phenotypic resistance to doravirine or islatravir. Adverse event rates were similar between treatment groups, with headache being the most common in both. However, decreases in CD4 cell and total lymphocyte counts were noted in the doravirine and islatravir group without increased risk of infection. Discontinuation due to adverse events was rare and occurred at a similar rate in both treatment groups.

Implications of all the available evidence

Doravirine and islatravir is a potential two-drug, single-tablet, once-daily regimen for switch therapy in adults with HIV-1 who are virologically suppressed on bictegravir, emtricitabine, and tenofovir alafenamide, a first-line INSTI-based regimen. The results of this double-blind study complement the results of a randomised phase 3 switch study that evaluated virologically suppressed adults who were stable on any two-drug or three-drug antiretroviral regimen before switching to open-label doravirine (100 mg) and islatravir (0·75 mg). Development of islatravir (0·75 mg) for virologically suppressed people with HIV was stopped; modelling and simulation studies predict islatravir (0·25 mg) daily will achieve similar exposures without decreases in total lymphocyte counts, supporting continuation of development at this lower dose. Phase 3 clinical trials are underway investigating doravirine (100 mg) and islatravir (0·25 mg) in adults who are virologically suppressed or naive to HIV-1 treatment.

nucleoside reverse transcriptase inhibitors (eg, Met184Ile, Met184Val, T analogue mutation, Lys65Arg, and Lys70Glu).[7,9] Islatravir is unlikely to interact with most other drugs because it does not induce or inhibit any drug metabolising enzymes or transporters.[10] Doravirine and islatravir are suitable agents to evaluate as an oral two-drug antiretroviral regimen given their complementary attributes.[11,12]

The concomitant use of islatravir (0·25 mg, 0·75 mg, and 2·25 mg) and doravirine (100 mg) was investigated in a phase 2b dose-ranging study in adults with HIV-1 who were treatment naive.[13] High rates of viral suppression were reached at 24 weeks with islatravir (0·25 mg, 0·75 mg, or 2·25 mg) plus doravirine (100 mg) and lamivudine (300 mg), regardless of islatravir dose. Participants then continued a two-drug regimen of their assigned islatravir dose with doravirine for at least 24 weeks, after which they all transitioned to islatravir 0·75 mg with doravirine for the duration of the study. Islatravir plus doravirine was well tolerated and participants had sustained viral suppression up to week 144.[13–15] Modelling and simulation studies, along with in-vitro potency data, showed that the expected concentrations of islatravir-triphosphate after a single 0·75 mg dose would be sufficient to suppress both wild-type virus and variants that are resistant to nucleoside reverse transcriptase inhibitors.[16] Islatravir 0·75 mg was therefore selected for further clinical development for populations who were naive to treatment for HIV-1, were virologically suppressed, or were heavily treatment-experienced (ie, people with multidrug-resistant HIV-1 with viral non-suppression on their current regimen and few, if any, remaining options for a fully suppressive regimen).

Integrase strand transfer inhibitor (INSTI)-based regimens are currently the standard of care for the treatment of people with HIV-1, given their efficacy, low rates of resistance, and safety.[1,5,17] The fixed-dose combination of bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) is an oral three-drug INSTI-based regimen recommended in European and US treatment guidelines.[1,5,17] However, concerns have been raised about cardiometabolic adverse effects in people with HIV who are treated with INSTIs and tenofovir alafenamide.[18,19] This phase 3 trial was designed to evaluate the efficacy and safety of switching virologically suppressed adults with HIV-1 who were taking bictegravir, emtricitabine, and tenofovir alafenamide to doravirine (100 mg) and islatravir (0·75 mg) for maintenance ART.

Methods

Study design and participants

We conducted a phase 3, multicentre, randomised, active-controlled, double-blind, double-dummy, non-inferiority trial designed to evaluate switching from bictegravir, emtricitabine, and tenofovir alafenamide to doravirine (100 mg) and islatravir (0·75 mg) in adults with HIV-1 infection. The trial was conducted at 89 research, community, and hospital-based clinics across Australia, Austria, Canada, Finland, France, Germany, Italy, Japan, Puerto Rico, Spain, and the USA. Recruitment was done by individual study sites.

Adults aged 18 years or older with HIV-1 infection who were virologically suppressed (ie, <50 copies plasma HIV-1 RNA per mL) for at least 3 months on bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) were eligible. Participants had to have a documented HIV-1 RNA of fewer than 50 copies per mL at screening with no previous history of virological failure on any past or current regimen and no known virological resistance to doravirine (Val106Ala, Val106Met, Val108Ile, Tyr188Leu, His221Tyr, Pro225His, Phe227Cys, Phe227Leu, Met230Ile, Met230Leu, Leu234Ile, Pro236Leu, or Tyr318Phe).

Participants were not eligible for inclusion if they had active hepatitis B virus infection (ie, tested positive for hepatitis B surface antigen or hepatitis B virus DNA); had a previous history of malignancy 5 years or less before signing informed consent; were taking or were anticipated to require systemic immunosuppressive therapy, immune modulators, or other prohibited therapies (eg, strong and moderate CYP3A inducers, dofetilide, pentostatin, or other investigational therapies or devices) from 45 days before day 1 until the end of the treatment period; were planning to conceive or donate eggs during the study; or had exclusionary laboratory values (ie, alkaline phosphatase >3×the upper limit of normal [ULN], aspartate aminotransferase or alanine aminotransferase >5×ULN, haemoglobin <9·0 g/dL in women or <10·0 g/dL in men, or Cockcroft–Gault creatinine clearance ≤30 mL/min). Chronic hepatitis C virus infection and treatment with direct-acting antiviral therapies were not exclusionary, provided the participant had stable liver function tests and no significant hepatic synthetic dysfunction.

This study was conducted in accordance with International Council for Harmonisation principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. All participants gave written informed consent before any study procedures were performed. This study is registered with ClinicalTrials.gov, NCT04223791 (protocol MK-8591A-018).

Randomisation and masking

A computer-generated randomisation allocation schedule was used to assign participants in a 1:1 ratio to switch to doravirine (100 mg) and islatravir (0·75 mg) on day 1 or continue treatment with bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg). Random assignment was implemented via interactive response technology, with block randomisation based on a block size of four. Doravirine and

islatravir and bictegravir, emtricitabine, and tenofovir alafenamide were packaged identically relative to their matching placebos.

Participants, investigators, study staff, and sponsor personnel involved in study drug administration or clinical evaluation of participants were masked to treatment assignment until after the week-48 database lock. Sponsor personnel and investigators involved in data analysis were unmasked to treatment assignment after the week 48 database lock. Participants, study staff, and remaining investigators and sponsor personnel were unmasked at week 96. Investigators enrolled participants and provided care throughout the trial.

Procedures

Participants received two bottles, one each of study drug and placebo, at each visit and were instructed to take one tablet from each bottle at the same time each day without regard to food. The placebo was identical in appearance to the active study drugs. Dose modifications were not allowed. Participants taking medications or oral supplements containing polyvalent cations (Mg^{2+}, Al^{3+}, Ca^{2+}, or Fe^{3+}) were counselled to take the study drugs 2 h before or 6 h after these medicines, given that the interaction can decrease concentrations of bictegravir, emtricitabine, and tenofovir alafenamide.[20]

Study visits occurred on day 1 (baseline) and at weeks 4, 12, 24, 36, and 48 (visit window ±7 days) while on treatment. Plasma HIV-1 RNA, physical examination, vital signs, chemistry and haematology parameters, concomitant medications, islatravir concentrations, and adverse events were assessed at baseline and at every study visit. Plasma HIV-1 RNA quantification was done at a central laboratory (PPD Laboratory Services, Wilmington, NC, USA) with the Abbott RealTime HIV-1 assay (Abbott Molecular, Des Plaines, IL, USA; lower limit of detection of 40 copies per mL). Participants confirmed to have greater than or equal to 200 HIV-1 RNA copies per mL (ie, by two consecutive samples 2–4 weeks apart) were assessed for viral resistance. Resistance testing was performed at Monogram Biosciences (South San Francisco, CA, USA). Participants who tested positive for hepatitis B core antibodies were tested for hepatitis B surface antigen and hepatitis B virus DNA at each study visit; reactivation of hepatitis B virus was defined as detection of hepatitis B surface antigen, hepatitis B virus DNA, or both in a participant who was positive for hepatitis B core antibody at enrolment. CD4 cell count and weight were measured at baseline and at weeks 24 and 48. Bone mineral density was assessed at baseline and at week 48. Adverse events and laboratory abnormalities were graded for intensity on the basis of the US National Institutes of Health Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.[21] The association between the study drug and adverse events was determined by the investigator. Participants who discontinued the study drug for any reason at any time had an end-of-treatment follow-up assessment 42 days (+7 days) after the last dose of study drug.

See Online for appendix

Outcomes

The primary efficacy endpoint was the proportion of participants with greater than or equal to 50 HIV-1 RNA copies per mL at week 48 in the full analysis set. Secondary efficacy endpoints were the proportion of participants with fewer than 50 HIV-1 RNA copies per mL and fewer than 40 copies per mL, and the mean change from baseline in CD4 cell count in the full analysis set. The development of viral drug resistance was assessed in participants with confirmed viraemia (≥200 HIV-1 RNA copies per mL 2–4 weeks apart). Virological efficacy endpoints (ie, HIV-1 RNA) were also assessed in the per-protocol set. Safety outcomes were assessed in all participants as treated. The primary safety endpoints were the proportion of participants with adverse events and the proportion who discontinued study drug due to an adverse event. Additional safety endpoints were the proportion of participants with treatment-related adverse events; the proportion with serious adverse events; and the changes from baseline to week 48 in bodyweight, fasting lipids (ie, LDL cholesterol, non-HDL cholesterol, and the ratio of total cholesterol to HDL cholesterol), routine laboratory values (ie, chemistry and haematology panels), and bone mineral density. Drug-induced liver injury was defined as alanine aminotransferase or aspartate aminotransferase greater than or equal to 3×ULN plus bilirubin greater than or equal to 2×ULN and alkaline phosphatase less than 2×ULN.

After decreases in total lymphocyte counts were observed in other clinical trials with higher doses of islatravir (ie, 20 mg once weekly and 60 mg once monthly),[22] post-hoc analyses of mean change from baseline in total lymphocyte count and the ratio of CD4 cell count to total lymphocyte count were conducted for this study in the full analysis set.

Statistical analysis

Statistical tests were done using SAS, version 9.4. The primary population for efficacy endpoints was the full analysis set, defined as all participants who took at least one dose of study drug (ie, active drug and placebo), with participants included in the treatment group to which they were randomly assigned. Analyses were also done for virological efficacy endpoints in a secondary population, the per-protocol set, which included all participants in the full analysis set who did not have any major protocol violations that could affect efficacy. Participants were not included in the per-protocol set if they did not meet the criteria for the full analysis set, received prohibited therapies for greater than or equal to 7 consecutive days, were non-adherent to study drug (ie, <95% adherence rate; appendix p 1), became pregnant, or were unmasked to assignment group for

any reason. Safety was analysed in all participants as treated, defined as all participants who were randomly assigned to a treatment group and received at least one dose of study drug, with participants included in the treatment group corresponding to the study drug received.

The proportion of participants with greater than or equal to 50 HIV-1 RNA copies per mL at week 48 was compared between the doravirine and islatravir group and the bictegravir, emtricitabine, and tenofovir alafenamide group, per the US Food and Drug Administration (FDA) snapshot approach for the primary endpoint in the full analysis set.[23] Non-inferiority would be concluded if the upper bound of the two-sided multiplicity-adjusted 95% CI for the difference between the groups was less than 4 percentage points. The 95% CI was based on the unstratified Miettinen and Nurminen method.[24] A sample size of 289 participants per group would provide 85% power to show non-inferiority of doravirine and islatravir to bictegravir, emtricitabine, and tenofovir alafenamide with an assumed rate of 2% of participants with more than or equal to 50 HIV-1 RNA copies per mL in the bictegravir, emtricitabine, and tenofovir alafenamide group at week 48 at a 4 percentage point margin, with a one-sided α of 0·02495.

The secondary endpoints of proportion of participants with fewer than 50 HIV-1 RNA copies per mL and fewer than 40 copies per mL were summarised by treatment group at week 48, per the FDA snapshot approach.[23] The difference in proportions between treatment groups and the associated two-sided nominal 95% CI was calculated using the unstratified Miettinen and Nurminen method.[24,25]

The mean change from baseline in CD4 cell count at week 48 was based on the data-as-observed approach, meaning that participants had to have a baseline and at least one post-baseline measurement. If baseline values were missing, the most recent screening value was used. The within-group, two-sided, nominal 95% CI was calculated on the basis of the t-distribution. The treatment difference was estimated using an ANCOVA model adjusted by baseline CD4 cell count and treatment group. Data for viral drug resistance were summarised for participants with confirmed viraemia, but no statistical analysis was performed.

Point estimates and two-sided nominal 95% CIs using the Miettinen and Nurminen methods were calculated for treatment differences in adverse events and changes in laboratory measurements.[24] Within-group two-sided nominal 95% CIs were calculated on the basis of the t-distribution for mean change in bodyweight; mean change in fasting LDL cholesterol, non-HDL cholesterol, and ratio of total cholesterol to HDL cholesterol; and mean change in hip and spine bone mineral density. Differences between groups for safety parameters were estimated using ANCOVA models (adjusted by baseline weight, sex, race, and treatment group for the weight analysis and adjusted by baseline value and treatment group for other safety parameters). Superiority of doravirine and islatravir in regard to increase in weight from baseline (eg, a lower mean increase) versus bictegravir, emtricitabine, and tenofovir alafenamide would be concluded if the upper bound of the two-sided multiplicity-adjusted 95% CI for the estimate of the treatment group difference was less than 0 kg.

An independent data monitoring committee periodically reviewed efficacy and safety data provided by an unmasked independent statistician throughout the study. An interim futility analysis was done by the statistician when 40% of target enrolment had completed week 24 assessments.

Between-group differences in the change from baseline were estimated for post-hoc analyses using ANCOVA models with terms for baseline value and treatment.

Role of the funding source

The funder of the study, Merck Sharp & Dohme, a subsidiary of Merck & Co, was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Feb 18 and Sept 3, 2020, 726 individuals were screened for eligibility, of whom 643 (88·6%) were randomly assigned to a treatment group. An unanticipated late increase in participant screening and more participants being eligible than expected resulted in the random assignment of 65 more participants to treatment groups than planned. Two (0·6%) of 321 participants who were randomly assigned to receive bictegravir, emtricitabine, and tenofovir alafenamide did not receive study drug, resulting in a full analysis set of 641 participants, of which 322 (50·2%) participants were assigned to switch to doravirine and islatravir and 319 (49·8%) were assigned to remain on bictegravir, emtricitabine, and tenofovir alafenamide. An additional 60 participants were excluded from the per-protocol set, which included a total of 581 participants (figure). Most participants in both groups completed the 48-week, double-blind treatment period (305 [94·7%] of 322 participants in the doravirine and islatravir group and 301 [94·4%] of 319 in the bictegravir, emtricitabine, and tenofovir alafenamide group) and were continuing their masked assigned treatment along with the placebo control at the timepoint for this analysis. 35 (5·5%) of 641 participants discontinued the study drug (17 [5·3%] of 322 in the doravirine and islatravir group and 18 [5·6%] of 319 in the bictegravir, emtricitabine, and tenofovir alafenamide group). The last follow-up visit for the week 48 analysis occurred on Aug 26, 2021.

Most participants were White (479 [74·7%] of 641 participants in the full analysis set) and assigned male sex at birth (459 [71·6%]), with a median age of

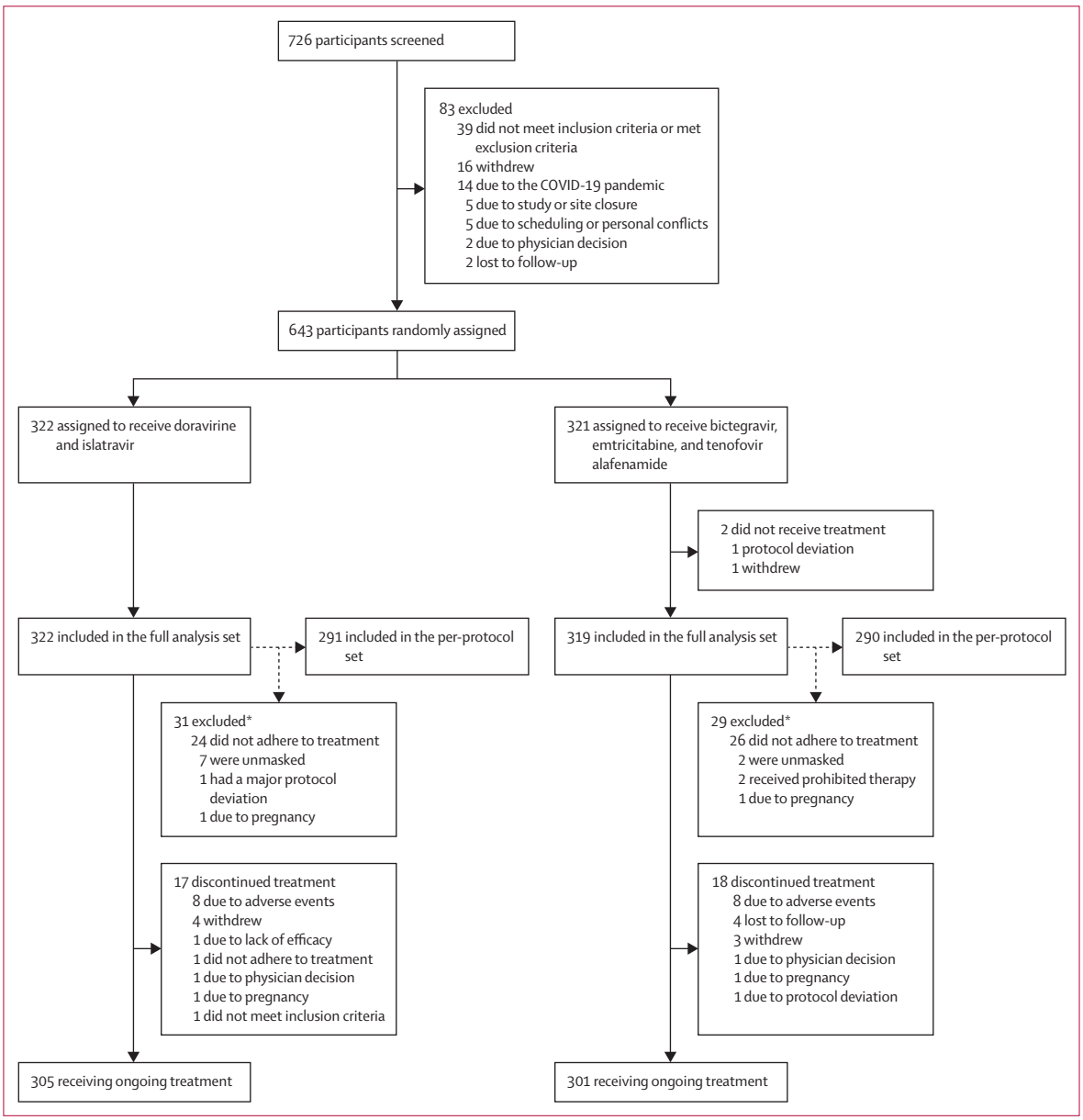

***Figure*: Trial profile**
*Participants could have more than one reason for exclusion from the per-protocol set.

48 years (IQR 39–57). 293 (45·7%) participants were aged 50 years or older and 52 (8·1%) were aged 65 years or older. Before enrolment, 437 (68·2%) of 641 participants had been receiving bictegravir, emtricitabine, and tenofovir alafenamide for longer than or equal to 1 year, with a median of 14·8 months (IQR 10·5–19·7). Baseline and disease characteristics were balanced between treatment groups (table 1), except for a higher proportion of women in the doravirine and islatravir group.

At week 48, two (0·6%) of 322 participants in the doravirine and islatravir group and one (0·3%) of 319 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group had greater than or equal to 50 HIV-1 RNA copies per mL, showing non-inferiority of switching to doravirine and islatravir to continuing bictegravir, emtricitabine, and tenofovir alafenamide (difference 0·3%, multiplicity-adjusted 95% CI –1·2 to 2·0). The proportion of participants with fewer than 50 HIV-1 RNA copies per mL at week 48 was similar across treatment groups (table 2) and demographic subgroups (appendix p 2). Most participants also maintained fewer than 40 HIV-1 RNA copies per mL. Results in the per-protocol set were consistent with the full analysis set.

The mean change from baseline to week 48 in CD4 cell counts showed a decrease in the doravirine and islatravir

	Doravirine and islatravir group (n=322)	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=319)
Age, years	48 (38–57)	48 (40–56)
18–49	173 (53·7%)	175 (54·9%)
50–64	121 (37·6%)	120 (37·6%)
≥65	28 (8·7%)	24 (7·5%)
Sex at birth		
Male	217 (67·4%)	242 (75·9%)
Female	105 (32·6%)	77 (24·1%)
Race		
White	240 (74·5%)	239 (74·9%)
Black or African American	58 (18·0%)	55 (17·2%)
Asian	14 (4·3%)	13 (4·1%)
Other	10 (3·1%)	9 (2·8%)
Unknown	0	3 (0·9%)
Hispanic or Latinx ethnicity	64 (19·9%)	55 (17·2%)
Hepatitis C co-infection	0	1 (0·3%)
CD4 count, cells per µL	645 (475–831)	704 (500–876)
>350	287 (89·1%)	294 (92·2%)
≥200 and ≤350	31 (9·6%)	21 (6·6%)
<200	4 (1·2%)	4 (1·3%)
Time since HIV-1 diagnosis, years	10·2 (5·0–16·8)	9·4 (5·3–17·6)
Duration of bictegravir, emtricitabine, and tenofovir alafenamide before enrolment, months	14·4 (10·5–19·7)	15·3 (10·5–20·5)
≥12 months	219 (68·0%)	218 (68·3%)

Data are median (IQR) or n (%).

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

	Doravirine and islatravir group	Bictegravir, emtricitabine, and tenofovir alafenamide group	Difference, % (95% CI)*
Full analysis set			
≥50 HIV-1 RNA copies per mL	2/322 (0·6%)	1/319 (0·3%)	0·3 (–1·2 to 2·0)
≥50 HIV-1 RNA copies per mL in week 48 window	1/322 (0·3%)	1/319 (0·3%)	..
Discontinued due to lack of efficacy	1/322 (0·3%)	0/319	..
<50 HIV-1 RNA copies per mL	302/322 (93·8%)	301/319 (94·4%)	–0·6 (–4·4 to 3·2)
No virological data in week 48 window	18/322 (5·6%)	17/319 (5·3%)	..
Discontinued due to adverse event or death and last measurement <50 HIV-1 RNA copies per mL	8/322 (2·5%)	7/319 (2·2%)	..
Discontinued for other reasons and last measurement <50 HIV-1 RNA copies per mL	8/322 (2·5%)	9/319 (2·8%)	..
On study treatment but missing data in window	2/322 (0·6%)	1/319 (0·3%)	..
<40 HIV-1 RNA copies per mL	300/322 (93·2%)	300/319 (94·0%)	–0·9 (–4·8 to 3·0)
Per-protocol set			
≥50 HIV-1 RNA copies per mL	2/291 (0·7%)	1/290 (0·3%)	0·3 (–1·3 to 2·2)
<50 HIV-1 RNA copies per mL	279/291 (95·9%)	276/290 (95·2%)	0·7 (–2·8 to 4·3)
<40 HIV-1 RNA copies per mL	277/291 (95·2%)	275/290 (94·8%)	0·4 (–3·3 to 4·1)

Data are n/N (%), unless otherwise stated. *Values were calculated before rounding.

Table 2: **Virological outcomes at week 48 based on the US Food and Drug Administration snapshot approach**

group versus an increase in the bictegravir, emtricitabine, and tenofovir alafenamide (difference of –68·1 cells per µL, 95% CI –94·8 to –41·4; table 3). At week 48, few participants had CD4 counts lower than 200 cells per µL (one participant in the doravirine and islatravir group *vs* three participants in the bictegravir, emtricitabine, and tenofovir alafenamide group).

Confirmed viraemia occurred in one participant taking doravirine and islatravir and none taking bictegravir, emtricitabine, and tenofovir alafenamide. The confirmed viraemia occurred at week 12 (773 copies per mL at week 12, 1507 copies per mL at week 14), resulting in discontinuation of doravirine and islatravir. Testing at week 12 did not detect genotypic or phenotypic resistance to either doravirine or islatravir. This participant did not have documented or known virological resistance to doravirine at screening. However, Lys103Lys, Lys103Asn, Tyr188Tyr, Tyr188Phe, Tyr188His, and Tyr188Leu resistance-associated substitutions were detected at week 4. Islatravir was not detected in pharmacokinetic samples collected at the time of confirmed viraemia. The participant was switched back to bictegravir, emtricitabine, and tenofovir alafenamide and resuppressed 7 weeks later. There was one participant with confirmed low-level viraemia (ie, two consecutive occurrences of ≥50 HIV-1 RNA copies per mL and <200 copies per mL) in each group at week 48. These participants continued their assigned study drug and had fewer than 50 HIV-1 RNA copies per mL at subsequent visits.

At least one adverse event was reported by week 48 in more than 70% of participants in both treatment groups (table 4). The most frequently reported adverse events in the doravirine and islatravir group were headache, COVID-19, and arthralgia. In the bictegravir, emtricitabine, and tenofovir alafenamide group, the most frequently reported adverse events were headache, diarrhoea, arthralgia, COVID-19, and back pain (table 4, appendix p 3). Infection rates were similar in both groups (101 [31·4%] of 322 participants *vs* 98 [30·7%] of 319 participants; appendix p 5). One participant in each group had a Centers for Disease Control and Prevention AIDS-Defining Category C event (oesophageal candidiasis in the doravirine and islatravir group and recurrent Kaposi sarcoma in the bictegravir, emtricitabine, and tenofovir alafenamide group). The profile of adverse events by toxicity (per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events) was similar across treatment groups (appendix p 7), with grade 3 or grade 4 adverse events reported in less than 10% of each group (table 4).

Adverse events leading to discontinuation of study drug were infrequent and similar across groups (table 4). The most frequently reported adverse events leading to study drug discontinuation (ie, occurring in ≥0·5% participants) were asthenia (n=2) and myalgia (n=2), both reported in the bictegravir, emtricitabine, and tenofovir alafenamide group. 11 participants discontinued the study drug due to treatment-related adverse events, six participants in the doravirine and islatravir group (due to hepatitis B virus reactivation; hyperhidrosis; insomnia; pruritic rash; pruritis; and dizziness, headache, and palpitations) and five participants in the bictegravir, emtricitabine, and tenofovir alafenamide group (skin irritation; sleep disorder; vertigo; asthenia and myalgia; and asthenia, dizziness, headache, hot flush, insomnia, muscle spasms, and nausea).

Adverse events considered by investigators to be treatment-related were reported in a total of 70 participants (table 4). The two most frequently reported treatment-related adverse events (ie, in greater than or equal to four participants) were nausea and headache in the doravirine and islatravir group. In the bictegravir, emtricitabine, and tenofovir alafenamide group, the most frequent treatment-related adverse events were dizziness, myalgia, headache, asthenia, and abnormal dreams. No individual treatment-related adverse event was reported for greater than 2·5% of participants in either group. Four participants had five grade 3 adverse events that were considered treatment-related by investigators (hyperhidrosis and rhabdomyolysis [n=1] and headache [n=1] in the doravirine and islatravir group; glaucoma [n=1] and sleep disorder [n=1] in the bictegravir, emtricitabine, and tenofovir alafenamide group). No grade 4 treatment-related adverse events were reported.

The number of participants reporting serious adverse events was less than 5·0% (table 4), and no individual serious adverse event was reported in more than one participant in either group (data not shown). Seven participants in the doravirine and islatravir group had serious infections (ie, resulting in hospitalisation): COVID-19 pneumonia (n=2), cystitis with *Escherichia coli* and *Clostridioides difficile* colitis (n=1), pneumonia and sepsis (n=1), colitis (n=1; unclear whether infectious), neurosyphilis (n=1), and atypical pneumonia (n=1). In the bictegravir, emtricitabine, and tenofovir alafenamide group, six participants had serious infections: sepsis (n=1), cystitis (n=1), pyelonephritis (n=1), bacterial endocarditis (n=1), pneumococcal pneumonia (n=1), and herpes zoster (n=1). No serious adverse events were considered to be related to the treatment by investigators.

Mean weight change from baseline to week 48 was 0·2 kg (95% CI −0·2 to 0·7) in the doravirine and islatravir group compared with 0·6 kg (0·1 to 1·1) in the bictegravir, emtricitabine, and tenofovir alafenamide group. The difference in mean weight gain was not significant (difference −0·3 kg, −1·0 to 0·4; p=0·39; appendix p 10).

At baseline, 67 (20·8%) of 322 participants in the doravirine and islatravir group and 80 (25·1%) of 319 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group were on lipid-lowering therapy. Nine participants in the doravirine and islatravir group and four participants in the bictegravir, emtricitabine, and tenofovir alafenamide group initiated lipid-lowering therapy during the study. There were no

	Doravirine and islatravir group				Bictegravir, emtricitabine, and tenofovir alafenamide group			
	Number of participants with data for timepoint	Baseline mean*	Post-baseline mean*	Mean change (95% CI)†	Number of participants with data for timepoint	Baseline mean*	Post-baseline mean*	Mean change (95% CI)†
CD4 count, cells per µL								
Baseline	322	680	..	..	319	715	..	..
Week 24	304	677	688	10·9 (−10·0 to 31·8)	302	715	782	67·6 (45·5 to 89·8)
Week 48	301	680	661	−19·7 (−39·8 to 0·5)	298	721	761	40·5 (20·7 to 60·4)
Total lymphocyte count, × 10^9/L								
Baseline	322	1·91	..	..	319	1·98	..	..
Week 24	309	1·91	1·82	−0·08 (−0·13 to −0·04)	300	1·98	2·06	0·08 (0·04 to 0·13)
Week 48	291	1·89	1·69	−0·20 (−0·25 to −0·15)	288	1·98	2·00	0·02 (−0·03 to 0·07)
Ratio of CD4 cell count to total lymphocyte count, %								
Baseline	322	36·66%	..	..	319	37·28%	..	..
Week 24	306	36·55%	37·67%	1·11 (0·68 to 1·55)	302	37·37%	37·35%	−0·02 (−0·54 to 0·51)
Week 48	290	36·91%	38·78%	1·87 (1·42 to 2·33)	291	37·34%	37·73%	0·38 (−0·18 to 0·95)

*Calculated on the basis of the number of participants with data available for the timepoint. †Mean change was calculated before rounding.

Table 3: **Summary of observed changes in CD4 cell and total lymphocyte counts in the full analysis set**

significant differences between groups for mean change in LDL cholesterol, non-HDL cholesterol, and ratio of total cholesterol to HDL cholesterol from baseline to week 48 in participants who were not receiving lipid-lowering therapy (appendix p 11).

There were no clinically meaningful differences between the groups in grade 3 or grade 4 laboratory changes. No participants in either group developed drug-induced liver injury or nephrotoxicity (appendix p 8). There were no significant differences between treatment groups in mean changes in hip bone mineral density (difference –0·002 g/cm², 95% CI –0·006 to 0·002) and spine bone mineral density (–0·005 g/cm², –0·011 to 0·001; appendix p 9) at week 48.

At enrolment, 87 participants in the doravirine and islatravir group were positive for hepatitis B core antibody and negative for hepatitis B virus DNA, ten of whom were negative for surface antibody. Two participants had hepatitis B virus reactivation at week 12 (ie, detection of hepatitis B virus DNA) without clinically relevant changes in total bilirubin, alanine aminotransferase, or aspartate aminotransferase. One participant had a peak hepatitis B virus DNA concentration of 885 IU per mL, discontinued study drug, and was switched back to bictegravir, emtricitabine, and tenofovir alafenamide with documented resolution. The other participant had a peak hepatitis B virus DNA concentration of 104 IU per mL, continued doravirine and islatravir, and the hepatitis B virus DNA concentration resolved spontaneously by week 24, with all subsequent tests for hepatitis B virus DNA showing no evidence of ongoing reactivation. Both participants showed seroconversion of hepatitis B antibody after reactivation.

Two pregnancies, one from each treatment group, were reported at the week 36 visit. Both participants discontinued study drug in the first trimester, had fewer than 50 HIV-1 RNA copies per mL when they discontinued study drug per protocol, and were switched to alternative antiretroviral regimens. The participant on doravirine and islatravir electively terminated the pregnancy without complications. The participant receiving bictegravir, emtricitabine, and tenofovir alafenamide had an uncomplicated pregnancy and delivered a healthy baby at term by emergency caesarean section due to malpresentation.

In the post-hoc analysis, the difference between the two groups in mean change from baseline to week 48 in total lymphocyte count was –0·24 (95% CI –0·31 to –0·18). Although the total lymphocyte count was reduced in the doravirine and islatravir group compared with no change in the bictegravir, emtricitabine, and tenofovir alafenamide group at week 48, the ratio of CD4 cell count to total lymphocyte count remained generally stable (table 3).

	Doravirine and islatravir group (n=322)	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=319)	Difference, % (95% CI)*
Any adverse event	229 (71·1%)	238 (74·6%)	–3·5 (–10·4 to 3·4)
Most common adverse events (≥5% in either group)			
Headache	25 (7·8%)	23 (7·2%)	0·6 (–3·6 to 4·8)
COVID-19	19 (5·9%)	18 (5·6%)	0·3 (–3·5 to 4·0)
Arthralgia	17 (5·3%)	19 (6·0%)	–0·7 (–4·4 to 3·0)
Back pain	13 (4·0%)	17 (5·3%)	–1·3 (–4·8 to 2·1)
Diarrhoea	8 (2·5%)	20 (6·3%)	–3·8 (–7·3 to –0·7)
Treatment-related† adverse events	32 (9·9%)	38 (11·9%)	–2·0 (–6·9 to 2·9)
Most common treatment-related† adverse events (≥4 participants in either group)			
Nausea	8 (2·5%)	2 (0·6%)	1·9 (–0·1 to 4·3)
Dizziness	1 (0·3%)	5 (1·6%)	–1·3 (–3·3 to 0·3)
Myalgia	0	5 (1·6%)	–1·6 (–3·6 to –0·4)
Headache	4 (1·2%)	4 (1·3%)	0·0 (–2·1 to 2·0)
Asthenia	0	4 (1·3%)	–1·3 (–3·2 to –0·1)
Abnormal dreams	0	4 (1·3%)	–1·3 (–3·2 to –0·1)
Serious adverse events	13 (4·0%)	15 (4·7%)	–0·7 (–4·0 to 2·6)
Serious treatment-related† adverse events	0	0	0·0 (–1·2 to 1·2)
Grade 3–4 adverse events	28 (8·7%)	27 (8·5%)	0·2 (–4·2 to 4·7)
Treatment-related† grade 3–4 adverse events	2 (0·6%)	2 (0·6%)	0·0 (–1·7 to 1·7)
Discontinuation due to adverse event	8 (2·5%)	8 (2·5%)	0·0 (–2·7 to 2·6)
Due to a treatment-related† adverse event	6 (1·9%)	5 (1·6%)	0·3 (–2·0 to 2·6)
Due to a serious adverse event	1 (0·3%)	0	0·3 (–0·9 to 1·7)
Due to a serious treatment-related† adverse event	0	0	0·0 (–1·2 to 1·2)

Data are n (%), unless otherwise stated. Adverse event terms were based on the Medical Dictionary for Regulatory Activities, version 24.0. *Values were calculated before rounding. †Considered by the investigator to be related to study drug.

Table 4: **Summary of adverse events until week 48**

Discussion

This trial shows that switching to doravirine (100 mg) and islatravir (0·75 mg) was non-inferior to remaining on bictegravir, emtricitabine, and tenofovir alafenamide for maintaining viral suppression at week 48. The non-inferiority margin of 4% was met for the primary endpoint. Two (0·6%) of 322 participants in the doravirine and islatravir group and one (0·3%) of 319 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group had greater than or equal to 50 HIV-1 RNA copies per mL at week 48. Secondary analyses corroborate the primary endpoint. The proportion of participants with sustained HIV-1 RNA concentrations below 50 copies per mL in the doravirine and islatravir group was similar to the bictegravir, emtricitabine, and tenofovir alafenamide group. The one participant with confirmed viraemia (ie, ≥200 HIV-1 RNA copies per mL) who received doravirine and islatravir had undetectable islatravir concentrations at the time of confirmed viraemia, suggesting non-adherence contributed to the viraemia.

Although there were decreases in mean CD4 cell counts and total lymphocyte counts in the doravirine and islatravir group from baseline to week 48 that were

statistically significant, these changes were not clinically significant and were not associated with an increased incidence of infections. The week 48 mean CD4 counts in both groups were greater than 500 cells per µL and were similar. Further, the CD4-to-lymphocyte ratio was similar to the ratio in the bictegravir, emtricitabine, and tenofovir alafenamide group and did not change over time.

Weight gain is a concerning adverse effect of ART, particularly with regimens containing INSTIs, tenofovir alafenamide, or both. Weight gain usually occurs early in switch studies, stabilises at approximately 48 weeks, and might not be reversible.[18,26] Participants who switched to doravirine and islatravir and participants who continued on bictegravir, emtricitabine, and tenofovir alafenamide had minimal (ie, <1 kg) mean increases in weight, with no significant difference between treatment groups. Most participants were long-term users of bictegravir, emtricitabine, and tenofovir alafenamide, and it is unknown whether they gained weight on this regimen before enrolment. Additional studies are needed to fully examine ART-related weight gain and reversibility after switching to a different regimen.

Reactivation of hepatitis B virus can occur after a switch in ART from a regimen with activity against hepatitis B virus (eg, tenofovir) to one without hepatitis B virus coverage.[27,28] Although it might be preferable to treat people with HIV and hepatitis B virus co-infection with a regimen containing an agent with activity against both viruses, this approach might not always be possible or preferred due to side-effect profiles. Hepatitis B virus reactivation occurred in two of the ten participants at highest risk (ie, positive for hepatitis B core antibody, negative for surface antibody at enrolment) after discontinuing bictegravir, emtricitabine, and tenofovir alafenamide, which provides hepatitis B virus suppression. The majority of participants in the doravirine and islatravir group with evidence of past hepatitis B virus did not have reactivation; further exploration is needed to delineate risk factors for reactivation in this setting. Furthermore, for people with HIV with core antibodies to hepatitis B virus but no surface antibodies, vaccination and periodic monitoring of surface antigen and hepatitis B virus DNA are recommended to ensure immunity and hepatitis B virus suppression are maintained.[1,17,27]

Adverse events occurred in both treatment groups at a similar rate. The most common adverse events (ie, occurring in >5% of the group) were similar and occurred at rates that were generally similar to those reported in previous bictegravir, emtricitabine, and tenofovir alafenamide trials, with the exception of COVID-19.[20] Approximately 10% of adverse events in both groups were considered by the investigator to be related to treatment, none of which were considered serious. No participants in either group had evidence of hepatic or renal toxicity, and no clinically significant differences between treatment groups for mean changes in LDL cholesterol and non-HDL cholesterol and bone mineral density were observed.

Strengths of this study were the large sample size, the specific use of bictegravir, emtricitabine, and tenofovir alafenamide as the active control, and the randomised, double-blind design, which minimised bias from participants and study investigators. This global study had a population representative of different regions where bictegravir, emtricitabine, and tenofovir alafenamide is currently available. Additionally, women and older adults (ie, ≥50 years) were well represented in this trial.

Similar to other studies investigating switch therapy, a limitation of this trial was the exclusion of participants with active hepatitis B or a history of or documented virological failure. Although this study was a global trial, the population might not represent people with HIV who live in areas of the world where bictegravir, emtricitabine, and tenofovir alafenamide is not available. A companion phase 3, open-label switch study enrolled participants receiving any baseline ART (NCT04223778) to account for the diversity of antiretroviral regimens worldwide and showed similar results in virological outcomes with doravirine (100 mg) and islatravir (0·75 mg).[29]

Switching to dual therapy provides an opportunity to reduce antiretroviral exposure, while optimising a regimen based on virological efficacy, adverse effects, or drug interactions. Doravirine (100 mg) and islatravir (0·75 mg) is the first two-drug oral regimen that does not contain an INSTI to show non-inferiority to bictegravir, emtricitabine, and tenofovir alafenamide in maintaining viral suppression. High rates of viral suppression and no treatment-emergent resistance were observed at 48 weeks in participants who switched to doravirine and islatravir without compromising tolerability and without detrimental consequences on weight, lipids, and hepatic, renal, and bone parameters. Altogether these results support the potential of doravirine and islatravir as a complete once-daily, two-drug, oral switch therapy for HIV-1 in virologically suppressed adults on bictegravir, emtricitabine, and tenofovir alafenamide.

Development of islatravir has been transitioned from 0·75 mg to 0·25 mg following population pharmacokinetic modelling, using data from the clinical programme to date that predicts that islatravir 0·25 mg will provide robust antiviral activity without a negative effect on lymphocytes.[30,31] Phase 3 clinical trials with doravirine (100 mg) and islatravir (0·25 mg) once daily have been initiated in people with HIV-1 who are starting treatment (NCT05705349) or are virologically suppressed (NCT05631093, NCT05630755).

Contributors

KE, RMP, TC, and MCF designed or monitored the study. AMM, GR, MNR, OOO, JRB, DPH, RP, JR, JKR, and AC enrolled participants in the study and accessed and verified the underlying data. F-HS and SOK analysed the data. All authors contributed to development of the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Declaration of interests

F-HS, SOK, KE, RMP, TC (former), and MCF are or were employees of Merck Sharp & Dohme, a subsidiary of Merck & Co, who might own stock, hold stock options, or both in the company. AMM has received research funding from AbbVie, Gilead Sciences, Merck, Taimed, GSK, and ViiV Healthcare; honoraria from Gilead Sciences, ViiV Healthcare, and EMD Serono; and served on advisory boards for Gilead Sciences and ViiV Healthcare. GR has received honoraria from MSD, Gilead Sciences, GSK, and ViiV Healthcare and meeting or travel support from Gilead Sciences. MNR has received consulting fees from Gilead Sciences, Merck, and ViiV Healthcare and honoraria from AbbVie, Gilead Sciences, Janssen, and ViiV Healthcare. OOO has received honoraria from Gilead Sciences and ViiV Healthcare. JRB has received consulting fees from Gilead Sciences, MSD, Pfizer, and ViiV Healthcare and honoraria from AbbVie, Gilead Sciences, MSD, Pfizer, AstraZeneca, GSK, Janssen, ViiV Healthcare, and NovoNordisk. DPH has received research funding from Gilead Sciences, MSD, ViiV Healthcare, GSK, Janssen; honoraria for speakers bureau from Gilead Sciences and ViiV Healthcare; meeting or travel support from Gilead Sciences, ViiV Healthcare, GSK, and MSD; and served on advisory boards for and received consulting fees from Gilead Sciences, ViiV Healthcare, and Janssen. RP has served on advisory boards for and received consulting fees from Pfizer, MSD, Gilead Sciences, ViiV Healthcare, GSK, Roche, Atea, and Lilly and has received research funds (awarded to institution) from MSD, Gilead Sciences, and ViiV Healthcare. JR has received honoraria from MSD, Gilead Sciences, ViiV Healthcare, and Theratechnologies, outside the submitted work; meeting or travel support from Gilead Sciences; and has served on advisory boards for MSD, Gilead Sciences, and ViiV Healthcare. JKR has received consulting fees from AbbVie, Boehringer, Gilead Sciences, Merck, and ViiV Healthcare; honoraria from Gilead, Merck, Janssen, and ViiV; has served on advisory board for Abivax; and is a member of the governing board of the European AIDS Clinical Society. AC has received research funding from MSD and ViiV Healthcare; lecture and travel sponsorships from Gilead Sciences and ViiV Healthcare; and has served on advisory boards for Gilead Sciences, MSD, and ViiV Healthcare.

Data sharing

The data sharing policy, including restrictions, of Merck Sharp & Dohme, a subsidiary of Merck & Co 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 Data Access mailbox.

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