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Switch to fixeddose doravirine 100 mg with islatravir 075 mg once daily in virologically suppressed adults with HIV1 on bictegravir emtricitabine and tenofovir alafenamide 48week results of a phase 3 randomised controlled doubleblind noninferiority t

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Switch to fixed-dose doravirine (100 mg) with islatravir (0·75 mg) once daily in virologically suppressed adults with HIV-1 on antiretroviral therapy: 48-week results of a phase 3, randomised, open-label, non-inferiority trial

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Summary

Background Doravirine and islatravir is an investigational, once-daily, single-tablet regimen with high antiviral potency, favourable safety and tolerability, and low propensity for resistance. We report week 48 results from a phase 3 trial evaluating switch from stable, oral antiretroviral therapy (ART) to the fixed combination of doravirine (100 mg) and islatravir (0·75 mg).

Methods This phase 3, multicentre, randomised, active-controlled, open-label, non-inferiority trial was conducted at 77 research, community, and hospital-based clinics in 15 countries. Adults aged 18 years or older with fewer than 50 HIV-1 RNA copies per mL on any oral, two-drug or three-drug ART regimen for at least 3 months, and no history of previous virological failure on any past or current regimen were randomly assigned (1:1) by a computer-generated randomisation schedule to switch to doravirine (100 mg) and islatravir (0·75 mg) or to continue their baseline ART regimen. Block randomisation was based on a block size of four, and randomisation was stratified by baseline regimen (ie, protease inhibitor, integrase inhibitor, or other). Participants in the doravirine and islatravir group were instructed to take one tablet at approximately the same time each day, and participants in the baseline ART group continued to take the medication according to the locally approved label. HIV-1 RNA and safety evaluations were done at baseline and weeks 4, 12, 24, 36, and 48. CD4 cell counts were measured at baseline, week 24, and week 48. The primary endpoint was 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) using the US Food and Drug Administration snapshot approach and prespecified non-inferiority margin of 4%. This study is registered with ClinicalTrials.gov (NCT04223778) and is completed.

Findings Between Feb 18 and Oct 2, 2020, 740 individuals were screened for eligibility, of whom 672 (90·8%) participants (249 [37·1%] women and 423 [62·9%] men; median CD4 count of 678 cells per µL [IQR 496–868]) were randomly assigned to doravirine (100 mg) and islatravir (0·75 mg; n=336) or to continue baseline ART (n=336). The last follow-up visit occurred on Sept 8, 2021. At week 48, zero of 336 participants in the doravirine and islatravir group versus five (1·5%) of 336 participants in the baseline ART group had greater than or equal to 50 HIV-1 RNA copies per mL (difference –1·5, 95% CI –3·4 to –0·3). The per-protocol analysis showed consistent results. Headache was the most common adverse event in both groups (35 [10·4%] of 336 participants in the doravirine and islatravir group, 16 [4·8%] of 336 in the baseline ART group), infection rates were similar (113 [33·6%] in both groups), and discontinuations due to adverse events were low (seven [2·1%] *vs* one [0·3%]). 66 (19·6%) of 336 participants had treatment-related adverse events in the doravirine and islatravir group compared with 30 (8·9%) of 336 in the baseline ART group. In the islatravir and doravirine group, CD4 cell counts (mean change –30·3 cells per µL) and total lymphocyte counts (mean change –0·26×10⁹/L) were decreased at 48 weeks.

Interpretation Switching to single-tablet doravirine (100 mg) and islatravir (0·75 mg) maintained viral suppression up to week 48 and was non-inferior to antiretroviral combinations used in clinical practice for adults with HIV-1; however, decreases in CD4 cell and total lymphocyte counts do not support further development of once-daily doravirine (100 mg) and islatravir (0·75 mg).

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See Comment page e346

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Introduction

For over two decades, the standard of care for the treatment of HIV-1 has been a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent from one of the following classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor.[1,2] Although these three-drug regimens are efficacious and have led to improved life expectancy for people with HIV,[3] the need for lifelong treatment raises concerns about the long-term safety, costs, and convenience of antiretroviral therapy (ART).[4] Two-drug ART regimens might address these concerns by minimising overall antiretroviral drug exposure and providing improved tolerability and quality of life for people with HIV.[1,2]

A two-drug, single-tablet regimen containing doravirine and islatravir is under clinical investigation for the treatment of HIV-1. Doravirine is an approved NNRTI with an improved overall drug profile compared with other NNRTIs, including robust in-vitro activity across commonly observed, clinically relevant, NNRTI-resistant variants; minimal risk for drug–drug interactions; and no food restrictions.[5,6] In clinical trials, doravirine has shown virological efficacy, a low propensity for resistance with a profile distinct from other NNRTIs, and a favourable safety profile.[7–9]

Islatravir is a highly potent, long-acting nucleoside analogue with multiple mechanisms of action, including translocation inhibition and delayed chain termination; a high barrier to the development of resistance;[10,11] and potent in-vitro antiviral activity with clinical exposures that cover clinically relevant, NRTI-resistant variants (eg, Met184Ile/Val, thymidine analogue mutations, Lys65Arg, and Lys70Glu).[12] Because islatravir does not induce or inhibit any metabolising enzymes or transporters, it is unlikely to interact with most other drugs.[13] Given their complementary attributes, doravirine and islatravir are ideal partners for a complete two-drug oral ART regimen.[14]

Research in context

Evidence before this study

We searched the US National Library of Medicine PubMed database using the terms "doravirine" and "islatravir" for research articles published in English 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 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 (ART) 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

Two-drug ART regimens might address concerns about the long-term safety, costs, and convenience of antiretroviral therapy by minimising overall antiretroviral drug exposure. People with HIV who are virologically suppressed on their existing regimen might choose to switch regimens for safety or tolerability reasons or for regimen simplification. This is the first phase 3 clinical trial to investigate switching from a stable, oral, two-drug or three-drug antiretroviral regimen to the fixed combination of doravirine (100 mg) and islatravir (0·75 mg). Switching to doravirine and islatravir was non-inferior to continuing baseline ART for the primary endpoint of greater than or equal to 50 HIV-1 RNA copies per mL at 48 weeks. Although treatment-related adverse events were more common in the doravirine and islatravir group, treatment discontinuation due to adverse events was low in both groups. Decreases in CD4 cell and total lymphocyte counts were noted in the doravirine and islatravir group but were not associated with an increased rate of infections.

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 a stable, oral, two-drug or three-drug antiretroviral regimen. The results of this open-label study complement the results of a randomised, double-blind, phase 3 study that evaluated virologically suppressed adults who were stable on bictegravir–emtricitabine–tenofovir alafenamide before switching to doravirine (100 mg) and islatravir (0·75 mg). Considering the exposure-dependent declines in CD4 cell and lymphocyte counts observed in the islatravir programme, development of once-daily doravirine (100 mg) and islatravir (0·75 mg) for virologically suppressed people with HIV has been stopped. Modelling and simulation studies predict that islatravir (0·25 mg) daily will achieve efficacious exposures without decreases in lymphocyte counts, supporting continuation of development at this lower dose. Phase 3 clinical trials are underway investigating the fixed combination of doravirine (100 mg) with islatravir (0·25 mg) in adults who are virologically suppressed or naive to HIV-1 treatment.

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The concomitant use of islatravir and doravirine was investigated in a phase 2b dose-ranging study in adults with HIV-1 who were treatment naive. In part 1, coadministration of islatravir (0·25 mg, 0·75 mg, or 2·25 mg) with doravirine (100 mg) and lamivudine (300 mg) resulted in high rates of viral suppression within 24 weeks regardless of the islatravir dose.[15] After discontinuation of lamivudine, all doses of islatravir with doravirine maintained viral suppression in the majority of participants and were generally well tolerated until week 48.[15] Islatravir (0·75 mg) was initially selected for clinical development on the basis of modelling and simulation studies showing that the expected concentrations of islatravir triphosphate after a single 0·75 mg dose would be sufficient to suppress both wild-type HIV-1 and NRTI-resistant variants.[16] We investigated the efficacy and safety of switching to a fixed-dose, once-daily combination of doravirine (100 mg) and islatravir (0·75 mg) in virologically suppressed adults with HIV-1 who were on an oral combination ART regimen for at least 3 months.

Methods

Study design and participants

We conducted a phase 3, multicentre, randomised, active-controlled, open-label, non-inferiority trial to evaluate switching from baseline ART to doravirine (100 mg) and islatravir (0·75 mg) in adults with HIV-1 infection. The trial was conducted at 77 research, community, and hospital-based clinics in 15 countries: Australia, Canada, Chile, Columbia, France, Italy, Japan, New Zealand, Poland, Russia, South Africa, Spain, Switzerland, the UK, and the USA.

The study investigators enrolled men and women with HIV-1 who were at least 18 years of age and had been virologically suppressed (ie, <50 plasma HIV-1 RNA copies per mL) for at least 3 months on a continuous, stable, oral, two-drug or three-drug (with or without pharmacokinetic booster) combination ART regimen, with no previous history of virological failure on any past or current regimen and no history of virological resistance to doravirine, as shown by any of the following substitutions in reverse transcriptase: Val106Ala, Val106Met, Val108Ile, Tyr188Leu, His221Tyr, Pro225His, Phe227Cys, Phe227Leu, Met230Ile, Met230Leu, Leu234Ile, Pro236Leu, or Tyr318Phe. Previous regimen switches for tolerability, side-effects, dosing convenience, or cost were permitted if they occurred more than 3 months before signing informed consent.

Participants were excluded if they had active hepatitis B virus infection (ie, tested positive for hepatitis B surface antigen or hepatitis B virus DNA); had a history of malignancy 5 years or less before signing informed consent; were taking or anticipated to require systemic immunosuppressive therapy, immune modulators, or other prohibited therapies (eg, strong and moderate CYP3A inducers, non-study ART, 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, NCT04223778 (MK-8591A Protocol 017).

Randomisation and masking

Investigators used a computer-generated randomisation schedule created by the sponsor to assign the participants in a 1:1 ratio to switch to the doravirine (100 mg) and islatravir (0·75 mg) once-daily, single-tablet regimen on day 1 or to continue their baseline ART regimen. Randomisation used a block size of four and was stratified by the baseline ART regimen as follows: protease-inhibitor-based regimens (including those with INSTIs), INSTI-based regimens (without protease inhibitors), and all other non-protease-inhibitor and non-INSTI regimens.

Procedures

Open-label doravirine and islatravir was provided by the sponsor, and participants were instructed to take one tablet at approximately the same time each day without regard to food. Baseline ART was provided by the participant, to be taken according to the locally approved label. Dose modifications were not allowed.

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 was measured at each study visit; quantification was done at a central laboratory (PPD Laboratory Services, Wilmington, NC, USA) using the Abbott RealTime HIV-1 assay (Abbott Molecular, Des Plaines, IL, USA) with lower limit of detection 40 copies per mL. All HIV-1 RNA measurements greater than or equal to 50 copies per mL were to be confirmed with a second sample collected within 2–4 weeks after the initial sample. Two consecutive occurrences of greater than or equal to 200 HIV-1 RNA copies per mL at any time during the study was defined as confirmed viraemia. For participants with confirmed viraemia, viral drug resistance testing was performed by Monogram Biosciences (South San Francisco, CA, USA) using the

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sample from the confirmation visit. CD4 cell counts were measured by the central laboratory at baseline, week 24, and week 48.

Safety evaluations (ie, physical examination, vital signs, and chemistry and haematology parameters) were done at each study visit. Participants who were positive for hepatitis B core antibodies without active infection at screening 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. Bone mineral density was assessed by dual x-ray absorptiometry at day 1 and week 48. Adverse events were evaluated at each visit and assessed for intensity according to the US National Institutes of Health Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.[17] The association between the study drug and adverse events was assessed by the investigator. Participants who discontinued 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 the proportion with fewer than 40 copies per mL, the mean change from baseline in CD4 cell count, and the development of viral drug resistance (in participants with confirmed viraemia) in the full analysis set. 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 outcomes 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 clinical trials evaluating higher doses of islatravir (20 mg once weekly and 60 mg once monthly),[18] post-hoc analyses of the mean change from baseline in total lymphocyte count and the ratio of CD4 cell count to total lymphocyte count were conducted for this study.

Statistical analysis

Statistical tests were done using SAS, version 9.4. The primary population for efficacy was the full analysis set, defined as all participants who received at least one dose of study drug, with participants included in the treatment group to which they were randomly assigned. The virological efficacy endpoints were also analysed in the per-protocol analysis set, which excluded participants who received prohibited therapies for more than 7 consecutive days, were less than 95% adherent to study drug (appendix p 2), or became pregnant. 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 primary approach for analysis of virological endpoints was the US Food and Drug Administration snapshot algorithm.[19] The proportion of participants with greater than or equal to 50 HIV-1 RNA copies per mL at week 48 was calculated using the Miettinen and Nurminen method[20] with Cochran-Mantel-Haenszel weights, stratified by baseline ART regimen (ie, protease inhibitor, INSTI, or other). Non-inferiority would be concluded if the upper bound of the two-sided multiplicity-adjusted 95% CI for the difference between treatment groups in the proportion of participants with greater than or equal to 50 HIV-1 RNA copies per mL was less than 4 percentage points. A sample size of 289 participants per group was chosen to achieve 85% power to show non-inferiority of doravirine and islatravir to baseline ART, on the basis of an assumed rate of 2% of participants in the baseline ART group having greater than or equal to 50 HIV-1 RNA copies per mL at week 48, with a 4-percentage-point margin and one-sided α of 0·02495.

For the secondary virological endpoints (ie, proportion of participants with fewer than 50 HIV-1 RNA copies per mL and fewer than 40 copies per mL), the treatment difference and associated two-sided nominal 95% CI were calculated using the Miettinen and Nurminen method[20] with Cochran-Mantel-Haenszel weights, stratified by baseline ART regimen. For the change from baseline in CD4 cell count, missing data were handled with the data-as-observed approach. 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, and the treatment difference at each timepoint was estimated using the ANCOVA model adjusted by baseline CD4 cell count, treatment group, and stratification factor. Data for viral drug resistance were summarised for participants with confirmed viraemia, but no statistical analysis was performed.

If the primary hypothesis of non-inferior efficacy was met, the secondary hypothesis that doravirine and islatravir is superior to baseline ART as measured by the change from baseline in fasting LDL cholesterol and

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non-HDL cholesterol at week 48 would be tested sequentially for each baseline ART stratum in the order of protease-inhibitor regimens, INSTI regimens, and all other regimens. The treatment difference and two-sided 95% CI were estimated using ANCOVA models adjusted by baseline lipid level and treatment group, excluding participants receiving lipid-lowering therapy at baseline. Separate ANCOVA models were constructed for each baseline ART stratum; within a stratum, each endpoint was tested independently at the one-sided $\alpha/2$ significance level. Doravirine and islatravir would be declared superior to continuation of baseline ART if the upper bound of the two-sided multiplicity-adjusted 95% CI for the estimate of the treatment difference was less than 0.

Adverse events and treatment-emergent laboratory abnormalities were assessed via point estimates and two-sided nominal 95% CIs for treatment differences in the proportion of participants with events, using the unstratified Miettinen and Nurminen method. For the change from baseline in weight and laboratory parameters, baseline was defined as the value at day 1 (or at the most recent screening visit if day 1 was not available). For dual x-ray absorptiometry scans, baseline was defined as any assessment taken on or before study day 30. Missing safety parameters were handled with the data-as-observed approach. To evaluate the effect on weight, the treatment difference and two-sided nominal 95% CI for the change from baseline were estimated using ANCOVA models adjusted by baseline weight, sex at birth, race, stratification factor, and treatment group. Changes from baseline in bone mineral density were assessed using ANCOVA models with terms for baseline measurement and treatment group.

An independent data monitoring committee periodically reviewed efficacy and safety data provided by an independent statistician throughout the study. An interim futility analysis was performed by the independent statistician when 40% of target enrolment had completed the week 24 assessments, and the data monitoring committee concluded that the trial could be continued on the basis of the efficacy and safety data available at that timepoint.

For the post-hoc analyses, the mean change from baseline in total lymphocyte count and the ratio of CD4 cell count to total lymphocyte count were analysed using the data-as-observed approach and the full analysis set. The within-group, two-sided, nominal 95% CI was calculated on the basis of the t-distribution, and the treatment difference was estimated using the ANCOVA model adjusted by baseline value, treatment group, and stratification factor.

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 Oct 2, 2020, 740 individuals were screened for eligibility, of whom 672 (90·8%) were randomly assigned to a treatment group. 336 participants were assigned to switch to the doravirine and islatravir single-tablet regimen, and 336 participants were assigned to remain on their previous ART regimen until week 48. Additional time for enrolment at some sites (due to delays related to COVID-19) and more participants being eligible than expected contributed to the random assignment of approximately 16% more participants than planned. 14 (4·2%) participants in the doravirine and islatravir group and 10 (3·0%) in the baseline ART group discontinued the study on or before week 48 (figure). The most common reason for discontinuation was adverse event in the doravirine and islatravir group (n=7) and loss to follow-up in the baseline ART group (n=5). The last follow-up visit occurred on Sept 8, 2021.

Demographic and baseline characteristics were balanced between the treatment groups (table 1). Of the 672 enrolled participants, 249 (37·1%) were women and 423 (62·9%) were men and 179 (26·6%) were Black or African American. The median age was 45 years (IQR 36–54), and 254 (37·8%) participants were aged 50 years or older. The median time since HIV diagnosis was 9·5 years (IQR 4·9–14·8), and most participants were receiving their first (225 [33·5%]) or second (178 [26·5%]) ART regimen. The median duration of baseline ART before the study was 33·3 months (IQR 15·6–52·9), and 560 (83·3%) participants had received the baseline regimen for 1 year or more. Before enrolment, 352 (52·4%) participants were receiving an INSTI, mainly dolutegravir (208 [31·0%]); 93 (13·8%) were receiving a protease inhibitor, mainly boosted darunavir (77 [11·5%]); and 227 (33·8%) were receiving an NNRTI, primarily efavirenz (97 [14·4%]), rilpivirine (73 [10·9%]), or doravirine (38 [5·7%]; appendix p 3). The baseline regimen included tenofovir alafenamide in 261 (38·8%) participants and tenofovir disoproxil fumarate in 204 (30·4%) participants. The mean baseline CD4 count was 703 cells per µL (SD 274) in the doravirine and islatravir group and 700 cells per µL (268) in the baseline ART group.

At week 48, no participants who switched to doravirine and islatravir had greater than or equal to 50 HIV-1 RNA copies per mL, compared with five (1·5%) of 336 participants who continued baseline ART, showing the non-inferiority of switching to doravirine and islatravir (difference –1·5, multiplicity-adjusted 95% CI –3·4 to –0·3; table 2).

The proportion of participants with fewer than 50 HIV-1 RNA copies per mL at week 48 was similar in the doravirine and islatravir group and the baseline ART group overall (table 2) and in each baseline ART stratum (appendix p 4) and across demographic subgroups based on age, sex, race, and ethnicity (appendix p 5). The

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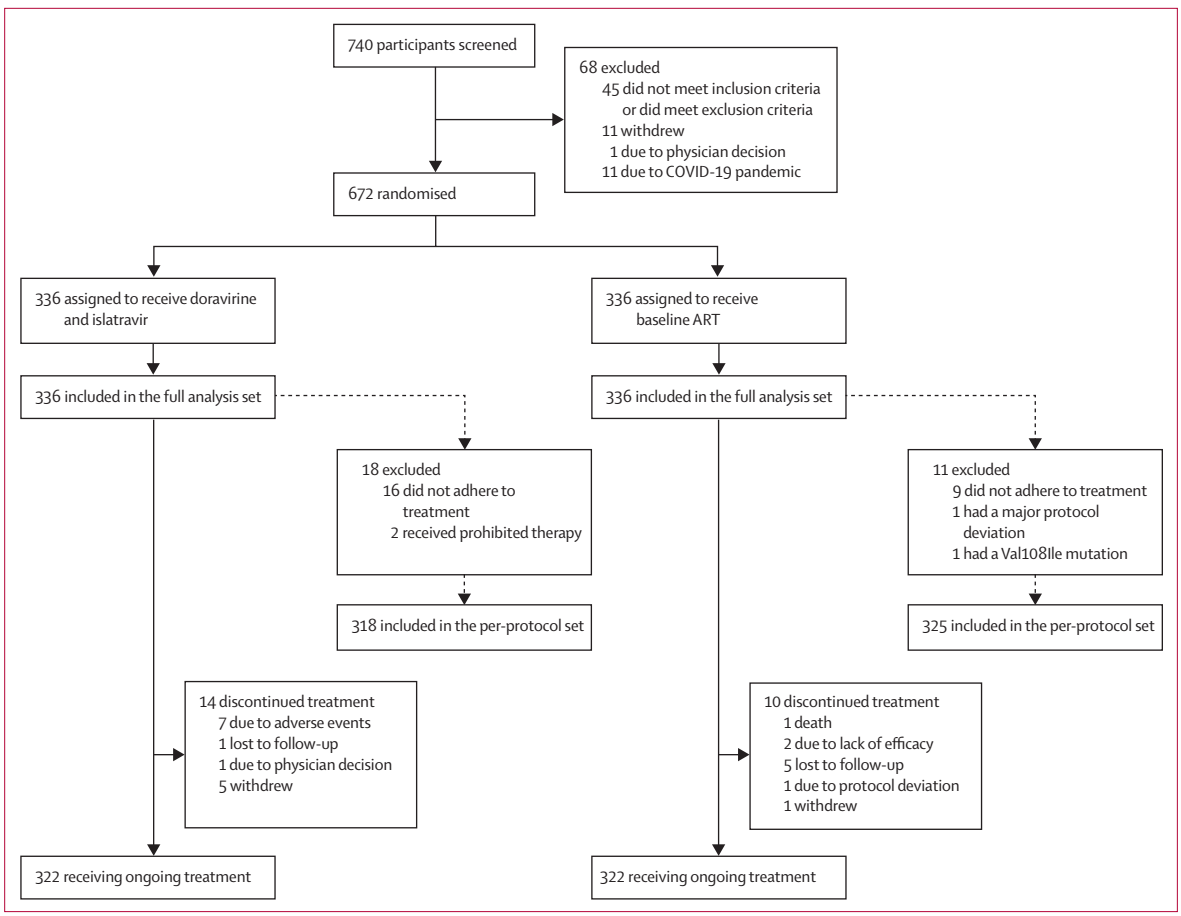


Figure: **Trial profile**

proportions with fewer than 40 HIV-1 RNA copies per mL were also high in both groups. Results for the per-protocol set were consistent with the full analysis set.

At week 48, the mean change from baseline in CD4 cell counts showed a decrease in the doravirine and islatravir group versus an increase in the baseline ART group (difference –66·7 cells per µL, 95% CI –95·8 to –37·7; table 3). However, only four (1·2%) of 336 participants in the doravirine and islatravir group had a decline in CD4 count to fewer than 200 cells per µL at week 48.

No participant who switched to doravirine and islatravir met the criteria for confirmed viraemia or resistance testing during the first 48 weeks of the study. Three participants who continued baseline ART met criteria for confirmed viraemia with more than 400 HIV-1 RNA copies per mL. Resistance testing showed treatment-emergent resistance to emtricitabine (Lys65Arg and Met184Val) in a participant receiving elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide; resistance to efavirenz (Lys103Asn, Val106Met, and Met230Leu) in a participant receiving efavirenz, emtricitabine, and tenofovir disoproxil fumarate; and resistance to efavirenz (Val179Glu) in a participant receiving efavirenz, abacavir, and lamivudine.

After switching to doravirine and islatravir, at least one adverse event was reported by week 48 in more than 70% of participants in both groups, with a slightly higher proportion in the doravirine and islatravir group (table 4). The most common adverse events were headache, accidental overdose, and COVID-19 in the doravirine and islatravir group and headache and COVID-19 in the baseline ART group. Infections were reported in 113 (33·6%) of 336 participants in the doravirine and islatravir group and 113 (33·6%) of 336 participants in the baseline ART group (appendix p 6), and no US Centers for Disease Control and Prevention AIDS-defining Category C events occurred. The profile of adverse events by the Division of AIDS toxicity grade was similar across the treatment groups, with the majority reported as grade 1 or 2 (appendix p 8). Grade 3 or 4 adverse events were reported in approximately 7% of each group (table 4).

A total of eight participants discontinued treatment due to adverse events, which were considered treatment-related by the investigator in five participants (all from the doravirine and islatravir group): paranoia (as previously mentioned); increased weight; fatigue, headache, and nausea; abnormal dreams, disorientation,

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	Doravirine and islatravir group (n=336)	Baseline ART group (n=336)
Age, years	46·0 (35·5–54·0)	45·0 (37·0–53·5)
18–49	204 (60·7%)	214 (63·7%)
50–64	117 (34·8%)	102 (30·4%)
≥65	15 (4·5%)	20 (6·0%)
Sex at birth		
Male	213 (63·4%)	210 (62·5%)
Female	123 (36·6%)	126 (37·5%)
Race		
White	210 (62·5%)	198 (58·9%)
Black or African American	88 (26·2%)	91 (27·1%)
Asian	19 (5·7%)	19 (5·7%)
Other	17 (5·1%)	26 (7·7%)
Hispanic or Latinx ethnicity	67 (19·9%)	64 (19·0%)
Hepatitis C co-infection	1 (0·3%)	1 (0·3%)
CD4 count, cells per µL	665 (496–889)	685 (499–845)
>350	308 (91·7%)	308 (91·7%)
≥200 to ≤350	19 (5·7%)	19 (5·7%)
<200	4 (1·2%)	6 (1·8%)
Time since HIV-1 diagnosis, years	9·9 (4·8–15·5)	8·8 (4·9–14·6)
Duration of baseline regimen before enrolment, months	32·8 (15·5–50·8)	34·1 (15·6–54·0)
≥12 months	281 (83·6%)	279 (83·0%)
Baseline antiretroviral therapy		
Protease-inhibitor-based regimens (including with INSTI)	47 (14·0%)	46 (13·7%)
INSTI-based regimens (without protease inhibitors)	176 (52·4%)	176 (52·4%)
All other non-protease-inhibitor and non-INSTI regimens*	113 (33·6%)	114 (33·9%)

Data are median (IQR) or n (%). ART=antiretroviral therapy. INSTI=integrase strand-transfer inhibitor. *Other baseline ART was NNRTI-based in all except one participant (appendix p 3).

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

	Doravirine and islatravir group	Baseline ART group	Difference, % (95% CI)
Full analysis set			
≥50 HIV-1 RNA copies per mL	0/336	5/336 (1·5%)	−1·5 (−3·4 to −0·3)
≥50 HIV-1 RNA copies per mL in week 48 window	0/336	2/336 (0·6%)	..
Discontinued due to lack of efficacy	0/336	3/336 (0·9%)	..
<50 HIV-1 RNA copies per mL	320/336 (95·2%)	317/336 (94·3%)	0·9 (−2·6 to 4·4)
No virological data in week 48 window	16/336 (4·8%)	14/336 (4·2%)	..
Discontinued due to adverse event or death and last measurement <50 HIV-1 RNA copies per mL	7/336 (2·1%)	1/336 (0·3%)	..
Discontinued for other reasons and last measurement <50 HIV-1 RNA copies per mL	7/336 (2·1%)	7/336 (2·1%)	..
On treatment but missing data in window	2/336 (0·6%)	6/336 (1·8%)	..
<40 HIV-1 RNA copies per mL	318/336 (94·6%)	317/336 (94·3%)	0·3 (−3·3 to 3·9)
Per-protocol set			
≥50 HIV-1 RNA copies per mL	0/318	5/325 (1·5%)	−1·5 (−3·6 to −0·3)
<50 HIV-1 RNA copies per mL	303/318 (95·3%)	308/325 (94·8%)	0·5 (−3·0 to 4·0)
<40 HIV-1 RNA copies per mL	301/318 (94·7%)	308/325 (94·8%)	−0·1 (−3·8 to 3·5)

Data are n/N (%), unless otherwise stated. ART=antiretroviral therapy.

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

and disturbance in attention; and headache, nasopharyngitis, ocular discomfort, and depressed mood. All of these events except increased weight resolved after study treatment was stopped.

Adverse events were considered to be treatment-related by the investigator in 96 participants overall, with a higher proportion in the doravirine and islatravir group (table 4). The most frequently reported treatment-related adverse events were insomnia, abnormal dreams, and headache in the doravirine and islatravir group (table 4) and diarrhoea, dizziness, and headache (two [0·6%] participants for each) in the baseline ART group. Grade 3 or 4 adverse events were considered treatment-related by the investigator in one participant from the doravirine and islatravir group (ie, grade 3 paranoia) and one participant from the baseline ART group (ie, grade 3 increased alanine transaminase with grade 4 increased aspartate transaminase).

Serious adverse events were reported in 27 participants overall, with similar proportions across the treatment groups. Serious infections occurred in four (1·2%) of 336 participants in the doravirine and islatravir group (ie, appendicitis, COVID-19 pneumonia, acute pyelonephritis, and tonsillitis) and in three (0·9%) of 336 participants in the baseline ART group (ie, appendicitis with peritoneal abscess, COVID-19, and urinary tract infection). One participant (from the doravirine and islatravir group) had a serious adverse event (ie, paranoia) that was considered treatment-related and resolved after study drug was discontinued. One participant (from the baseline ART group) died during the study; the death resulted from a motor vehicle accident and was considered not related to study treatment. No pregnancies occurred in either treatment group.

Mean weight gain from baseline to week 48 was 1·4 kg (95% CI 0·9 to 2·0) in participants who switched to doravirine and islatravir and 0·2 kg (–0·3 to 0·7) in those who continued baseline ART (difference 1·3 kg, 0·6 to 2·0). Among participants who switched from an INSTI regimen to doravirine and islatravir, mean weight gain was not significantly different from participants who remained on their INSTI regimen (0·7 kg *vs* 0·1 kg; difference 0·4 kg, –0·6 to 1·5). Among participants who switched from a protease-inhibitor regimen, mean weight gain was higher than in participants who remained on their protease inhibitor regimen (1·8 kg *vs* 0·1 kg; difference 2·0 kg, 0·1 to 3·9). Similarly, participants who switched from an NNRTI regimen had higher mean

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	Doravirine and islatravir group				Baseline ART 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	331	703			333	700		
Week 24	315	705	701	−3·6 (−24·5 to 17·4)	316	704	763	59·5 (38·6 to 80·3)
Week 48	313	708	677	−30·3 (−51·8 to −8·7)	311	693	732	38·9 (17·4 to 60·3)
Total lymphocyte count, × 10^9/L								
Baseline	332	1·97			335	1·95		
Week 24	303	1·96	1·81	−0·15 (−0·20 to −0·10)	313	1·95	2·03	0·08 (0·03 to 0·12)
Week 48	286	1·96	1·69	−0·26 (−0·32 to −0·21)	302	1·92	1·94	0·01 (−0·04 to 0·07)
Ratio of CD4 cell count to total lymphocyte count, %								
Baseline	331	37·26%			333	36·81%		
Week 24	315	37·31%	38·32%	1·01 (0·58 to 1·45)	316	36·93%	37·22%	0·29 (−0·18 to 0·75)
Week 48	313	37·46%	39·40%	1·94 (1·45 to 2·42)	311	36·83%	37·79%	0·95 (0·45 to 1·46)

ART=antiretroviral therapy. *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**

	Doravirine and islatravir group (n=336)	Baseline ART group (n=336)	Difference, % (95% CI)*
Any adverse event	269 (80·1%)	236 (70·2%)	9·8 (3·3 to 16·3)
Most common adverse events (≥5% in either group)			
Headache	35 (10·4%)	16 (4·8%)	5·7 (1·7 to 9·9)
Accidental overdose	24 (7·1%)	2 (0·6%)	6·5 (4·0 to 9·9)
COVID-19	18 (5·4%)	16 (4·8%)	0·6 (−2·8 to 4·1)
Treatment-related† adverse events	66 (19·6%)	30 (8·9%)	10·7 (5·5 to 16·1)
Most common treatment-related† adverse events (≥5 participants in either group			
Insomnia	7 (2·1%)	1 (0·3%)	1·8 (0·2 to 4·0)
Abnormal dreams	6 (1·8%)	1 (0·3%)	1·5 (−0·1 to 3·6)
Headache	6 (1·8%)	2 (0·6%)	1·2 (−0·6 to 3·3)
Nausea	5 (1·5%)	1 (0·3%)	1·2 (−0·3 to 3·2)
Pruritus	5 (1·5%)	0	1·5 (0·3 to 3·4)
Weight increase	5 (1·5%)	0	1·5 (0·3 to 3·4)
Serious adverse events	14 (4·2%)	13 (3·9%)	0·3 (−2·8 to 3·5)
Serious treatment-related† adverse event	1 (0·3%)	0	0·3 (−0·8 to 1·7)
Grade 3–4 adverse events	23 (6·8%)	25 (7·4%)	−0·6 (−4·6 to 3·4)
Treatment-related† grade 3–4 adverse events	1 (0·3%)	1 (0·3%)	0·0 (−1·4 to 1·4)
Discontinuation due to adverse event	7 (2·1%)	1 (0·3%)	1·8 (0·2 to 4·0)
Due to a treatment-related† adverse event	5 (1·5%)	0	1·5 (0·3 to 3·4)
Due to a serious adverse event	2 (0·6%)	0	0·6 (−0·5 to 2·1)
Due to a serious treatment-related† adverse event	1 (0·3%)	0	0·3 (−0·8 to 1·7)
Deaths	0	1 (0·3%)	−0·3 (−1·7 to 0·8)

Data are n (%). Adverse event terms are based on the Medical Dictionary for Regulatory Activities, version 24.0. ART=antiretroviral therapy. *Calculated before rounding. †Considered by the investigator to be related to study drug.

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

weight gain than those who remained on their NNRTI regimen (2·5 kg *vs* 0·4 kg; difference 2·3, 1·0 to 3·5).

Among participants who were previously on a protease-inhibitor-based regimen, the mean change in fasting LDL cholesterol from baseline to week 48 was significantly lower in those who switched to doravirine and islatravir compared with those who continued their baseline ART (table 5). The mean change in fasting non-HDL cholesterol was also significantly lower in the doravirine and islatravir group than in the baseline ART group for participants previously on a protease-inhibitor-based regimen. Among participants previously on an INSTI-based or NNRTI-based regimen, the mean changes in fasting LDL cholesterol and non-HDL cholesterol were not significantly different between the treatment groups (table 5). For all baseline ART groups, the mean change in the ratio of total cholesterol to HDL was not significantly different between the treatment groups (table 5). Eight (2·4%) of 336 participants in each group started lipid-lowering therapy during the study.

Other laboratory and radiological data showed no meaningful differences between the treatment groups. Grade 3 and grade 4 laboratory anomalies were uncommon and similar between the groups (appendix p 9). One participant who switched to doravirine and islatravir had laboratory values that met criteria for potential drug-induced liver injury and was subsequently diagnosed with acute hepatitis B infection. At baseline, the participant was negative for hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis C antibody; study treatment was stopped due to initiation of hepatitis B antiviral therapy consisting of prohibited medications, and the hepatitis B infection was reported as resolving. No events of hepatitis B reactivation were reported, and no participants in either group developed evidence of nephrotoxicity. Mean changes in hip and spine bone mineral density were minimal and not significantly different between the treatment groups (appendix p 10).

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	Doravirine and islatravir group (n=336)	Baseline ART group (n=336)	Treatment difference (95% CI)	p value for treatment difference*
Protease-inhibitor-based regimens, n	29	35	..	..
LDL cholesterol (mg/dL)	−8·6 (−19·7 to 2·5)	3·4 (−3·3 to 10·0)	−14·1 (−27·6 to −0·7)	0·0094
Non-HDL cholesterol (mg/dL)	−13·9 (−25·3 to −2·5)	2·8 (−4·4 to 10·0)	−18·2 (−32·3 to −4·2)	0·0021
Ratio of total cholesterol to HDL	−0·14 (−0·34 to 0·06)	0·15 (−0·06 to 0·36)	−0·29 (−0·59 to 0·01)	NPS
INSTI-based regimens, n	129	133	..	..
LDL cholesterol (mg/dL)	2·7 (−1·3 to 6·8)	3·4 (−0·9 to 7·8)	0·6 (−5·6 to 6·9)	0·41
Non-HDL cholesterol (mg/dL)	2·0 (−3·2 to 7·2)	4·4 (−0·2 to 9·0)	−0·5 (−7·7 to 6·8)	0·44
Ratio of total cholesterol to HDL	−0·02 (−0·24 to 0·20)	0·16 (−0·01 to 0·34)	−0·11 (−0·35 to 0·14)	NPS
NNRTI-based regimens, n	90	94	..	..
LDL cholesterol (mg/dL)	9·3 (4·1 to 14·5)	7·3 (4·0 to 10·6)	2·3 (−3·7 to 8·4)	NA
Non-HDL cholesterol (mg/dL)	9·9 (4·2 to 15·7)	6·6 (3·1 to 10·1)	4·0 (−2·6 to 10·6)	NA
Ratio of total cholesterol to HDL	0·32 (0·17 to 0·47)	0·20 (0·09 to 0·30)	0·14 (−0·05 to 0·32)	NPS

Data are mean change (95% CI), unless otherwise stated. Within-group 95% CIs were based on the t-distribution. Participants taking lipid-lowering therapy during the study were excluded from this analysis. ART=antiretroviral therapy. NA=not applicable per hierarchical testing strategy (testing stopped when superiority was not established for the INSTI stratum). NPS=not prespecified for hypothesis testing. *The p value is considered statistically significant if p<0·012485, based on the small alpha adjustments made for each data monitoring committee efficacy review before the primary analysis.

Table 5: **Change from baseline in fasting lipids at week 48, by baseline ART strata**

In the post-hoc analysis, the mean change in the total lymphocyte count at week 48 was a decrease in the doravirine and islatravir group versus no change in the baseline ART group (difference −0·27×10⁹/L, 95% CI −0·34 to −0·19). Minimal change was observed in the ratio of CD4 cell count to total lymphocyte count for both groups (table 3).

Discussion

In this phase 3, randomised, active-controlled, open-label trial, switching to the doravirine (100 mg) and islatravir (0·75 mg) single-tablet regimen was non-inferior to remaining on the previous two-drug or three-drug oral ART regimen for maintenance of viral suppression. No participants in the doravirine and islatravir group had greater than or equal to 50 HIV-1 RNA copies per mL at week 48, compared with five (1·5%) of 336 participants in the baseline ART group. Viral suppression (ie, <50 HIV-1 RNA copies per mL and <40 copies per mL) was sustained in a high proportion of participants in both groups at week 48. No participant in the doravirine and islatravir group had confirmed viraemia or met criteria for resistance testing, whereas three participants in the baseline ART group had confirmed viraemia and developed viral resistance to at least one component of their regimen. The absence of resistance observed in participants receiving doravirine and islatravir reflects the favourable resistance profile of this two-drug combination.[14]

The mean decrease in CD4 cell count after switching to doravirine and islatravir was modest and not associated with an increase in infection-related adverse events. At week 48, the mean CD4 count was similar between the treatment groups, and only four (1·2%) participants in the doravirine and islatravir group had a decline in CD4 count to fewer than 200 cells per µL. The mean total lymphocyte count was also decreased in the doravirine and islatravir group, and the ratio of CD4 cell count to total lymphocyte count remained stable. Similar effects on CD4 cell and total lymphocyte counts were observed in a double-blind study of adults who switched from bictegravir, emtricitabine, and tenofovir alafenamide to doravirine and islatravir.[21]

Among participants who switched to doravirine and islatravir, discontinuations due to treatment-related adverse events were infrequent (1·5%), and the rates of serious adverse events and grade 3–4 adverse events were similar to those in the baseline ART group. Higher rates of overall adverse events and treatment-related adverse events were observed in the doravirine and islatravir group, possibly because participants in the baseline ART group had tolerated their current regimen for a substantial amount of time (median 34·1 months [IQR 15·6–54·0]) before entering the study and were less likely to report new adverse events while remaining on a familiar regimen. Additionally, all participants knew which regimen they were receiving, allowing ascertainment bias to influence the reporting of adverse events. Our results are consistent with other open-label studies that have reported higher adverse event rates in participants who switched to a new ART regimen.[22–24]

Among participants who were previously on a protease-inhibitor regimen, switching to doravirine and islatravir was superior to continuing baseline ART with respect to improvements in fasting LDL cholesterol and non-HDL cholesterol. Other studies have shown improvement in lipid profiles after switch from a protease-inhibitor regimen to an NNRTI regimen.[22,25] By contrast, the changes in LDL cholesterol and non-HDL cholesterol were not significantly different between participants who switched to doravirine and islatravir and those who remained on an INSTI or NNRTI regimen. This finding is

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consistent with the results of the double-blind study of switching from bictegravir, emtricitabine, and tenofovir alafenamide to doravirine and islatravir, which reported that the mean changes in LDL cholesterol and non-HDL cholesterol were not significantly different between treatment groups.[21] There were no clinically meaningful changes in other laboratory tests, no evidence of liver or renal toxicity, and no changes in hip or spine bone mineral density in either treatment group at week 48.

Mean weight gain after switching to doravirine and islatravir was related to the previous ART regimen. Participants who switched from an INSTI regimen had minimal weight gain that was not significantly different from those who continued their baseline INSTI regimen. Similar results were observed in the double-blind study of adults who switched from bictegravir, emtricitabine, and tenofovir alafenamide to doravirine and islatravir.[21] By contrast, participants in our study who switched from a protease-inhibitor or NNRTI regimen to doravirine and islatravir had higher weight gain than those who remained on their baseline ART. A subsequent post-hoc analysis showed that significant weight gain in the doravirine and islatravir group was limited to participants who switched from a regimen containing efavirenz or tenofovir disoproxil fumarate, or both;[26] this finding is consistent with an analysis of 12 switch trials, which reported that baseline ART was a predictor of post-switch weight gain, with the greatest weight gain observed in participants who switched from efavirenz or tenofovir disoproxil fumarate.[27]

An important limitation of this study is the open-label study design, which was used because blinding of the study drug was not feasible due to the wide variety of previous regimens received by the study participants and continued in the baseline ART group. Thus, participants and investigators were aware of the treatment group assignment, and this knowledge might have influenced the reporting of subjective endpoints, such as adverse events. Another limitation is the exclusion of participants with previous virological failure or active hepatitis B infection. An important strength of our study is the substantial enrolment of women, non-White participants, and participants aged 50 years or older. The diversity of our study population is an improvement over previous HIV clinical trials[28,29] and contributes to the generalisability of our results.

The primary results of this phase 3 study in virologically suppressed adults show that switching to doravirine and islatravir from a stable oral ART regimen maintained viral suppression up to week 48 and was non-inferior to continuing the previous regimen. No participant who switched to doravirine and islatravir had confirmed viraemia or met resistance testing criteria. These findings support the potential of doravirine and islatravir once daily as an oral switch option for adults who are virologically suppressed but desire a change from a protease-inhibitor, INSTI, or NNRTI regimen. As a two-drug complete regimen for the treatment of HIV, doravirine and islatravir would offer regimen simplification, reduced drug exposure, decreased risk of drug interactions, and a high barrier to resistance[14] that might allow its use in people with lamivudine or rilpivirine resistance. However, the decreased CD4 cell and lymphocyte counts observed in this study do not support the further development of doravirine and islatravir at these doses. Decreases in CD4 cell and total lymphocyte counts were also observed in other islatravir studies, with greater decreases seen at higher islatravir doses given once weekly (20 mg) or once monthly (60 mg) compared with once daily (0·75 mg) administration.[18] Population pharmacokinetic modelling using data from the islatravir clinical programme predicts that islatravir (0·25 mg) will provide robust antiviral activity without a negative effect on lymphocytes.[30,31] Therefore, the development of once-daily doravirine and islatravir has been transitioned from islatravir 0·75 mg to 0·25 mg, and clinical trials have been initiated to evaluate the fixed combination of doravirine (100 mg) and islatravir (0·25 mg) once daily in people with HIV-1 who are virologically suppressed (NCT05631093, NCT05630755) or naive to treatment (NCT05705349).

Contributors

JK, MCF, TAC, KE, and IG designed or monitored the study. J-MM, GR, CO, AA, AC, SO, FH, PK, PT, and SW enrolled participants in the study and accessed and verified the underlying data. AG and SK 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

J-MM reports a grant to his institution from Gilead; consulting fees from Gilead, ViiV, and Merck for advisory boards; payment from Merck for expert testimony; and participation on a data safety monitoring board for Aelix. GR reports honoraria for lectures from ViiV, GSK, and MSD and support from Gilead for attending meetings or travel. CO reports payment to the Desmond Tutu Health Foundation for the current study and honoraria and travel support from MSD for attendance and presentation at Expert Input Forum. AA declares no competing interests. AC reports unrestricted educational grants with MSD, Gilead Sciences, and ViiV Healthcare. SO reports research grants from MSD, ViiV Healthcare, and Gilead Sciences and honoraria for lectures from ViiV Healthcare and Gilead Sciences. FH reports research grants from AbbVie, VIR, Merck, and GSK; payment from AbbVie, Gilead, ViiV, and Merck for Speakers Bureau; and participation on a data safety monitoring board or advisory board for Viiv and Gilead. PK reports grants from Merck, Gilead, GSD/ViiV, and Theratechnologies; consulting fees from Merck, Gilead, Johnson & Johnson, GSK/ViiV, and Theratechnologies; participation on a data safety monitoring board or advisory board for Gilead, Merck, GSK/ViiV, Theratechnologies, and Johnson & Johnson; and stock or stock options with Merck, Gilead, Johnson & Johnson, Pfizer, and GSK. PT reports a grant from Merck to the University of Pennsylvania for the current study and consulting fees from Merck, Gilead, and ViiV. SW reports funding and provision of study materials from Merck for the current study; grants from Merck, ViiV Healthcare, Gilead Sciences, and Janssen; and consulting fees and honoraria for lectures from Merck and ViiV Healthcare. AG, SK, IG, KE, TAC, MCF, and JK are current or former employees of Merck Sharp & Dohme, a subsidiary of Merck & Co, and might own stock or stock options, or both, in the company.

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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 the Data Access mailbox.

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