Fixed-dose daily doravirine (100 mg) with islatravir (0·25 mg) versus bictegravir, emtricitabine, and tenofovir alafenamide for initial HIV-1 therapy: 48-week results of a phase 3, randomised, controlled, double-blind, non-inferiority trial

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Summary

Background Doravirine and islatravir is a two-drug regimen being investigated for the treatment of HIV-1. This study evaluated efficacy and safety of once daily doravirine and islatravir versus bictegravir, emtricitabine, and tenofovir alafenamide in adults with HIV-1 who were treatment-naive.

Methods MK-8591A-053 is a phase 3, randomised, double-blind, active-controlled, non-inferiority study being done at 116 research, community, and hospital-based clinics across 20 countries. Adults aged at least 18 years with HIV-1 RNA of 500 copies per mL or more never previously treated for HIV-1 were randomly assigned (1:1), stratified by screening HIV-1 RNA viral load and CD4-cell count, to received either doravirine (100 mg) and islatravir (0·25 mg) or bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) orally once daily. The primary endpoint was percentage of participants with HIV-1 RNA less than 50 copies per mL at week 48 (FDA snapshot; prespecified non-inferiority margin –10%). Participants who received at least one dose of study intervention were analysed for safety. This trial is ongoing and is registered with ClinicalTrials.gov NCT05705349.

Findings We screened 756 participants for eligibility between March 8, 2023, and Oct 11, 2024. 269 participants were treated with doravirine–islatravir and 267 with bictegravir–emtricitabine–tenofovir. The last study visit for this analysis occurred on Oct 13, 2025. Median age was 32 years (IQR 26–40), 134 (25%) participants were assigned female at birth, 225 (42%) were White, 92 (17%) had CD4 counts less than 200 cells per µL, 197 (37%) had an HIV-1 RNA greater than 100 000 copies per mL, and 314 (59%) had pre-existing resistance-associated mutations. At week 48, doravirine–islatravir was non-inferior to bictegravir–emtricitabine–tenofovir: 247 (91·8%) of 269 versus 242 (90·6%) of 267 had HIV-1 RNA less than 50 copies per mL (estimated difference 1·2%, 95% CI –3·7 to 6·2). Mean increase in CD4 count was 218 cells per µL in the doravirine–islatravir group and 226 cells per µL in the bictegravir–emtricitabine–tenofovir group (estimated difference –6·8, 95% CI –35·8 to 22·2). Two participants in the doravirine–islatravir group and one in the bictegravir–emtricitabine–tenofovir group with pretreatment HIV-1 RNA greater than 1 million copies per mL and CD4 counts less than 200 cells per µL acquired treatment-emergent mutations. Phenotypic analysis revealed resistance to doravirine in two participants treated with doravirine–islatravir. 38 (14%) of 269 participants in the doravirine–islatravir group and 48 (18%) of 267 in the bictegravir–emtricitabine–tenofovir group had treatment-related adverse events: the most common were increased weight (7, 3%), headache (6, 2%), and dizziness (5, 2%) in the doravirine–islatravir group and increased weight (9, 3%), headache (9, 3%), and decreased estimated glomerular filtration rate (8, 3%) in the bictegravir–emtricitabine–tenofovir group.

Interpretation Doravirine (100 mg) and islatravir (0·25 mg) is a two-drug, once daily regimen with efficacy and safety similar to bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) for initial treatment of HIV-1, which could provide an option for treatment without an integrase strand transfer inhibitor.

Funding Merck Sharp & Dohme, a subsidiary of Merck & Co.

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Lancet HIV 2026

Published Online
February 25, 2026
https://doi.org/10.1016/S2352-3018(26)00033-0

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Introduction

Life expectancy of people with HIV approximates that of people without HIV when effective antiretroviral therapy (ART) is initiated early after acquisition of the virus and before development of immunodeficiency.[1] High rates of viral suppression can be achieved and maintained with available antiretroviral regimens. The continued need for life-long ART to prevent HIV-related comorbidities in an ageing population with HIV has shifted focus from virological to non-virological sequelae of antiretroviral

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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 Nov 4, 2025, restricted to phase 3 clinical trials that reported on concurrent administration of doravirine and islatravir in humans. Three publications on randomised, controlled studies with doravirine (100 mg) and islatravir (0·75 mg) were identified: an open-label switch study (MK-8591A-017), a double-blind switch study (MK-8591A-018), and an initial treatment study (MK-8591A-020). In these trials, doravirine and islatravir (0·75 mg) was non-inferior to comparators (any oral antiretroviral regimen [MK-8591A-017] and bictegravir, emtricitabine, and tenofovir alafenamide [MK-8591A-018 and MK-8591A-020]) for primary efficacy endpoints. Development of doravirine and islatravir (0·75 mg) was discontinued because of dose-dependent decreases in CD4 cell and total lymphocyte counts observed in doravirine and islatravir (0·75 mg)-treated participants in the switch studies. The programme was restarted with a lower dose of islatravir and subsequently, two randomised, controlled switch studies with doravirine (100 mg) and islatravir (0·25 mg) showed non-inferiority to the same comparators (MK-8591A-051 and MK-8591A-052) with no adverse effect on CD4 cell and total lymphocyte counts at week 48 in doravirine and islatravir (0·25 mg)-treated participants.

Added value of this study

This phase 3, randomised, double-blind study (MK-8591A-053; NCT05705349) compared doravirine (100 mg) and islatravir (0·25 mg) with bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) in adults with HIV-1 who were initiating antiretroviral therapy for the first time. The study enrolled a diverse population with representation of participants with HIV-1 RNA greater than 100 000 copies per mL, CD4 counts less than 200 cells per µL, and pre-existing resistance-associated mutations at baseline. Doravirine–islatravir was non-inferior to bictegravir–emtricitabine–tenofovir for the primary efficacy endpoint of percentage of participants with less than 50 copies per mL of HIV-1 RNA at week 48. Treatment-emergent mutations were detected in three participants (two in the doravirine–islatravir group and one in the bictegravir–emtricitabine–tenofovir group); phenotypic analysis revealed resistance to doravirine in the two doravirine and islatravir participants and no resistance to the comparator regimen. Both regimens were well tolerated.

Implications of all the available evidence

Second-generation integrase strand transfer inhibitor (INSTI)-based (bictegravir or dolutegravir) three-drug and two-drug regimens are currently preferred for initial therapy of HIV-1. Because of emerging concerns of INSTI resistance, or for people with HIV who may experience intolerance to INSTIs, alternative efficacious and safe non-INSTI-based regimens are needed. Doravirine (100 mg) and islatravir (0·25 mg) is a potential non-INSTI-based two-drug, single-tablet, once daily regimen for the initial treatment of HIV-1 in adults.

drugs. There is increased scrutiny on lifetime exposure to antiretroviral agents and their impact on factors including weight, lipids, organ function, adverse effects, and drug interactions as people with HIV develop premature age-related events possibly due to HIV-associated inflammation in the setting of controlled HIV replication.[2,3] One approach to reduce exposure to antiretrovirals and minimise unwanted effects is to use two-drug regimens.[4]

The fixed-dose combination of doravirine (100 mg) and islatravir (0·25 mg) is being investigated as a two-drug, once daily, single-tablet, non-integrase-strand-transfer inhibitor (INSTI)-based antiretroviral regimen for treatment of HIV-1. Doravirine, a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), has previously shown efficacy and safety in clinical trials for initial therapy of HIV-1 in combination with two nucleoside reverse transcriptase inhibitors (NRTIs).[5,6] Islatravir is an investigational nucleoside reverse transcriptase translocation inhibitor with potent activity against HIV-1.[7,8] Doravirine and islatravir are suitable to combine for a two-drug oral ART given their complementary mechanisms of action and resistance profiles, including activity against common NRTI and NNRTI resistance-associated variants.[9,10] Two phase 3 switch studies of doravirine (100 mg) and islatravir (0·25 mg) once daily demonstrated non-inferiority to continuing baseline ART for the endpoint of HIV-1 RNA greater than or equal to 50 copies per mL at week 48.[11,12] This study was designed to evaluate efficacy and safety of a fixed-dose combination of doravirine (100 mg) and islatravir (0·25 mg) compared with a fixed-dose combination of bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg), a preferred three-drug INSTI-based regimen for initial treatment,[13,14] in adults with HIV-1 who were treatment-naive.

Methods

Study design and participants

MK-8591A-053 (NCT05705349) is an ongoing phase 3, multicentre, randomised, active-controlled, double-blind, non-inferiority study. The trial was done at 116 research, community, and hospital-based clinics across 20 countries (Argentina, Canada, Chile, Colombia, Dominican Republic, France, Germany, Guatemala, Israel, Japan, Kenya, Malaysia, Mexico, South Africa,

Spain, Switzerland, Thailand, Turkey, the UK, and the USA including Puerto Rico).

Adults aged 18 years or older with plasma HIV-1 RNA greater than or equal to 500 copies per mL at screening (within 45 days before randomisation) who had never been treated for HIV were eligible for inclusion. HIV-1 genotyping was done at screening, and participants were excluded if they had virological resistance to study intervention or reverse transcriptase inhibitors as determined by detection of any of the following reverse transcriptase mutations: K65R/E/N (Lys65Arg/Glu/Asn), T69insert (Thr69insert), K70E (Lys70Glu), V106A/M (Val106Ala/Met), V108I (Val108Ile), Q151M (Gln151Met), M184I/V (Met184Ile/Val), Y188L (Tyr188Leu), H221Y (His221Tyr), P225H (Pro225His), F227C/L/V (Phe227Cys/Leu/Val), M230I/L (Met230Ile/Leu), L234I (Leu234Ile), P236L (Pro236Leu), Y318F (Tyr318Phe), or three or more thymidine analogue-associated mutations (M41L [Met41Leu], D67N [Asp67Asn], K70R [Lys70Arg], L210W [Leu210Trp], T215F/Y [Thr215Phe/Tyr], K219E/Q [Lys219Glu/Gln]).[15] Participants were ineligible if they had active hepatitis B virus (HBV) infection (positive hepatitis B surface antigen or HBV DNA); had chronic hepatitis C virus (HCV) infection (detectable HCV RNA) with cirrhosis; had an active AIDS-defining opportunistic infection; had been previously treated with an antiviral active against HIV-1 (use of an antiretroviral for prevention of HIV was permitted before diagnosis of HIV, with the exception of long-acting agents); or had a Cockcroft–Gault creatinine clearance less than or equal to 30 mL per min. Complete inclusion and exclusion criteria are provided in the protocol (appendix p 27). Participants assigned female sex at birth were required to have a negative pregnancy test before the first dose of study intervention and to use contraception during the intervention period; however, participants who became pregnant during the study could continue their assigned intervention open-label if their CD4 counts were 200 cells per µL or greater and they maintained HIV-1 RNA less than 50 copies per mL for 3 months.

Community advisory boards provided feedback on the design, acceptance in the community, and participant burden of the study protocol. The study is being done in accordance with the principles of International Council for Harmonisation Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki regarding independent ethics committee review, informed consent, and the protection of human participants in biomedical research and was approved by the institutional review boards and regulatory agencies for each study site (appendix pp 18–26). All participants provided written, informed consent.

Randomisation and masking

A central interactive response technology system was used to assign participants randomly (1:1) to receive a single tablet of either doravirine (100 mg) and islatravir (0·25 mg) or bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) orally once daily, stratified by screening HIV-1 RNA (less than or equal to 100 000 or greater than 100 000 copies per mL) and screening CD4 count (less than 200 cells per µL or greater than or equal to 200 cells per µL; appendix p 15). Block randomisation was based on a block size of 4. Active study drugs were packaged identically to matching placebos.

Participants, investigators, study staff, and sponsor personnel involved in study intervention administration or clinical evaluation of participants were masked to the treatment assignment through week 48. 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 will remain masked until week 144.

Procedures

Participants received two bottles, one for active drug and one for placebo, provided centrally by the sponsor, and were instructed to take one tablet from each bottle at the same time every day without regard to food. Participants taking medications or oral supplements containing polyvalent cations (Mg^{2+}, Al^{3+}, Ca^{2+}, or Fe^{3+}) were counselled to take the study intervention 2 h before or 6 h after these medicines, given that the interaction can decrease concentrations of bictegravir. Close monitoring of blood glucose was recommended for participants taking metformin because bictegravir can increase metformin concentrations.[16]

See Online for appendix

Study visits occurred at screening, baseline (day 1 of treatment), and at weeks 4, 8, 16, 24, 36, and 48. Physical examination, vital signs, weight, chemistry and haematology parameters, a T and B lymphocyte and natural killer cell panel, and plasma HIV-1 RNA were assessed at screening and every visit. Plasma HIV-1 RNA quantification was done at a central laboratory (LabCorp, Burlington, NC, USA) using the Cobas HIV-1 assay (Roche Diagnostics, Rotkreuz, Switzerland; lower limit of detection 20 copies per mL). Participants were required to discontinue study intervention if they had two consecutive samples 4 weeks (±1 week) apart with HIV-1 RNA greater than or equal to 200 copies per mL, at any time during the study after suppression to less than 50 copies per mL (virological rebound), or at or after week 24 without previous suppression to less than 200 copies per mL (incomplete virological response). Viral resistance was assessed in participants with HIV-1 RNA of 200 copies per mL or more at the time of study intervention discontinuation. Resistance testing was done at Monogram Biosciences (GenoSure PRIme, PhenoSense, and PhenoSense Integrase, San Francisco, CA, USA). Islatravir concentrations were assessed at every study visit; doravirine concentrations were assessed per protocol for participants who discontinued due to lack of efficacy.

Serology for HBV, with reflex HBV DNA testing, was done at screening and at week 48. HBV vaccination of participants who were not immune was recommended. Pill counts were done at study visits to assess treatment adherence. Fasting lipids and kidney function were assessed at baseline, week 24, and week 48. Adverse events were assessed at all visits and graded for intensity based on US National Institutes of Health Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, July 17 (version 2.1).[17] Investigators assessed the relationship between the study intervention and adverse events. The study intervention had to be discontinued for protocol-specific decreases in CD4-cell and total lymphocyte counts (appendix p 3).

Outcomes

The primary efficacy endpoint was percentage of participants with HIV-1 RNA less than 50 copies per mL at week 48. Secondary efficacy outcomes were percentage of participants with HIV-1 RNA less than 200 copies per mL, mean change from baseline in CD4-cell count, and development of viral drug resistance. Safety outcomes were percentage of participants with adverse events, treatment-related adverse events, grade 3 or 4 adverse events, serious adverse events, adverse events that led to discontinuation of study intervention, and grade 3 or 4 changes in laboratory parameters. Additional outcomes included the mean change in fasting LDL cholesterol, HDL cholesterol (HDL-C), non-HDL-C, and the ratio of total cholesterol to HDL-C; estimated glomerular filtration rate (eGFR) based on creatinine and cystatin C; total lymphocyte count; and body weight.

Statistical analysis

The primary population for efficacy was the full analysis set, which comprised participants who received at least one dose of study intervention and had baseline data for analyses that required baseline data. The secondary population for the efficacy analysis was 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 (ie, received prohibited therapies, had adherence rate less than 95%, became pregnant, or were unmasked to the treatment group for any reason). All participants who were randomly assigned to a treatment group and received at least one dose of study intervention were analysed for safety.

Initial enrolment was limited to participants with screening HIV-1 RNA less than or equal to 100 000 copies per mL. An external unblinded statistician did a futility analysis when this sentinel cohort of at least 30 participants in each group completed the week 24 visit. A type I error adjustment of α=0·00001 was set aside for the week 24 futility analysis. If the lower bound of the two-sided 95% CI for the difference between the groups for the percentage of participants with HIV-1 RNA less than 200 copies per mL at week 24 was less than −30 percentage points, consideration would be given to stopping the study. An independent external data monitoring committee periodically reviewed efficacy and safety data, including the unblinded futility analysis. Following review of the futility analysis, the external data monitoring committee recommended continuing the study without HIV-1 RNA restriction for enrolment.

For the primary efficacy endpoint in the full analysis set, the percentage of participants with HIV-1 RNA less than 50 copies per mL at week 48 was compared between the doravirine and islatravir and the bictegravir–emtricitabine–tenofovir groups, per the US Food and Drug Administration (FDA) snapshot approach.[18] Non-inferiority would be concluded if the lower bound of the two-sided multiplicity-adjusted 95% CI for the difference between the groups was greater than −10 percentage points. The 95% CI was based on the stratified Miettinen and Nurminen method with Cochran–Mantel–Haenszel weights stratified by screening HIV-1 RNA and screening CD4-cell count.[19] The planned sample size of 500 participants (250 per group) would provide 95·4% power to show non-inferiority of doravirine–islatravir to bictegravir–emtricitabine–tenofovir with an assumed rate of 90·0% of participants with HIV-1 RNA less than 50 copies per mL in both groups at week 48 at a one-sided type I error of α=0·02499 (adjusted for the futility analysis at week 24).

Prespecified subgroup analyses on the rate of participants with HIV-1 RNA less than 50 copies per mL at week 48 were performed by baseline HIV-1 RNA and CD4-cell count and participant baseline demographics and characteristics. A post-hoc subgroup analysis was performed by baseline presence of reverse transcriptase and integrase resistance-associated mutations. The between-treatment-group difference, with a nominal 95% CI based on the unstratified Miettinen and Nurminen method, was estimated within each subgroup with the FDA snapshot approach.[18,19]

The secondary endpoint of the percentage of participants with HIV-1 RNA less than 200 copies per mL was analysed by treatment group at week 48 per the FDA snapshot approach.[18] The associated two-sided nominal 95% CIs were calculated with the same approach as the primary endpoint.[19] The difference between the groups for mean change in CD4-cell count at week 48, and the corresponding two-sided nominal 95% CI, was determined by the constrained longitudinal data analysis model,[20] adjusting for treatment group, time, stratum, the interaction of time by treatment group, and the interaction of time by stratum. An unstructured covariance matrix was used to model the correlation among repeated measurements, with the Kenward–Roger adjustment to make proper statistical inference.[21]

Point estimates and two-sided nominal 95% CIs were determined with the unstratified Miettinen and

Nurminen method for the difference between treatment groups in the percentage of participants with adverse events. Point estimates and two-sided nominal 95% CIs were calculated similarly for laboratory parameters that met predetermined limits of change in at least four participants in either treatment group.[19] For the mean change from baseline to week 48 in fasting lipids, eGFR, and total lymphocyte count, the treatment difference and corresponding two-sided nominal 95% CIs were estimated using ANCOVA models adjusted by baseline value and treatment group.

The treatment difference for the mean change in weight from baseline and the corresponding CI was determined with the constrained longitudinal data analysis model, adjusting for treatment group, time, stratum, sex at birth, race, the interaction of time by treatment group, the interaction of time by stratum, the interaction of time-by-sex at birth, and the interaction of time by race.[20] Superiority of doravirine–islatravir to bictegravir–emtricitabine–tenofovir for a lower mean increase from baseline weight would be concluded if the upper bound of the two-sided multiplicity-adjusted CI (corresponding to a one-sided α=0·01%) for the estimate of the between-group treatment difference was less than 0 kg. Statistical tests were done with SAS (version 9.4).

Role of the funding source

The funder of the study, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc (Rahway, NJ, USA), was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between March 8, 2023, and Oct 11, 2024, 756 individuals were screened for eligibility, of whom 537 were randomly assigned to study intervention (figure 1). The most common reason for screen failure was HIV-1 RNA greater than 100 000 copies per mL in the sentinel cohort. One participant randomly assigned to receive bictegravir–emtricitabine–tenofovir did not receive the study intervention, resulting in 269 participants in the doravirine–islatravir group and 267 in the bictegravir–emtricitabine–tenofovir group (full analysis set). At week 48, 249 participants were continuing doravirine–islatravir and 245 were continuing bictegravir–emtricitabine–tenofovir. The last study visit

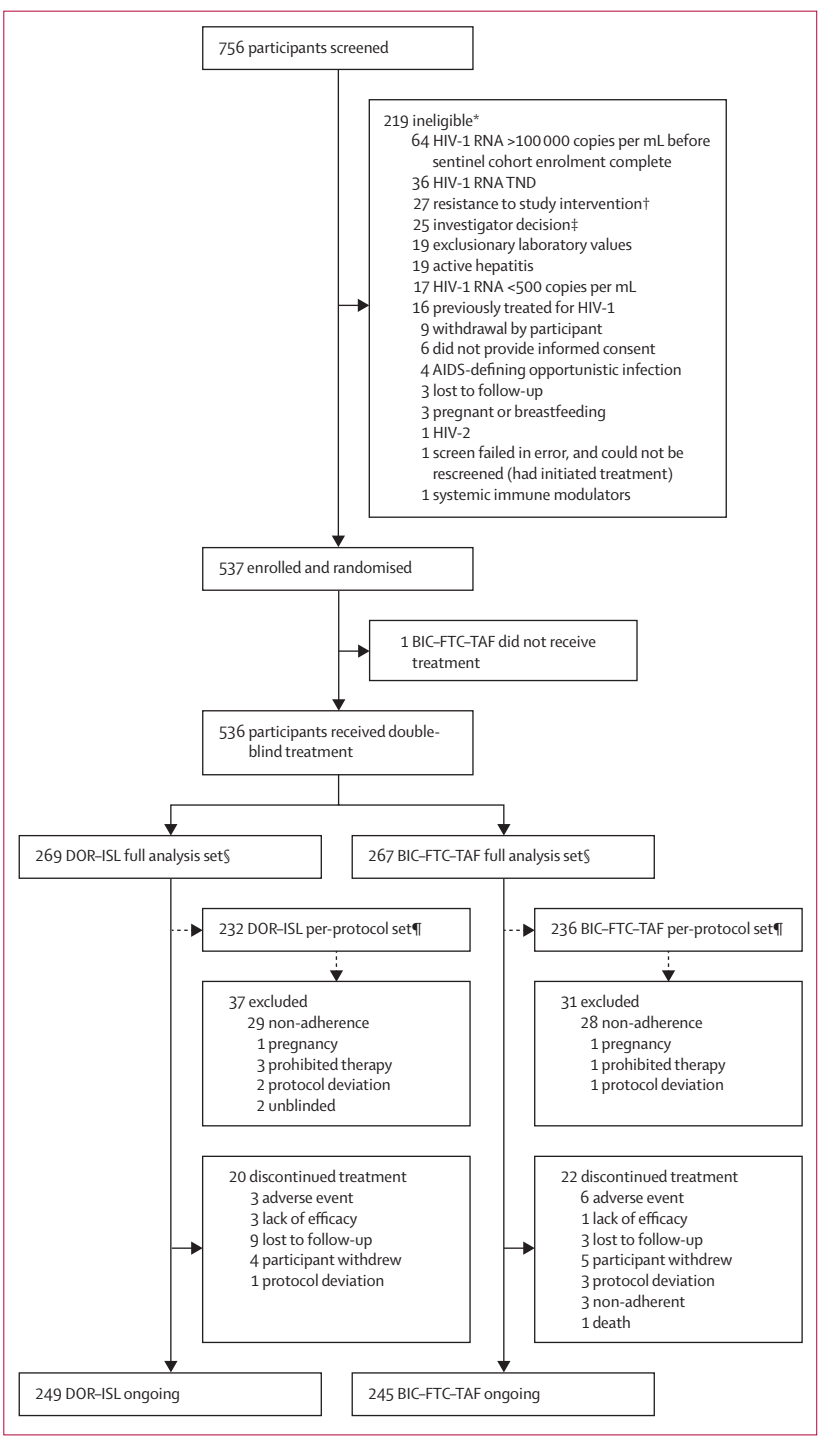

Figure 1: **Trial profile**
BIC–FTC–TAF=bictegravir–emtricitabine–tenofovir alafenamide. DOR–ISL=doravirine–islatravir. TND=target not detected. *Participants could have one or more reasons for ineligibility. †21 were ineligible due to pre-existing mutations (13 doravirine resistance-associated mutations, 7 M184V, and 1 INSTI resistance-associated mutation); resistance could not be assessed in an additional six because of genotypic assay failure. ‡Had a history or current evidence of any condition (including active tuberculosis infection), therapy, laboratory abnormality, or other circumstance (including drug or alcohol use or dependence) that might, in the opinion of the investigator, confound study results or interfere with a participant's participation for the full duration of the study, such that it was not in the best interest of the participant to participate. §Full analysis set included all randomised participants who received at least 1 dose of study intervention (study drug and placebo) and had baseline measurements for those analyses that required baseline measurements. ¶Per-protocol set included all participants in the full analysis set who did not have any major protocol violations that could impact the assessment of efficacy, including violation of key entry criteria.

for the week 48 analysis occurred on Oct 13, 2025, with a database lock on Nov 6, 2025.

Baseline demographics and characteristics were balanced between the treatment groups overall (table 1).

	Doravirine–islatravir (n=269)	Bictegravir–emtricitabine–tenofovir alafenamide (n=267)
Age, years	33 (26–41)	32 (26–39)
18–49	242 (90%)	247 (93%)
50–64	24 (9%)	16 (6%)
≥65	3 (1%)	4 (1%)
Sex at birth		
Male	204 (76%)	198 (74%)
Female	65 (24%)	69 (26%)
Participant-identified gender		
Male	197 (73%)	192 (72%)
Female	65 (24%)	67 (25%)
Transgender female	6 (2%)	5 (3%)
Transgender male	0	1 (0%)
Other*	1 (0%)	2 (1%)
Race and ethnicity		
White	110 (41%)	115 (43%)
Black or African American	89 (33%)	82 (31%)
Asian	29 (11%)	29 (11%)
Multiple	28 (10%)	26 (10%)
American Indian or Alaska Native	10 (4%)	12 (4%)
Hispanic or Latino/a ethnicity	104 (39%)	110 (41%)
Region		
Latin America	63 (23%)	73 (27%)
North America	58 (22%)	57 (21%)
Africa	58 (22%)	54 (20%)
Europe	49 (18%)	50 (19%)
Asia and Pacific Islands	41 (15%)	33 (12%)
Time from HIV-1 diagnosis to screening, months	0·7 (0·2–1·6)	0·6 (0·2–1·6)
<1	158 (59%)	176 (66%)
1 to <3	75 (28%)	53 (20%)
3 to <6	11 (4%)	19 (7%)
6 to <12	9 (3%)	9 (3%)
12 to <24	4 (1%)	5 (2%)
≥24	12 (4%)	5 (2%)
HIV-1 RNA, copies per mL	53 800 (15 000–190 000)	56 700 (17 600–179 000)
≤100 000	173 (64%)	166 (62%)
>100 000	96 (36%)	101 (38%)
≤500 000	242 (90%)	239 (90%)
>500 000	27 (10%)	28 (10%)
CD4 count, cells per µL	384 (238–531)	359 (254–531)
≥200	215 (80%)	229 (86%)
<200	54 (20%)	38 (14%)
HIV-1 subtype		
B	138 (51%)	145 (54%)
C	59 (22%)	43 (16%)
Non B or C	72 (27%)	79 (30%)

(Table 1 continues on next page)

Median age was 32 years (IQR 26–40), with 47 (8·8%) of 536 participants aged 50 years or older. 25% of participants were assigned female sex at birth, and 25% identified as female; 42% were White and 32% were Black or African American. Most participants were diagnosed with HIV less than 1 month before enrolment. 37% of participants had HIV-1 RNA greater than 100 000 copies per mL, 10% had HIV-1 RNA greater than 500 000 copies per mL, 53% had subtype B, and 19% had subtype C. 17% of participants had CD4 counts less than 200 cells per µL. 55% of participants were non-immune to hepatitis B. 2% reported prior use of pre-exposure or post-exposure prophylaxis. 114 participants (21%) had pre-existing NNRTI resistance-associated mutations in viral RNA at screening, with K103N (Lys103Asn) the most prevalent. 74 participants (14%) had pre-existing NRTI resistance-associated mutations and 126 (24%) had INSTI resistance-associated mutations (appendix p 4).

The five most frequently reported non-HIV medical conditions among the 536 participants were syphilis (82, 15%), headache (54, 10%), depression (52, 10%), hypertension (52, 10%), and osteopenia (47, 9%), and the five most frequently reported concomitant medications were paracetamol (182, 34%), a hepatitis B vaccine (115, 21%), ibuprofen (96, 18%), co-trimoxazole (95, 18%), and isoniazid (58, 11%). 260 (97%) in the doravirine–islatravir group and 255 (96%) in the bictegravir–emtricitabine–tenofovir group had adherence of 90% or greater (appendix p 8).

At week 48, 247 (92%) of 269 participants in the doravirine–islatravir group and 242 (91%) of 267 participants in the bictegravir–emtricitabine–tenofovir group had HIV-1 RNA less than 50 copies per mL, demonstrating non-inferiority of doravirine–islatravir to bictegravir–emtricitabine–tenofovir (estimated difference 1·2%, multiplicity-adjusted 95% CI −3·7 to 6·2). Results in the per-protocol set were consistent with the full analysis set for the primary efficacy endpoint (table 2). No differences in efficacy were identified in subgroups by baseline demographics and characteristics or pre-existing mutations (figure 2). Proportions of participants with HIV-1 RNA less than 50 copies per mL at week 48 were comparable across the stratification criteria for screening HIV-1 RNA and CD4-cell count subgroups (appendix p 16).

Six participants in the doravirine–islatravir group had HIV-1 RNA greater than or equal to 50 copies per mL at week 48 or discontinued the study intervention before week 48 with HIV-1 RNA greater than 50 copies per mL. One participant achieved an HIV-1 RNA less than 200 copies per mL at week 24 but had not suppressed to less than 50 copies per mL; criteria for discontinuation and resistance testing were not met and the participant is continuing in the study. Five participants met criteria for resistance testing: one was lost to follow-up after week 4 and had no treatment-emergent mutations; four discontinued study intervention due to lack of

efficacy. Two participants discontinued with virological rebound (one at week 16 and one at week 48). Both participants had plasma doravirine–islatravir concentrations below the limit of quantification at the time of virological rebound, consistent with non-adherence. Resistance testing did not identify treatment-emergent mutations. Two participants (both with pretreatment HIV-1 RNA greater than 1 million copies per mL, baseline CD4-cell count less than 200 cells per µL, and non-exclusionary mutations at baseline in reverse transcriptase) discontinued at week 16 and week 24 without suppressing to less than 50 HIV-1 RNA copies per mL. No history of pre-exposure or post-exposure prophylaxis was reported for either participant. The former participant had relatively low doravirine and islatravir plasma concentrations at week 8, suggesting possible incomplete adherence between weeks 4 and 8, although the reported adherence was 100%. The other participant had quantifiable doravirine and islatravir concentrations at all study visits, supporting adherence at the time of visits (reported adherence 97·2%). Both participants acquired treatment-emergent mutations (M184I [Met184Ile], Y188L [Tyr188Leu]; L74I [Leu74Ile], V106A [Val106Ala], M184V [Met184Val], F227L [Phe227Leu]) and phenotypic analysis revealed a 2·4-fold to 6·7-fold decreased susceptibility to islatravir and resistance to doravirine (appendix p 9). The first participant was started on dolutegravir, emtricitabine, and tenofovir disoproxil fumarate at discontinuation and a 3-log decline in HIV-1 RNA viral load was observed at the last follow-up. No post-study intervention information is available for the latter participant.

Nine participants in the bictegravir–emtricitabine–tenofovir group had HIV-1 RNA greater than or equal to 50 copies per mL at week 48 or at the time of study intervention discontinuation before week 48. Three participants who discontinued the study intervention (one lost to follow-up, one withdrew, and one for personal reasons) did not meet criteria for resistance testing. Six participants met criteria for resistance testing, of which two discontinued the study intervention due to lack of efficacy. One participant had virological rebound at week 48 and no treatment-emergent resistance was identified. The other participant had incomplete virological response at week 24 and acquired minor treatment-emergent mutations that did not result in loss of phenotypic susceptibility to bictegravir–emtricitabine–tenofovir (appendix p 9). This participant had pretreatment HIV-1 RNA greater than 1 million copies per mL and baseline CD4 count less than 200 cells per µL. No history of pre-exposure or post-exposure prophylaxis was reported. The participant reported missing one dose of study intervention. Plasma bictegravir, emtricitabine, and tenofovir concentrations were not measured per protocol. The participant was started on dolutegravir, lamivudine, and tenofovir disoproxil fumarate at discontinuation and HIV-1 RNA was 484 copies per mL at the last follow-up. The four other participants who discontinued the study intervention (three due to non-adherence, one due to a protocol deviation) met the criteria for resistance testing and no treatment-emergent resistance was detected.

16 participants had pretreatment HIV-1 RNA greater than 1 million copies per mL and CD4 counts less than 200 cells per µL, including the three participants above who developed treatment-emergent resistance. Of the other 13 participants, six were in the doravirine–islatravir group and seven were in the bictegravir–emtricitabine–tenofovir group. Four in the doravirine–islatravir group had major non-exclusionary resistance-associated mutations in reverse transcriptase at baseline and two did not; all six achieved HIV-1 RNA less than 50 copies

	Doravirine–islatravir (n=269)	Bictegravir–emtricitabine–tenofovir alafenamide (n=267)
(Continued from previous page)		
Positive hepatitis B surface antibody	133 (49%)	109 (41%)
Kidney function†		
Normal: eGFR ≥90 mL/min/1·73 m²	208 (77%)	216 (81%)
Mild: eGFR 60–89 mL/min/1·73 m²	58 (22%)	51 (19%)
Moderate: eGFR 30–59 mL/min/1·73 m²	2 (1%)	0

Data are median (IQR) or n (%). eGFR=estimated glomerular filtration rate. *Includes gender queer, non-binary, gender non-conforming, or unknown. †eGFR-creatinine by Modification of Diet in Renal Disease equation: $175 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203}$ [×0·742 if female], [×1·212 if Black], [×0·808 if Japanese].

Table 1: **Baseline characteristics in the full analysis set**

	Doravirine–islatravir	Bictegravir–emtricitabine–tenofovir alafenamide	Treatment difference (95% CI)*
Full analysis set	269	267	..
HIV-1 RNA <50 copies per mL	247 (92%)	242 (91%)	1·2 (−3·7 to 6·2)
HIV-1 RNA ≥50 copies per mL	6 (2%)	9 (3%)	..
HIV-1 RNA ≥50 copies per mL in week 48 window	2 (1%)	2 (1%)	..
Discontinued due to lack of efficacy	3 (1%)	1 (0%)	..
Discontinued for other reasons and last HIV-1 RNA ≥50 copies per mL†	1 (0%)	6 (2%)	..
No virological data in week 48 window	16 (6%)	16 (6%)	..
Discontinued due to adverse event or death	3 (1%)	7 (3%)	..
Discontinued for other reasons and last HIV-1 RNA <50 copies per mL	9 (3%)	7 (3%)	..
Discontinued for other reasons and no HIV-1 RNA	4 (1%)	0	..
On study intervention but missing data in window	0	2 (1%)	..
HIV-1 RNA <200 copies per mL	248 (92%)	243 (91%)	1·2 (−3·6 to 6·1)
Per-protocol set	232	236	
HIV-1 RNA <50 copies per mL	218 (94%)	215 (91%)	2·9 (−1·9 to 7·9)
HIV-1 RNA <200 copies per mL	219 (94%)	216 (91%)	2·9 (−1·8 to 7·8)

Data are n or n (%). *The two-sided 95% CIs for the between group differences in percent response were calculated using the Miettinen and Nurminen method stratified by screening HIV-1 RNA and CD4 count with Cochran–Mantel–Haenszel weights. †Reasons other than lack of efficacy and adverse event or death.

Table 2: **Virological efficacy outcomes at week 48 (FDA snapshot approach)**

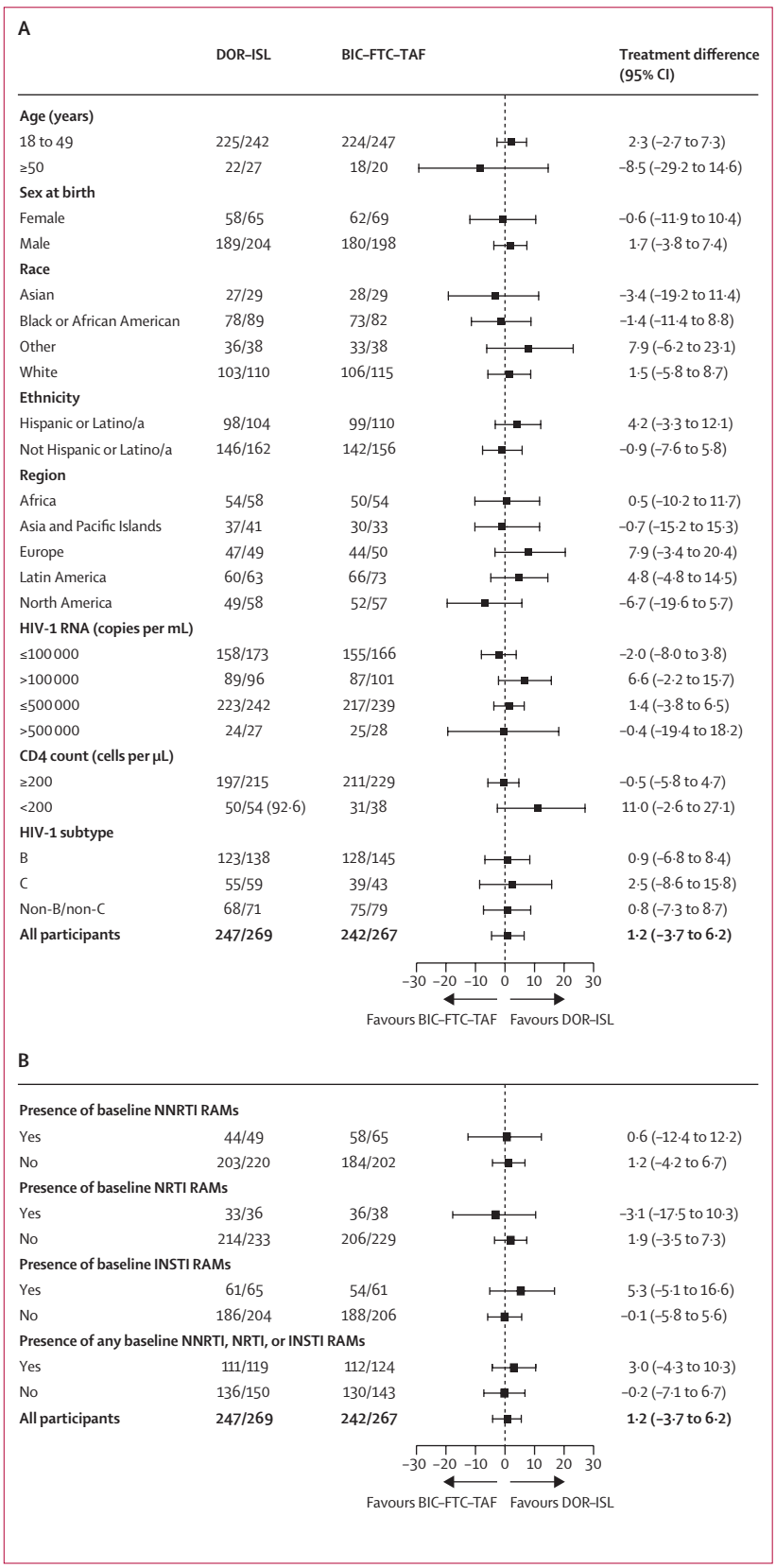

Figure 2: **HIV-1 RNA <50 copies per mL at week 48**
Analysed by baseline demographics and characteristics (A) and pre-existing resistance-associated mutations at baseline (B) with FDA snapshot approach. For all participants, the 95% CI was based on the stratified Miettinen and Nurminen method with Cochran–Mantel–Haenszel weights stratified by screening HIV-1 RNA and screening CD4-cell count. For subgroups, the 95% CI was based on the unstratified Miettinen and Nurminen method. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. INSTI=integrase strand transfer inhibitor. RAM=resistance-associated mutations.

per mL by week 48. No participants in the bictegravir–emtricitabine–tenofovir group had major INSTI resistance-associated mutations at baseline and all had an HIV-1 RNA less than 50 copies per mL by week 48.

Mean change in CD4 count from baseline to week 48 was 218 cells per µL (95% CI 198 to 239) in the doravirine–islatravir group and 226 cells per µL (95% CI 205 to 248) in the bictegravir–emtricitabine–tenofovir group (estimated difference –6·8, 95% CI –35·8 to 22·2). At week 48, the mean CD4 count was 613 cells per µL in the doravirine–islatravir group and 640 cells per µL in the bictegravir–emtricitabine–tenofovir group. Few participants had CD4 counts less than 200 cells per µL at week 48 (three versus five participants, respectively).

At week 48, adverse events (at least one or more) were comparable between treatment groups (table 3). The three most commonly reported adverse events in both groups were upper respiratory tract infection, nasopharyngitis, and headache (table 3, appendix p 10).

Treatment-related adverse events were reported in 14% of participants in the doravirine–islatravir group and 18% in the bictegravir–emtricitabine–tenofovir group. Increased weight (3%), headache (2%), and dizziness (2%) were the three most commonly reported treatment-related adverse events in the doravirine–islatravir group. In the bictegravir–emtricitabine–tenofovir group, the three most commonly reported treatment-related adverse events were increased weight (3%), headache (3%), and decreased GFR (3%) (table 3).

There was no difference between groups for grade 3 to 4 adverse events (table 3). Three (1%) of 269 participants in the doravirine–islatravir group had a grade 3 to 4 treatment-related adverse event (two grade 3 decreased GFR, one grade 4 drug reaction with eosinophilia and systemic symptoms [DRESS]) compared with four (1%) of 267 participants in the bictegravir–emtricitabine–tenofovir group (two with grade 3 decreased creatinine clearance and two with grade 3 decreased GFR).

Serious adverse events occurred in 8% of participants in the doravirine–islatravir group and 7% of participants in the bictegravir–emtricitabine–tenofovir group (table 3). Two participants in the doravirine–islatravir group had a serious adverse event considered to be treatment-related by the investigator and discontinued the study intervention prior to week 48. One participant

had a grade 4 adverse event of DRESS at week 10 that resolved after discontinuation of study intervention. This participant had no history of similar reactions to other medications in the past. The other participant had a grade 2 serious adverse event reported as a drug-induced liver injury at week 36 that resolved after discontinuation of the study intervention and concomitant medications and herbal supplements with potential hepatotoxicity. The participant was asymptomatic with a grade 4 peak alanine aminotransferase and aspartate aminotransferase (Hy's Law not met). Liver biopsy was consistent with viral or drug-related hepatitis. No serious treatment-related adverse events were reported in the bictegravir–emtricitabine–tenofovir group. No deaths were reported in the doravirine–islatravir group, and two deaths reported in the bictegravir–emtricitabine–tenofovir group were considered unrelated to study intervention (alcoholic cirrhosis and unknown cause).

No difference was identified for adverse events leading to discontinuation between the treatment groups (table 3). In the doravirine–islatravir group, one participant discontinued due to DRESS, one due to grade 2 drug-induced liver injury, and one due to grade 3 intentional self-injury unrelated to the study intervention. The adverse events that led to discontinuation in the bictegravir–emtricitabine–tenofovir group were disseminated *Mycobacterium avium* complex infection, disseminated tuberculosis, paraesthesia (considered treatment-related), acute stress disorder, primary effusion lymphoma, and tuberculosis. No participants discontinued the study intervention for protocol-specified decreases in CD-cell and total lymphocyte counts.

No participants in the doravirine–islatravir group had Centers for Disease Control and Prevention AIDS-defining category C events (appendix p 12) through week 48. Five participants in the bictegravir–emtricitabine–tenofovir group had six category C events. One participant had disseminated *M avium* complex infection and Kaposi's sarcoma. One participant each had disseminated tuberculosis, primary effusion lymphoma, tuberculosis, and recurrent pneumonia. Immune reconstitution inflammatory syndrome occurred in three participants (one in the doravirine–islatravir group and two in the bictegravir–emtricitabine–tenofovir group).

Grade 3 or 4 laboratory changes were comparable in the treatment groups, except for creatinine clearance and creatinine-based eGFR (appendix p 13). Grade 3 decreases in creatinine clearance and creatinine-based eGFR were more common in the bictegravir–emtricitabine–tenofovir group than in the doravirine–islatravir group. Mean improvement in creatinine-based eGFR from baseline was greater in the doravirine–islatravir group than in the bictegravir–emtricitabine–tenofovir group; however, mean increase in cystatin C-based eGFR was similar (appendix p 14). Mean HDL-C increased in both groups, though slightly more in the doravirine–islatravir group but there were no significant differences for mean change from baseline in fasting LDL-C, non-HDL-C, or total-cholesterol-to-HDL-C ratio. At week 48, mean change from baseline in total lymphocyte count was $0{\cdot}14\times10^9$ cells per L versus $0{\cdot}10\times10^9$ cells per L (estimated difference –0·01, 95% CI –0·09 to 0·07).

Mean weight change from baseline to week 48 was 3·6 kg (95% CI 2·8 to 4·4) in the doravirine–islatravir group compared with 3·9 kg (95% CI 3·2 to 4·7) in the bictegravir–emtricitabine–tenofovir group (estimated difference –0·3 kg, 98% CI –1·5 to 0·9; p=0·57), demonstrating that doravirine–islatravir was not superior to bictegravir–emtricitabine–tenofovir.

133 participants (49%) in the doravirine–islatravir group and 109 participants (41%) in the bictegravir–emtricitabine–tenofovir group were immune to HBV

	Doravirine–islatravir (n=269)	Bictegravir–emtricitabine–tenofovir alafenamide (n=267)	Treatment difference (95% CI)*
Any adverse event	228 (85%)	235 (88%)	–3·3 (–9·2 to 2·6)
Most common adverse events (≥5% in either group)			
Upper respiratory tract infection	30 (11%)	29 (11%)	0·3 (–5·1 to 5·7)
Nasopharyngitis	29 (11%)	33 (12%)	–1·6 (–7·1 to 3·9)
Headache	23 (9%)	29 (11%)	–2·3 (–7·5 to 2·8)
Increased weight	17 (6%)	17 (6%)	–0·0 (–4·4 to 4·2)
Diarrhoea	16 (6%)	20 (7%)	–1·5 (–6·0 to 2·8)
Urinary tract infection	16 (6%)	10 (4%)	2·2 (–1·5 to 6·1)
Influenza	15 (6%)	10 (4%)	1·8 (–1·9 to 5·7)
Insomnia	15 (6%)	11 (4%)	1·5 (–2·3 to 5·4)
Treatment-related† adverse events	38 (14%)	48 (18%)	–3·9 (–10·1 to 2·4)
Treatment-related† adverse events (≥1% in either group)			
Increased weight	7 (3%)	9 (3%)	–0·8 (–4·0 to 2·3)
Headache	6 (2%)	9 (3%)	–1·1 (–4·3 to 1·8)
Dizziness	5 (2%)	4 (1%)	0·4 (–2·2 to 3·0)
Insomnia	3 (1%)	4 (1%)	–0·4 (–2·8 to 1·9)
Decreased eGFR	2 (1%)	8 (3%)	–2·3 (–5·1 to 0·0)
Abdominal distension	1 (0%)	6 (2%)	–1·9 (–4·5 to 0·1)
Nausea	1 (0%)	4 (1%)	–1·1 (–3·5 to 0·7)
Flatulence	1 (0%)	3 (1%)	–0·8 (–2·9 to 1·1)
Fatigue	1 (0%)	3 (1%)	–0·8 (–2·9 to 1·1)
Gastro-oesophageal reflux disease	0	3 (1%)	–1·1 (–3·3 to 0·3)
Grade 3 to 4 adverse events	31 (12%)	28 (10%)	1·0 (–4·4 to 6·4)
Treatment-related† grade 3 to 4 adverse events	3 (1%)	4 (1%)	–0·4 (–2·8 to 1·9)
Serious adverse events	22 (8%)	19 (7%)	1·1 (–3·6 to 5·7)
Serious treatment-related† adverse events	2 (1%)	0	0·7 (–0·7 to 2·7)
Deaths	0	2 (1%)	–0·7 (–2·7 to 0·7)
Discontinuation due to adverse event	3 (1%)	6 (2%)	–1·1 (–3·8 to 1·3)
Due to a treatment-related adverse event	2 (1%)	1 (0%)	0·4 (–1·4 to 2·3)
Due to a serious adverse event	3 (1%)	4 (1%)	–0·4 (–2·8 to 1·9)
Due to a treatment-related serious adverse event	2 (1%)	0	0·7 (–0·7 to 2·7)

Data are n (%). eGFR=estimated glomerular filtration rate. *Based on Miettinen and Nurminen method. †Considered by the investigator to be related to study treatment.

Table 3: **Summary of adverse events through week 48 in the safety population**

(hepatitis B surface antibody positive) at screening. 52 participants (10%) in the doravirine–islatravir group and 43 (16%) in the bictegravir–emtricitabine–tenofovir group had serological evidence of prior HBV (hepatitis B core antibody positive, surface antigen negative, and HBV DNA negative) at screening. Three adverse events of HBV were reported in the doravirine–islatravir group through week 48. Two participants developed elevated alanine aminotransferase (grade 3) and were subsequently noted to have newly detected hepatitis B core antibody; however, neither had documented HBV DNA or hepatitis B surface antigen. Both were asymptomatic and continued doravirine–islatravir with normalisation of liver enzymes. The third participant acquired HBV a few days after the week 48 adverse event reporting window, discontinued doravirine–islatravir, and HBV infection is resolving on bictegravir–emtricitabine–tenofovir.

Two pregnancies were reported in the doravirine–islatravir group. One participant experienced an incomplete miscarriage at 8 weeks gestation and continued study intervention. The other participant was unblinded to treatment assignment and has an ongoing pregnancy without reported complications. One participant in the bictegravir–emtricitabine–tenofovir group became pregnant, had elective pregnancy termination, and continued study intervention.

Discussion

This phase 3, randomised, double-blind study demonstrated that the efficacy of doravirine (100 mg) and islatravir (0·25 mg) once daily for the initial treatment of HIV-1 was high and non-inferior to once daily bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg), with a small treatment difference of 1·2% and a 95% CI lower bound of –3·7%—well above the prespecified non-inferiority margin. At week 48, no difference in the efficacy endpoint was identified within subgroups, including among participants with pre-existing non-exclusionary mutations at baseline.

The efficacy of doravirine–islatravir at week 48 in this study is similar to results observed in the bictegravir–emtricitabine–tenofovir alafenamide and the dolutegravir–lamivudine registrational treatment-naive studies.[22–24] Notably, those studies enrolled a lower proportion of participants with CD4 counts less than 200 cells per µL or HIV-1 RNA greater than 100 000 copies per mL, and enrolment of participants with HIV-1 RNA greater than 500 000 copies per mL was limited or excluded.[22–24] The two participants in the doravirine–islatravir group who acquired treatment-emergent resistance had multiple factors that might have contributed, including HIV-1 RNA greater than 1 million copies per mL, CD4 counts less than 200 cells per µL, and pre-existing mutations in reverse transcriptase, as well as potential incomplete adherence. Notably, other participants in both treatment groups with similar pretreatment characteristics achieved HIV-1 RNA less than 50 copies per mL. The prevalence of non-exclusionary pre-existing resistance-associated mutations in reverse transcriptase in the study (13% NRTI and 21% NNRTI), the high and comparable efficacy in participants with and without pre-existing mutations, and the rare occurrence of treatment-emergent mutations in this study highlight the strength of the combination of doravirine–islatravir (0·25 mg).

Doravirine–islatravir was generally well tolerated with a safety profile comparable to bictegravir–emtricitabine–tenofovir. One case of DRESS was reported in this study; this is the first report of DRESS within a clinical trial of doravirine or islatravir. Rare severe skin reactions have been reported in the postmarketing experience with doravirine-containing regimens.[25] Overall, treatment-related, grade 3 or 4, serious adverse events, and discontinuations due to adverse events were similar between groups. A small difference in increase in HDL-C was observed, favouring doravirine–islatravir. The observed difference between groups in the creatinine-based eGFR is attributable to inhibitory effect of bictegravir on creatinine secretion and no participant was discontinued due to a renal adverse event.[16] There were no differences in other laboratory parameters. Through 48 weeks of treatment, participants in both groups gained a similar amount of weight, possibly indicative of a return to health.

In a prior phase 3 study, the efficacy of doravirine (100 mg) and a higher dose of islatravir (0·75 mg) was non-inferior to bictegravir, emtricitabine, and tenofovir alafenamide at week 48 in people with HIV-1 who were naive to treatment.[26] Due to a dose-dependent effect of islatravir-triphosphate which preferentially accumulated in lymphocytes causing inhibition of cell growth,[27] an imbalance in lymphocytes and a small difference in the increase in CD4-cell counts was observed between the treatment groups.[26] In this study of doravirine with a reduced dose of islatravir (0·25 mg), effective exposures were maintained with no difference between the treatment groups in the mean change in total lymphocyte and CD4-cell counts at week 48. The mean CD4 count had similarly increased to more than 600 cells per µL in both groups, demonstrating comparable immunological recovery.

The combination of doravirine–islatravir does not provide activity against HBV. Accordingly, participants with active HBV infection were excluded from this study and those who were not immune to HBV were encouraged to receive vaccination. Three adverse events of HBV were reported in the doravirine–islatravir group. All three participants were hepatitis B surface antibody negative at enrolment, emphasising the importance of vaccination in people with HIV as per current guidelines.[13,14,28]

This study has several limitations that may affect the generalisability of the results. Globally, females represent

about 50% of the population with HIV,[29] but they have been historically under-represented in clinical trials.[30] This study enrolled in several geographic regions resulting in a diverse study population including 25% female sex at birth, an improvement in representation compared with other registrational treatment-naive studies.[22–24] Data on the safety profile of doravirine–islatravir are limited in pregnancy. Participants of child-bearing potential were required to use contraception while in the study, but in the event a pregnancy did occur, participants could elect to continue their assigned intervention and participate in data collection. In addition, data characterising participants at higher risk of acquiring HIV infection, such as men who have sex with men and people who inject drugs, were not collected. The results of this analysis are limited to data up to week 48. Data will be evaluated in this ongoing study through week 144.

Doravirine (100 mg) and islatravir (0·25 mg) demonstrated comparable efficacy with similar tolerability to a recommended three-drug INSTI-based regimen for the initial treatment of HIV-1 at week 48. This study showed no discernible differences across multiple subgroups, including those with HIV-1 RNA greater than 100 000 and 500 000 copies per mL, those with low CD4-cell counts, and those with pre-existing reverse transcriptase mutations. The key discriminator of the combination of doravirine–islatravir is that it is a two-drug regimen without an INSTI. Three-drug and two-drug INSTI-based regimens are preferred for initial therapy of HIV-1 in multiple guidelines.[13,14,28] In light of concerns of emerging resistance to INSTIs,[31] which may affect their efficacy in the future, or for people who may not tolerate INSTIs, a non-INSTI-based regimen, such as doravirine–islatravir, with comparable efficacy to an INSTI-based regimen may provide an alternative option for people with HIV. These findings, in addition to the strong safety and efficacy results observed in the two phase 3 trials in virologically suppressed populations,[11,12] support doravirine–islatravir as a promising non-INSTI-based two-drug regimen for the treatment of HIV-1 in a broad population.

Contributors

MCF, MLP, MV, SOK, and YX designed the study. MCF, MLP, MV, TLD, and YX monitored the study. LMS, MCF, MLP, MV, SOK, TLD, and YX analysed the data. JKR, SK, RP, CB, GS, AA, NM, JMM, BCR, and HG enrolled participants in the study and accessed and verified the underlying data. All authors interpreted the study data and contributed to development of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JKR: honoraria for consulting or speaking at educational events from Abbott, Abbvie, Boehringer, Gilead, Janssen, MSD, and ViiV. SK: nothing to disclose. RP: advisory boards for Gilead Sciences, Pfizer, Shionogi, MSD, Atea, AstraZeneca and GSK; research grants paid to his institution from MSD, ViiV Healthcare, Gilead Sciences, and PharmaMar. CB: nothing to disclose. GS: Gilead Sciences (advisor/consultant and grant/research support), Jannsen (advisor/consultant, grant/research support, honoraria), ViiV (advisor/consultant, grant/research support, and honoraria), Theratechnologies (grant/research support, honoraria, and advisor/consultant), Merck (advisor/consultant, honoraria, and grant/research support), AbbVie (grant/research support, advisor/consultant). AA: my institution receives grants from MSD, Gilead sciences, GSK/ViiV healthcare, and Janssen for conducting clinical trials. NM: institution received grants from MSD for conducting this clinical trial; participation on data safety monitoring board for PATH. JMM: institution and ANRS receive grants from Gilead, ViiV, and Merck; honoraria for consulting from Gilead, ViiV, Merck. BCR: institution receives grants from MSD, ViiV, and Janssen for conducting clinical trials; honoraria for consulting from Merck Sharpe & Dohme, ViiV, and GlaxoSmithKline. HG: honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from MSD, ViiV, and Gilead. YX, SOK, TLD, MV, LMS, MCF, MLP are employees of Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA (MSD), who may own stock or hold stock options in Merck & Co, Rahway, NJ, USA.

Data sharing

The data sharing policy, including procedures and restrictions, of Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA (MSD), is available at https://externaldatasharing-msd.com/.

Acknowledgments

Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. We thank the study participants, their families and caregivers, and all investigators (appendix p 17) and site personnel. We thank Ernest Asante-Appiah for his review of the resistance data. Medical writing and editorial assistance were provided by Dorothy McCoy, PharmD, BCPS, BCIDP, and Carol Zecca, BS, who are employees of MSD.

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