



Islatravir in combination with doravirine for treatment-naive adults with HIV-1 infection receiving initial treatment with islatravir, doravirine, and lamivudine: a phase 2b, randomised, double-blind, dose-ranging trial

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Summary

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Background Islatravir is a nucleoside reverse transcriptase translocation inhibitor in development for the treatment and prevention of HIV-1 infection. We aimed to assess the efficacy and safety of islatravir-based regimens for the treatment of HIV-1.

Methods We did a phase 2b, randomised, double-blind, comparator-controlled, dose-ranging trial at 24 clinics or hospitals in four countries (Chile, France, the UK, and the USA). Treatment-naive adults (≥ 18 years) with plasma HIV-1 RNA concentrations of at least 1000 copies per mL, CD4 T-cell counts of at least 200 cells per mL, and a calculated creatinine clearance of at least 50 mL/min (all within 60 days before study treatment) were eligible for inclusion. Participants were randomly assigned (1:1:1:1) with a block size of four via an interactive voice and web response system to receive oral treatment with one of three doses of islatravir (0.25 mg, 0.75 mg, or 2.25 mg) plus doravirine (100 mg) and lamivudine (300 mg) or to doravirine (100 mg) plus lamivudine (300 mg) plus tenofovir disoproxil fumarate (TDF; 300 mg) once daily with placebo (part 1). Treatment groups were stratified according to screening HIV-1 RNA concentration ($\leq 100\,000$ copies per mL or $>100\,000$ copies per mL). After at least 24 weeks of treatment, participants taking islatravir who achieved an HIV-1 RNA concentration lower than 50 copies per mL switched to a two-drug regimen of islatravir and doravirine (part 2). All participants and study investigators were masked to treatment in part 1; in part 2, the islatravir dose was masked to all participants and investigators, but the other drugs were given open label. The primary efficacy outcomes were the proportions of participants with an HIV-1 RNA concentration lower than 50 copies per mL at weeks 24 and 48 (US Food and Drug Administration snapshot approach). The primary safety outcomes were the number of participants experiencing adverse events and the number of participants discontinuing study drug owing to adverse events. All participants who received at least one dose of any study drug were included in the analyses. This trial is ongoing, but closed to enrolment of new participants; herein, we report study findings through 48 weeks of treatment. This trial is registered with ClinicalTrials.gov, NCT03272347.

Findings Between Nov 27, 2017, and April 25, 2019, 121 participants (mean age 31 years [SD 10.9], 112 [93%] male, 92 [76%] white, 27 [22%] with HIV-1 RNA concentration $>100\,000$ copies per mL) were randomly assigned: 29 to the 0.25 mg, 30 to the 0.75 mg, and 31 to the 2.25 mg islatravir groups, and 31 to the doravirine, lamivudine, and TDF group. At week 24, 26 (90%) of 29 participants in the 0.25 mg islatravir group, 30 (100%) of 30 in the 0.75 mg islatravir group, and 27 (87%) of 31 in the 2.25 mg islatravir group achieved HIV-1 RNA concentrations lower than 50 copies per mL compared with 27 (87%) of 31 in the doravirine plus lamivudine plus TDF group (difference 2.8%, 95% CI -14.9 to 20.4 , for the 0.25 mg islatravir group; 12.9%, -1.6 to 27.5 , for the 0.75 mg islatravir group; and 0.3%, -17.9 to 18.5 , for the 2.25 mg islatravir group). At week 48, these data were 26 (90%) of 29 in the 0.25 mg islatravir group, 27 (90%) of 30 in the 0.75 mg islatravir group, and 24 (77%) of 31 in the 2.25 mg islatravir group compared with 26 (84%) of 31 in the doravirine plus lamivudine plus TDF group (difference 6.1%, 95% CI -12.4 to 24.4 , for the 0.25 mg islatravir group; 6.2%, -12.2 to 24.6 , for the 0.75 mg islatravir group; and -6.1% , -27.1 to 14.8 , for the 2.75 mg islatravir group). 66 (73%) of participants in the islatravir groups combined and 24 (77%) of those in the doravirine plus lamivudine plus TDF group reported at least one adverse event. Two participants in the 2.25 mg islatravir group and one participant in the doravirine plus lamivudine plus TDF group discontinued owing to an adverse event. No deaths were reported up to week 48.

Interpretation Treatment regimens containing islatravir and doravirine showed antiviral efficacy and were well tolerated regardless of dose. Doravirine in combination with islatravir has the potential to be a potent two-drug regimen that warrants further clinical development.

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Research in context

Evidence before this study

We searched the US National Library of Medicine PubMed database without language restrictions for research articles published between database inception and April 20, 2020, for the terms "islatravir", "MK-8591", and "EFdA". We identified studies from the reference lists of the articles returned using these search terms and our knowledge of the literature.

Previous publications have focused on in-vitro and preclinical studies of islatravir and have shown that islatravir is a nucleoside reverse transcriptase translocation inhibitor with potent activity in vitro against HIV-1 replication and a high genetic barrier to the development of drug resistance. In preclinical studies, islatravir suppressed HIV-1 viraemia in mice and rhesus macaques and showed pharmacokinetics amenable to extended-duration dosing. In a phase 1b trial, islatravir had robust antiviral activity with single doses as low as 0.5 mg causing a more than 1.0 log decline in HIV-1 RNA concentrations over 7–10 days of follow-up, and islatravir was well tolerated by participants in this trial.

Added value of this study

Here, we present, to our knowledge, the first clinical data showing the efficacy and safety of antiretroviral regimens containing islatravir and doravirine in a phase 2b dose-ranging study. A high proportion of participants who initiated islatravir plus doravirine in combination with lamivudine and switched to islatravir plus doravirine had HIV-1 RNA concentrations lower than 50 copies per mL at week 48. Regimens containing islatravir and doravirine were generally well tolerated regardless of islatravir dose.

Implications of all the available evidence

Collective data support the further development of islatravir as a novel antiretroviral agent for the treatment of HIV-1. The promising efficacy and safety profile of doravirine plus islatravir create the potential for an efficacious two-drug regimen that would have a high barrier to resistance and would be an important milestone in the evolving treatment options for people living with HIV.

Introduction

Islatravir is the first-in-class nucleoside reverse transcriptase translocation inhibitor in development for the treatment and prevention of HIV-1 infection.^{1,2} Islatravir inhibits reverse transcriptase through several mechanisms of action.^{1,3–5} Unlike currently approved nucleoside reverse transcriptase inhibitors, islatravir contains the 3'-hydroxyl group found in endogenous nucleosides, which is associated with high affinity for reverse transcriptase. After intracellular phosphorylation to islatravir triphosphate, islatravir triphosphate inhibits reverse transcriptase translocation with the interaction of the 4'-ethynyl group with a conserved hydrophobic pocket near the active site of HIV-1 reverse transcriptase, which results in immediate chain termination and prevention of nucleotide incorporation to the viral DNA chain.³ In some instances, translocation might still occur, in which case islatravir causes delayed chain termination by preventing incorporation of further nucleotides owing to additional steric interactions of the 4'-ethynyl group. Additionally, islatravir inhibits reverse transcriptase via misincorporation into viral DNA, which occurs more efficiently than with deoxyadenosine triphosphate, resulting in mismatched bp that are difficult to extend.^{1,3–5}

In in-vitro studies,^{2,4} islatravir had more than ten-times greater potency than all other approved antiretroviral agents and has a high barrier to the development of resistance. Islatravir had robust antiviral activity in preclinical animal models of HIV-1 infection,^{6,7} including HIV infection in humanised mice and simian immunodeficiency virus infection in rhesus macaques. In a phase 1b clinical trial,⁸ islatravir showed robust antiviral activity with single doses as low as 0.5 mg causing a more than 1.0 log decline in HIV-1 RNA concentrations

over 7–10 days of follow-up; islatravir was well tolerated by participants, and these results supported its further clinical development.⁸

Doravirine is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) approved in more than 30 countries for the treatment of HIV-1. Doravirine is active in vitro against both wild-type HIV-1 and most common NNRTI-resistant variants (reverse transcriptase Lys103Asn, Tyr181Cys, Gly190Ala, Lys103Asn/Tyr181Cys, and Glu138Lys) at concentrations achieved with 100 mg once-daily dosing.⁹ The in-vitro resistance profile of doravirine is unique among NNRTIs, with lower half-maximal inhibitory concentration values against NNRTI-resistant variants compared with other NNRTIs.^{9,10} Additionally, doravirine has a low potential for drug–drug interactions, including with acid-reducing agents, statins, and metformin.¹¹ In phase 2 and 3 studies,^{12–15} doravirine has shown virological efficacy and a favourable safety profile. Compared with efavirenz and ritonavir-boosted darunavir, doravirine has a superior lipid profile.^{12,14} Doravirine also has a superior neuropsychiatric profile compared with efavirenz.¹⁴ The potent antiviral activity and complimentary in-vitro resistance profile of doravirine and islatravir create the potential for an efficacious two-drug regimen that would have a high barrier to resistance and a favourable safety profile. In this study, we aimed to assess the efficacy and safety of antiretroviral regimens containing islatravir and doravirine.

Methods

Study design and participants

We did a randomised, double-blind, active-controlled, dose-ranging phase 2b trial at 24 clinics, research medical centres, or hospitals in four countries (Chile, France,

the UK, and the USA) to evaluate the antiretroviral activity, tolerability, and safety of different doses of islatravir administered with doravirine compared with doravirine plus lamivudine plus tenofovir disoproxil fumarate (TDF) in antiretroviral treatment-naïve adults (≥ 18 years) with HIV-1 infection.

Men and women with no previous antiretroviral therapy and with plasma HIV-1 RNA concentrations of at least 1000 copies per mL, CD4 T-cell counts of at least 200 cells per mL, and a calculated creatinine clearance of at least 50 mL/min (all within 60 days before study treatment) were eligible for inclusion. Participants were required to have no known or documented virological resistance to any approved HIV-1 reverse transcriptase inhibitors, protease inhibitors, integrase strand transfer inhibitors, or to any study drug. Participants were also required to be considered clinically stable by the investigator, and to have no signs or symptoms of acute infection, at the time of entry into the study (ie, clinical status and all chronic medications should be unchanged for ≥ 2 weeks before the start of treatment in this study). Additionally, people with current (ie, active) diagnosis of acute hepatitis of any cause were excluded, as were those with an active hepatitis C virus (HCV) co-infection (defined as detectable HCV RNA) or hepatitis B virus (HBV) co-infection (defined as HBsAg positive; completed by the central laboratory). However, participants with previous or inactive HCV infection (defined as undetectable HCV RNA) or past HBV infection or vaccination (defined as HBsAg negative and positive for antibodies against HBsAg) were eligible for inclusion. Previous vaccination for HBV was not required for inclusion (appendix pp 72–75).

The trial was done in accordance with the principles of Good Clinical Practice and was approved by institutional review boards at each study site and by the appropriate regulatory agencies (Merck ensured all ethics approvals were met at individual sites). All participants provided written informed consent before enrolment. This trial is ongoing, but closed to enrolment of new participants.

Randomisation and masking

The trial was done in four parts. In part 1, participants were randomly assigned (1:1:1:1) with a block size of four via an interactive voice and web response system to receive oral treatment with either islatravir (0.25 mg, 0.75 mg, or 2.25 mg) in combination with doravirine (100 mg) and lamivudine (300 mg) or to the fixed-dose combination of doravirine (100 mg) plus lamivudine (300 mg) plus TDF (300 mg) and matching placebo daily for at least 24 weeks (appendix p 1). The participants, investigators, and sponsor personnel or delegates who were involved in the study treatment administration or clinical evaluation of the participants were unaware of the group assignments. During the double-blind portion of the trial, all active drug treatments were packaged identically, relative to their matching placebos. Treatment groups were stratified according to screening HIV-1 RNA

concentration ($\leq 100\,000$ copies per mL or $>100\,000$ copies per mL). Patients who achieved virological suppression (HIV-1 RNA concentration <50 copies per mL) and who had not met the protocol-defined virological failure criteria (PDVF) between weeks 24 and 48 of treatment on the initially assigned three-drug regimen progressed to part 2. Participants who met the criteria for PDVF were discontinued from study treatment. In part 2, participants in the islatravir groups received a two-drug regimen consisting of the initially assigned dose of islatravir in combination with 100 mg of doravirine, whereas participants in the doravirine plus lamivudine plus TDF group continued with the same initial regimen (appendix p 1). The doses of islatravir remained masked to study participants and investigators, and doravirine and doravirine plus lamivudine plus TDF were provided as open-label treatments. Dose selection for islatravir was planned to occur after all participants had received 48 weeks of study drug. Once the dose of islatravir was selected, participants transitioned to an open-label maintenance phase of the trial to week 144 (part 3). At week 144, all participants will switch to the fixed-dose combination of the selected dose of islatravir and doravirine (100 mg) as open-label treatment until the end of the trial at week 192 (part 4).

Procedures

Plasma HIV-1 RNA concentrations were measured at all study visits (appendix pp 44–51) by the central laboratory (Covance Central Laboratory Services, Indianapolis, IN, USA) using the Abbott RealTime PCR assay (Abbott Park, IL, USA) with a lower limit of detection of 40 copies per mL. CD4 T-cell counts (absolute and percentage) were measured by the central laboratory every 4 weeks during part 1 of the trial and every 12 weeks during part 2 of the trial. PDVF was defined as viral rebound if an HIV-1 RNA concentration of at least 50 copies per mL was confirmed (two consecutive measures ≥ 1 week apart) after an initial response with an HIV-1 RNA concentration lower than 50 copies per mL at any time during the study, or if confirmed (two consecutive measures ≥ 1 week apart) HIV-1 RNA concentration greater than 1 log increase from the HIV-1 RNA nadir after a greater than 1 log decrease in HIV-1 RNA concentration from baseline occurred at any time during the study. PDVF non-response was defined as a confirmed (two consecutive measures ≥ 1 week apart) HIV-1 RNA concentration of at least 200 copies per mL at any time from week 24 until week 48 or a confirmed (two consecutive measures ≥ 1 week apart) HIV-1 RNA concentration of at least 50 copies per mL at week 48. Initial viraemia measurement for PDVF required an additional confirmatory measurement of HIV-1 RNA taken at least 7–14 days after initial measurement. Viral resistance testing was done for participants who discontinued owing to PDVF or discontinued for any other reason and had HIV-1 RNA concentrations of more than 400 copies per mL.

See Online for appendix

Safety was monitored by adverse event reporting, treatment in emergent laboratory abnormalities, and physical examinations (weeks 4, 12, 24, and 48 as well as the early discontinuation visit and at the end of the follow-up period). Adverse events were assessed by the investigator for intensity (mild, moderate, or severe) and relationship to study treatment. Laboratory values were graded in severity based on Division of Acquired Immunodeficiency Syndrome (DAIDS) criteria.¹⁶

Outcomes

The primary efficacy endpoints for this trial were the proportions of participants achieving HIV-1 RNA concentrations lower than 50 copies per mL at week 24 and at week 48 (using the US Food and Drug Administration [FDA] snapshot approach). Secondary efficacy endpoints were the proportion of participants achieving HIV-1 RNA concentrations lower than 50 copies per mL 24 weeks after switching to the two-drug regimen (US FDA snapshot approach), the immunological response (change from baseline in CD4 T-cell counts), and virological response by prespecified subgroups (age, sex assigned at birth, race, region, baseline HIV-1 RNA concentration, and baseline CD4 T-cell count). The primary safety

endpoints were the number of participants experiencing adverse events and the number of participants discontinuing owing to adverse events. Additional prespecified safety endpoints were the number of participants with drug-related or serious adverse events, and the number of treatment-emergent laboratory abnormalities.

Statistical analysis

We aimed to enrol a total of approximately 120 participants (30 per treatment group). All randomly assigned participants who received at least one dose of any study drug were included in the efficacy and safety analyses. With the selected sample size, the maximum observed difference in the primary endpoint that can be ruled out between any islatravir treatment group and the doravirine plus lamivudine plus TDF group with 95% confidence and 80% power is 33.0%. The threshold for significance was 5%.

The US FDA snapshot approach, which applies a virology first approach and only classifies people with observed HIV-1 RNA concentrations lower than 50 copies per mL within the specified analysis window for the timepoint as a treatment success, was used for the analysis of suppression of HIV-1.¹⁷ For the primary endpoints,

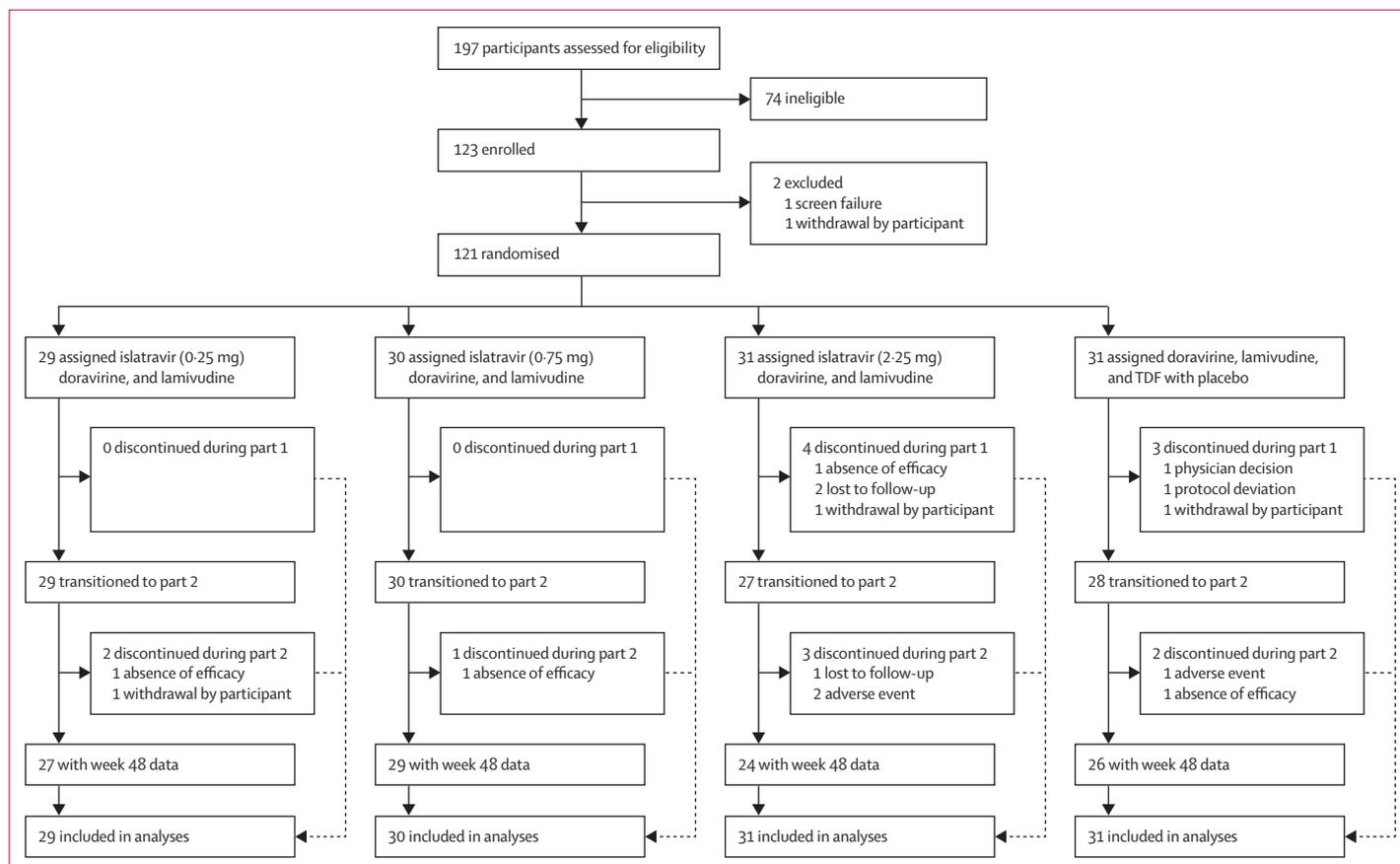


Figure 1: Trial profile

TDF=tenofovir disoproxil fumarate.

	Islatravir 0.25 mg group (n=29)	Islatravir 0.75 mg group (n=30)	Islatravir 2.25 mg group (n=31)	Islatravir groups combined (n=90)	Doravirine plus lamivudine plus TDF group (n=31)
Sex					
Male	29 (100%)	27 (90%)	28 (90%)	84 (93%)	28 (90%)
Female	0	3 (10%)	3 (10%)	6 (7%)	3 (10%)
Age, years					
	27.0 (25–34)	28.0 (23–36)	29.0 (25–37)	28.5 (25–36)	27.0 (23–33)
Race					
Black or African American	5 (17%)	6 (20%)	8 (26%)	19 (21%)	5 (16%)
White	23 (79%)	24 (80%)	21 (68%)	68 (76%)	24 (77%)
Other*	1 (3%)	0	2 (6%)	3 (3%)	2 (6%)
Region					
France or UK	6 (21%)	6 (20%)	9 (29%)	21 (23%)	9 (29%)
Chile	10 (34%)	11 (37%)	8 (26%)	29 (32%)	11 (35%)
USA	13 (45%)	13 (43%)	14 (45%)	40 (44%)	11 (35%)
Baseline CD4 T-cell count (cells per μL)					
	415 (331–546)	536 (416–647)	416 (343–543)	446 (353–605)	473 (392–616)
<350	10 (34%)	4 (13%)	8 (26%)	22 (24%)	5 (16%)
\geq 350	19 (66%)	26 (87%)	23 (74%)	68 (76%)	26 (84%)
Baseline plasma HIV-1 RNA concentration (log₁₀ copies per mL)					
	4.6 (4.1–4.9)	4.5 (4.1–4.9)	4.7 (4.3–5.1)	4.6 (4.1–5.0)	4.2 (3.9–4.9)
\leq 100 000	22 (76%)	24 (80%)	22 (71%)	68 (76%)	26 (84%)
>100 000	7 (24%)	6 (20%)	9 (29%)	22 (24%)	5 (16%)

Data are number (%) or median (IQR). Some percentages do not sum to 100 because of rounding. TDF=tenofovir disoproxil fumarate. *Asian, multiple, or unknown race.

Table 1: Demographics and baseline characteristics

we used the stratum-adjusted Mantel-Haenszel method to calculate the treatment difference and associated 95% CIs, with the differences weighted by the harmonic mean of the sample size per treatment for each stratum.¹⁸ For analysis of the primary efficacy endpoint and for the change from baseline in CD4 T-cell count and subgroup efficacy analyses, we used the observed failure (OF) approach, which excludes participants with any reasons other than absence of efficacy (assumed as treatment failures) for missing data. For these endpoints, we calculated Wald-type 95% CIs using the stratum-adjusted Mantel-Haenszel method. No multiplicity adjustment was used. We also did a post-hoc analysis of pooled islatravir groups for both efficacy and safety endpoints.

Analyses were done in SAS (version 9.4). This trial is registered with ClinicalTrials.gov, NCT03272347.

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Participant screening began on Nov 27, 2017 (initiation date), and the last participant was screened and enrolled on April 20, 2018. The last participant's last study visit for

this database lock occurred on April 25, 2019. 121 participants were randomly assigned, received study drug, and were included in analyses (figure 1). Key demographic and baseline clinical characteristics were well balanced between all treatment groups (table 1). Mean age was 31 years (SD 10.9), 112 (93%) were male, and 92 (76%) were white. Median baseline HIV-1 RNA concentration was 39 808 copies per mL (IQR 12 949–95 876), 27 participants (22%) had a baseline HIV-1 RNA concentration of more than 100 000 copies per mL, and seven (6%) had a baseline HIV-1 RNA concentration greater than 500 000 copies per mL. Median baseline HIV-1 RNA concentration was numerically higher in the islatravir groups than in the doravirine plus lamivudine plus TDF group (table 1). Median CD4 T-cell count was 456 cells per μ L (IQR 369–605). In part 1 of the trial, four (13%) of 31 participants in the 2.25 mg islatravir group and three (10%) of 31 in the doravirine plus lamivudine plus TDF group discontinued (figure 1). All participants in the islatravir 0.25 mg and 0.75 mg groups and 27 of 31 in the 2.25 mg group achieved HIV-1 RNA concentrations lower than 50 copies per mL and stopped taking lamivudine and transitioned to part 2 of the trial from week 24 (appendix p 2). During part 2 of the trial, two (7%) of 29 participants in the 0.25 mg islatravir group, one (3%) of 30 in the 0.75 mg group, three (10%) of 31 in the 2.25 mg group, and two (6%) of 31 in the doravirine plus lamivudine plus TDF group discontinued (figure 1). For the cumulative 48-week period, two (7%) of 29 participants in the 0.25 mg islatravir group, one (3%) of 30 in the 0.75 mg group, seven (23%) of 31 in the 2.25 mg group, and five (16%) of 31 in the doravirine plus lamivudine plus TDF group discontinued (figure 1). By week 48, the most common reasons for discontinuation were absence of efficacy (one participant in each treatment group), discontinuation owing to adverse events (two participants in the islatravir 2.25 mg group and one in the doravirine plus lamivudine plus TDF group), lost to follow-up (three participants in the islatravir 2.25 mg group), and patient withdrawals (one participant in the islatravir 0.25 mg group, one participant in the islatravir 2.25 mg group, and one participant in the doravirine plus lamivudine plus TDF group). More participants in the 2.25 mg islatravir group were lost to follow-up or withdrew than in the other groups (figure 1).

At week 24, 26 (90%) of 29 participants in the 0.25 mg islatravir group, 30 (100%) of 30 in the 0.75 mg islatravir group, and 27 (87%) of 31 in the 2.25 mg islatravir group achieved HIV-1 RNA concentrations lower than 50 copies per mL compared with 27 (87%) of 31 in the doravirine plus lamivudine plus TDF group (difference 2.8%, 95% CI –14.9 to 20.4, for the 0.25 mg islatravir group; 12.9%, –1.6 to 27.5, for the 0.75 mg islatravir group; and 0.3%, –17.9 to 18.5, for the 2.25 mg islatravir group; figure 2A). At week 48, these data were 26 (90%) of 29 in the 0.25 mg islatravir group, 27 (90%) of 30 in the 0.75 mg islatravir group, and 24 (77%) of 31 in the 2.25 mg islatravir group compared with 26 (84%)

of 31 in the doravirine plus lamivudine plus TDF group (difference 6.1%, 95% CI -12.4 to 24.4, for the 0.25 mg islatravir group; 6.2%, -12.2 to 24.6, for the 0.75 mg islatravir group; and -6.1%, -27.1 to 14.8, for the 2.75 mg islatravir group; figure 2B; table 2). 25 (89%) of 28 participants in the 0.25 mg, 27 (90%) of 30 in the 0.75 mg, and 24 (89%) of 27 in the 2.25 mg islatravir dose groups were on the two-drug regimen 24 weeks after entering part 2 of the trial and maintained HIV-1 RNA concentrations lower than 50 copies per mL; these data were similar to that for the doravirine plus lamivudine plus TDF group (27 [96%] of 28; figure 2C). At week 48, virological response rates were similar between treatment groups across the prespecified subgroups (age, sex assigned at birth, race, region, baseline HIV-1 RNA concentration, and baseline CD4 T-cell count; OF approach; appendix pp 3, 4). At week 48, four (100%) of four participants in the 0.25 mg, zero of one in the 0.75 mg, and one (100%) of one in the 2.25 mg islatravir dose groups (five [83%] of six for the islatravir groups combined) and one (100%) of one participant in the doravirine plus lamivudine plus TDF group had HIV-1 RNA concentrations lower than 50 copies per mL with baseline HIV-1 RNA concentrations greater than 500 000 copies per mL. The immunological response as measured by mean change in CD4 T-cell count from baseline to week 48 was similar for all groups (appendix p 5). Up to week 24, no participants met the criteria for PDVF. At week 48, the proportions of participants who met the criteria for PDVF were low and similar between groups (table 3). Six participants discontinued owing to PDVF up to week 48: two rebounders in the 0.25 mg islatravir group, two rebounders in the 0.75 mg islatravir group, one non-responder in the 2.25 mg islatravir group, and one rebounder in the doravirine plus lamivudine plus TDF group (table 3). All HIV-1 RNA concentrations at the confirmatory visit were lower than 80 copies per mL (appendix p 6). Four of the six participants with PDVF had a baseline HIV-1 RNA concentration of more than 100 000 copies per mL. Four of the six participants with PDVF had an additional HIV-1 RNA concentration of less than 50 copies per mL before switching to a new regimen in the follow-up period. During the follow-up period, three of six participants achieved HIV-1 RNA concentrations of less than 50 copies per mL on the new regimen (appendix p 6). None of the participants who discontinued with PDVF met the threshold for resistance testing (HIV-1 RNA concentrations of 400 copies per mL or higher). Four participants who did not meet the criteria for PDVF (three in the 2.25 mg islatravir group and one in the doravirine plus lamivudine plus TDF group) had HIV-1 RNA concentrations of at least 50 copies per mL under the US FDA snapshot approach owing to early discontinuation.

No deaths were reported in the study up to week 48. Overall rates of drug-related adverse events, and dis-

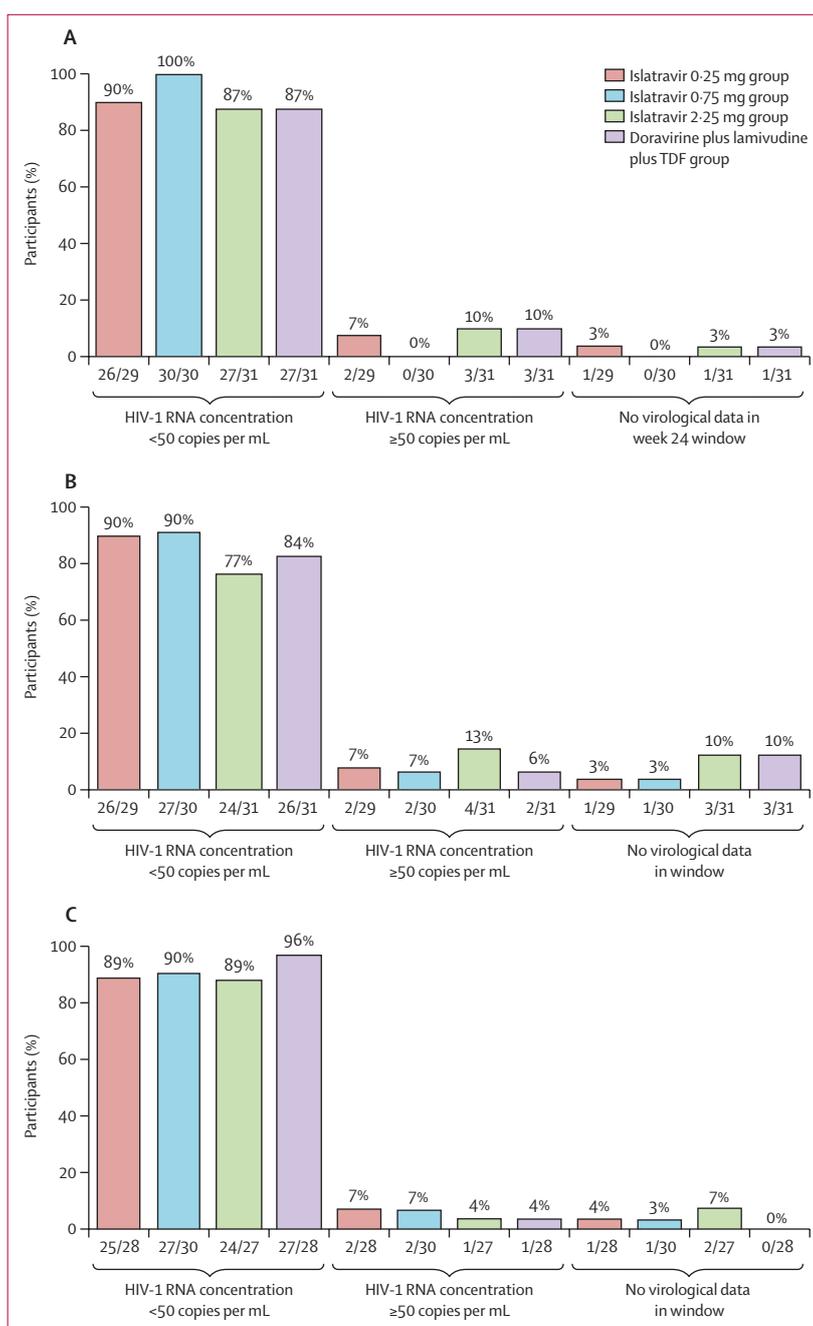


Figure 2: Virological outcomes

Virological outcomes at week 24 (A), at week 48 (B), and 24 weeks after entering part 2 (C). All outcomes are as per the US Food and Drug Administration snapshot approach. TDF=tenofovir disoproxil fumarate.

continuations owing to adverse events up to week 48 were low (table 4). No serious drug-related adverse events were reported by islatravir participants. A higher proportion of participants in the doravirine plus lamivudine plus TDF group reported drug-related adverse events (six [19%] of 31) compared with any of the islatravir groups (seven [8%] of 90 overall; table 4). We report the adverse events with incidences greater than

	Islatravir 0·25 mg group (n=29)	Islatravir 0·75 mg group (n=30)	Islatravir 2·25 mg group (n=31)	Islatravir groups combined (n=90)	Doravirine plus lamivudine plus TDF group (n=31)
Outcome (US FDA snapshot approach)					
HIV-1 RNA concentration <50 copies per mL	26 (90%)	27 (90%)	24 (77%)	77 (86%)	26 (84%)
HIV-1 RNA concentration ≥50 copies per mL	2 (7%)	2 (7%)	4 (13%)	8 (9%)	2 (6%)
No virological data at week 48	1 (3%)	1 (3%)	3 (10%)	5 (6%)	3 (10%)
Response (HIV-1 RNA concentration <50 copies per mL) by baseline HIV-1 RNA concentration (copies per mL)					
≤100 000	20/22 (91%)	22/24 (92%)	18/22 (82%)	60/68 (88%)	23/26 (88%)
>100 000	6/7 (86%)	5/6 (83%)	6/9 (67%)	17/22 (77%)	3/5 (60%)
Reasons for no virological data					
Discontinued owing to death or adverse event*	0 (0%)	0 (0%)	2 (6%)	2 (2%)	0 (0%)
Discontinued for other reasons†	1 (3%)	0 (0%)	1 (3%)	2 (2%)	2 (6%)
On treatment, but missing data	0 (0%)	1 (3%)	0 (0%)	1 (1%)	1 (3%)
Outcome (observed failure approach)‡					
HIV-1 RNA concentration <50 copies per mL	26/28 (93%)	27/29 (93%)	24/28 (86%)	77/85 (91%)	26/28 (93%)

Data are number (%) or n/N (%). The treatment groups are the original group designations given at randomisation. Some percentages do not sum to 100 because of rounding. FDA=Food and Drug Administration. TDF=tenofovir disoproxil fumarate. *At any timepoint from day 1 to week 48 if this resulted in no virological data on treatment during that time. †Lost to follow-up, physician decision, protocol deviation, or withdrawal by participant. ‡Missing data were dropped from the analysis if the last on-treatment result was a success.

Table 2: Virological outcomes at week 48

	Islatravir 0·25 mg group (n=29)*	Islatravir 0·75 mg group (n=30)*	Islatravir 2·25 mg group (n=31)*	Islatravir groups combined (n=90)*	Doravirine plus lamivudine plus TDF group (n=31)
Non-responder	0	0	1 (3%)	1 (1%)	0 (0%)
Rebounder with HIV-1 RNA concentration >50 copies per mL	2 (7%)	2 (7%)	0	4 (4%)	1 (3%)
Rebounder with HIV-1 RNA concentration >200 copies per mL	0	0	0	0	0

Data are number (%). TDF=tenofovir disoproxil fumarate. *Participants initially received islatravir plus doravirine plus lamivudine and switched to islatravir plus doravirine during weeks 24–48.

Table 3: Protocol-defined virological failure at week 48

10% in one or more treatment groups in table 5 and all adverse events in the appendix (pp 8–16). Of the most frequently reported adverse events, diarrhoea was more frequently reported in the doravirine plus lamivudine plus TDF group than in the combined islatravir group, whereas headache was more common in the combined islatravir group compared with the doravirine plus lamivudine plus TDF group (table 5). The frequency of DAIDS grade 3 or 4 laboratory abnormalities was low and similar between treatment groups (appendix p 7). No islatravir dose-dependent difference was observed in

reported adverse events or grade 3 or 4 laboratory abnormalities.

Three (2%) of 121 participants discontinued from the trial owing to an adverse event. Two participants in the 2·25 mg group discontinued owing to an adverse event. The first participant reported an adverse event that was listed as diarrhoea, nausea, or vomiting, which was classified as of moderate severity, with onset at day 200 and lasting for approximately 2 weeks. The second participant discontinued owing to HBV reactivation with onset at day 201. This participant was previously vaccinated against HBV. At screening, the central laboratory reported that this participant had a qualitative positive result for anti-hepatitis B antibody and a negative result for HBsAg. Local laboratory testing showed that this participant was positive for anti-hepatitis B antibody during the time period the participant was monitored for safety. After the participant discontinued taking lamivudine upon entry to part 2 of the trial, the central laboratory reported a positive HBsAg result in the absence of elevations in aminotransferases. This participant was retested for HBsAg and qualitative anti-HBsAg via the central laboratory and was confirmed to be positive for both. Previous HBsAg results were negative. HBV DNA was 3·43 log IU/mL as assessed by the local laboratory. This participant was listed as having an adverse event of HBV reactivation and discontinued the trial. One participant in the doravirine plus lamivudine plus TDF group discontinued owing to a serious drug-related adverse event of worsening of congenital long QT syndrome. This participant was diagnosed with congenital long QT syndrome more than 32 years before entering this study. On day 335, this participant experienced an asymptomatic worsening of congenital long QT (classified as severe) with a reported QTc elongation of 534 ms. The participant stopped taking study medication on day 335 and did not receive additional treatment for this adverse event. On day 342, the participant recovered from the adverse event and QTc returned to baseline.

Weight gain was similar between treatment groups and occurred primarily during the first 24 weeks. At week 24, a greater than 5% increase in weight occurred in 11 (38%) of 29 participants in the islatravir 0·25 mg group, 12 (40%) of 30 in the islatravir 0·75 mg group, seven (23%) of 31 in the islatravir 2·25 mg group, and five (16%) of 31 in the doravirine plus lamivudine plus TDF group. At week 48, a greater than 5% increase in weight occurred in 15 (52%) of 29 participants in the islatravir 0·25 mg group, 11 (37%) of 30 in the islatravir 0·75 mg group, eight (26%) of 31 in the islatravir 2·25 mg group, and seven (23%) of 31 in the doravirine plus lamivudine plus TDF group.

Dose selection for islatravir occurred between weeks 60 and 72. The dose selected for use in parts 3 and 4 of the trial was 0·75 mg.

Discussion

This phase 2b trial of islatravir in combination with doravirine is, to our knowledge, the first double-blind,

randomised, clinical trial to show that an islatravir-based antiviral regimen has high clinical efficacy. Almost all participants who initiated antiviral therapy on islatravir and doravirine in combination with lamivudine achieved HIV-1 RNA concentrations lower than 50 copies per mL within the first 24 weeks of treatment, which was similar to that observed with doravirine plus lamivudine plus TDF. Up to week 48, a similar proportion of participants across all treatment groups maintained viral suppression. Although the 2.25 mg group had a numerically lower proportion of participants with HIV-1 RNA concentrations lower than 50 copies per mL at week 48 (77%), this was not statistically significantly different from the other islatravir groups. One explanation for this lower percentage is the disproportionate number of discontinuations (three of which were owing to loss to follow-up) in this group compared with the other groups. When the OF approach was applied to account for missing data, the proportion of participants with HIV-1 RNA concentrations lower than 50 copies per mL at week 48 was 86%, which is numerically closer to the rates in the other islatravir groups. Since this is a small study, a few discontinuations have a large effect on the efficacy outcome under the US FDA snapshot approach. Furthermore, the efficacy of the two-drug regimen of doravirine in combination with islatravir was comparable with doravirine plus lamivudine plus TDF, with a similar number of participants maintaining viral suppression with HIV-1 RNA concentrations lower than 50 copies per mL for 24 weeks after removal of lamivudine regardless of islatravir dose. Efficacy was consistent across the examined baseline and demographic subgroups.

We defined PDVF conservatively using an HIV-1 RNA concentration of at least 50 copies per mL as the threshold for failure. This conservative threshold was recommended by the protocol development team at Merck when designing the trial since both islatravir and doravirine were classified as investigational compounds with limited clinical data at that time (August, 2017). Rates of PDVF were low throughout the first 48 weeks of the trial; only six participants discontinued owing to PDVF, five of whom were randomly assigned to one of the three islatravir groups and one to the doravirine plus lamivudine plus TDF group. HIV-1 RNA concentrations at the viral confirmation visit were below 80 copies per mL for all participants with PDVF, which is below the clinically significant concentration of 200 copies per mL, and were most likely viral blips. Furthermore, four of the six participants with PDVF had an additional HIV-1 RNA concentration of less than 50 copies per mL before switching to a new regimen in the follow-up period. Based on these results, in future clinical trials evaluating doravirine plus islatravir we will use 200 copies per mL as the threshold for PDVF and so participants with low-level viraemia will not be required to discontinue study therapy and further efficacy outcomes will be able to be assessed for these participants.

	Islatravir 0.25 mg group (n=29)*	Islatravir 0.75 mg group (n=30)*	Islatravir 2.25 mg group (n=31)*	Islatravir groups combined (n=90)*	Doravirine plus lamivudine plus TDF group (n=31)
≥1 adverse event	21 (72%)	26 (87%)	19 (61%)	66 (73%)	24 (77%)
Drug-related adverse events	0	3 (10%)	4 (13%)	7 (8%)	6 (19%)
Serious adverse events	1 (3%)	2 (7%)	0	3 (3%)	2 (6%)
Discontinued owing to adverse events	0	0	2 (6%)	2 (2%)	1 (3%)

Data are number of participants (%). TDF=tenofovir disoproxil fumarate. *Participants initially received islatravir plus doravirine plus lamivudine and switched to islatravir plus doravirine during weeks 24–48.

Table 4: Adverse event summary (weeks 0–48)

	Islatravir 0.25 mg group (n=29)*	Islatravir 0.75 mg group (n=30)*	Islatravir 2.25 mg group (n=31)*	Islatravir groups combined (n=90)*	Doravirine plus lamivudine plus TDF group (n=31)
Diarrhoea	0	4 (13%)	2 (6%)	6 (7%)	5 (16%)
Nausea	1 (3%)	4 (13%)	3 (10%)	8 (9%)	3 (10%)
Bronchitis	2 (7%)	4 (13%)	0	6 (7%)	4 (13%)
Nasopharyngitis	1 (3%)	4 (13%)	1 (3%)	6 (7%)	3 (10%)
Sinusitis	3 (10%)	0	0	3 (3%)	1 (3%)
Syphilis	2 (7%)	3 (10%)	2 (6%)	7 (8%)	4 (13%)
Vitamin D deficiency	0	4 (13%)	2 (6%)	6 (7%)	1 (3%)
Arthralgia	1 (3%)	2 (7%)	4 (13%)	7 (8%)	1 (3%)
Pain in extremity	3 (10%)	0	0	3 (3%)	0
Headache	4 (14%)	2 (7%)	4 (13%)	10 (11%)	2 (6%)

Data are number of participants (%). TDF=tenofovir disoproxil fumarate. *Participants initially received islatravir plus doravirine plus lamivudine and switched to islatravir plus doravirine during weeks 24–48.

Table 5: Most common adverse events with incidence greater than 10% in at least one treatment group (weeks 0–48)

Overall safety and tolerability profiles to week 48 were similar for both the islatravir-based regimens and the doravirine plus lamivudine plus TDF regimen. Islatravir in combination with doravirine was generally well tolerated by trial participants throughout the trial. Few drug-related adverse events were reported, and only two of the 90 participants receiving islatravir discontinued owing to an adverse event. A higher rate of drug-related adverse events was reported for doravirine plus lamivudine plus TDF participants than for any of the doses of islatravir. No islatravir dose-dependent difference in frequency of adverse events or grade 3 or 4 laboratory abnormalities were observed. The most commonly reported adverse event for participants taking islatravir was headache, whereas the most commonly reported adverse event for doravirine plus lamivudine plus TDF was diarrhoea. The primary difference in the regimens up to week 24 was the inclusion of TDF or islatravir and thus the differences observed in the type of adverse events and the higher rate of drug-related adverse events for doravirine plus lamivudine plus TDF participants could be attributed to the safety profile of TDF. Gastrointestinal adverse events have previously been reported frequently for regimens containing TDF.¹⁹

This study has several limitations and caveats. The trial evaluated the initial virological response for treatment-naïve adults with a regimen that consisted of islatravir and doravirine in combination with lamivudine, a regimen that is not in clinical development. The planned phase 3 trials will evaluate the safety and efficacy of the selected dose (0.75 mg) of islatravir in combination with doravirine. At the time the trial was designed (August, 2017), both islatravir and doravirine were classified as investigational compounds because doravirine had not yet been approved, and no two-drug antiretroviral regimen was approved for the initiation of treatment of HIV-1 infection. Therefore, initiation of all therapies with a two-drug regimen was mandated by regulatory agencies (US FDA and European Medicines Agency), with lamivudine added as a third drug to islatravir and doravirine, followed by simplification to a two-drug regimen of islatravir and doravirine once viral suppression was achieved after week 20. An ongoing clinical trial (NCT04233879) is assessing the efficacy of islatravir and doravirine as a two-drug regimen in treatment-naïve adults with HIV-1. Since this was a phase 2b trial, the number of participants was small, and the participants enrolled in the trial do not fully represent the worldwide population of people living with HIV. Most participants were young, male, and white. Although efficacy was consistent across the examined demographic subgroups, numbers for these groups were small and results will need to be confirmed in larger phase 3 studies. One strength of this trial is the inclusion of participants with high baseline HIV-1 RNA concentrations. Other trials²⁰ excluded participants with HIV-1 RNA concentrations greater than 500 000 copies per mL, which limits the ability to assess efficacy in this population. In this trial, 22% of participants had HIV-1 RNA concentrations greater than 100 000 copies per mL and 6% had HIV-1 RNA concentrations greater than 500 000 copies per mL, and our data suggest that virological efficacy was consistent for participants with high baseline HIV-1 RNA. Additional clinical studies are needed to confirm efficacy for these participants. Furthermore, a high percentage of participants with HIV-1 RNA concentrations greater than 500 000 copies per mL were in the 0.25 mg islatravir group (14%) compared with 3% each for the 0.75 mg and 2.25 mg islatravir groups, and despite having a larger percentage of participants with high HIV-1 RNA concentrations, efficacy was comparable with the other groups. Participants with baseline CD4 T-cell counts below 200 cells per μ L were excluded from the trial and thus we do not have data on the immunological outcomes for participants with impaired immune systems. Additionally, participants with HIV-1 with any documented resistance mutations to any antiretroviral drug were excluded from the study; thus, no data are provided on clinical efficacy for islatravir regimens in people with transmitted resistance. Furthermore, all participants who

discontinued the study had HIV-1 RNA concentrations below the threshold for resistance testing and so were not analysed for resistance mutations, thus we could not establish whether treatment-emergent drug resistance occurred. Finally, one patient had reactivation of HBV infection upon discontinuation of lamivudine, underlining the need to monitor HBV reactivation with the islatravir plus doravirine combination.

Overall, this phase 2b trial showed that islatravir regimens have high antiviral efficacy and a favourable safety profile and suggests that doravirine in combination with islatravir has the potential to be a potent two-drug regimen. These results support the initiation of a broad phase 3 development programme with a diverse patient population. The 0.75 mg dose of islatravir has been selected as the dose for phase 3 studies. The phase 3 development programme will include trials for treatment-naïve participants (NCT04233879), participants switching regimens (NCT04223778 and NCT04223791), and a trial for heavily treatment experienced participants who have multidrug resistance (NCT04233216).

Contributors

KE, MNR, CH, GJH, and PS conceived, designed, and planned the study. AAS, CB, CCA, ED, AG, KE, TC, CH, and GJH acquired data. SOK and AG assessed and verified the underlying data. J-MM, AAS, SOK, AG, TC, CH, GJH, and PS analysed data. J-MM, YY, CB, SOK, AG, KE, MNR, TC, CH, GJH, and PS interpreted results. AG, KE, TC, CH, and GJH drafted the manuscript. J-MM, YY, AAS, CB, CCA, ED, SOK, AG, MNR, TC, CH, GJH, and PS reviewed and revised 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

J-MM has received grants from Gilead, Merck, ViiV, and Sanofi. ED has received personal fees from Gilead Science and Janssen Therapeutics, outside the submitted work. SOK, AG, KE, MNR, TC, CH, GJH, and PS are employees of Merck, Sharp, & Dohme Corp, a subsidiary of Merck & Co., Inc. YY, AAS, CB, and CCA declare no competing interests.

Data sharing

The data sharing policy, including restrictions, of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., is available at EngageZone. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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