Safety and efficacy of switching to bictegravir–lenacapavir versus continuing bictegravir–emtricitabine–tenofovir alafenamide in virologically suppressed people with HIV-1 (ARTISTRY-2): a double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial

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Summary

Background There is a continued need to expand the repertoire of effective single-tablet regimens to address the diverse needs of people with HIV-1. We aimed to evaluate the safety and efficacy of switching to bictegravir–lenacapavir compared with continuing bictegravir–emtricitabine–tenofovir alafenamide in virologically suppressed people with HIV-1.

Methods This double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial was conducted in 100 hospitals and HIV clinics across Argentina, Australia, Canada, Dominican Republic, Germany, Italy, Japan, Mexico, Puerto Rico, South Korea, Spain, Taiwan, the UK, and the USA. Eligible participants were aged 18 years or older, receiving bictegravir–emtricitabine–tenofovir alafenamide (for ≥6 months), and virologically suppressed (HIV-1 RNA <50 copies per mL for ≥6 months). Participants were randomly assigned (2:1) using an interactive response system (stratified by geographical region) to switch to bictegravir–lenacapavir (75–50 mg) or continue bictegravir–emtricitabine–tenofovir alafenamide (50–200–25 mg) once a day as single-tablet regimens for 48 weeks. The primary endpoint was the proportion of participants with HIV-1 RNA of 50 copies per mL or higher at week 48 (as per the US Food and Drug Administration Snapshot algorithm) assessed in the full analysis set (defined as all randomly assigned participants who received any dose of the study drug), with a non-inferiority margin of 4%. This trial is registered with ClinicalTrials.gov, NCT06333808 (active, not recruiting).

Findings Between March 25 and Oct 30, 2024, 666 people with HIV-1 were assessed for eligibility, 89 were ineligible, and 577 were randomly assigned (384 to bictegravir–lenacapavir and 193 to continue bictegravir–emtricitabine–tenofovir alafenamide). 574 participants received at least one dose of the study drug (full analysis set). The median age was 49 years (IQR 39–58). 111 (19%) of 574 participants were female and 463 (81%) were male at birth. At baseline, the median duration of HIV-1 treatment was 12·0 years (6·5–18·7). At week 48, five (1·3%) of 383 participants in the bictegravir–lenacapavir group and two (1·0%) of 191 in the bictegravir–emtricitabine–tenofovir alafenamide group had HIV-1 RNA of 50 copies per mL or higher (percentage difference 0·3% [95·002% CI –1·9 to 2·4]), meeting the non-inferiority criteria. Drug-related adverse events occurred in 40 (10%) participants in the bictegravir–lenacapavir group versus 23 (12%) in the bictegravir–emtricitabine–tenofovir alafenamide group; and serious adverse events occurred in 27 (7%) versus 13 (7%), with none deemed related to treatment. One participant in the bictegravir–emtricitabine–tenofovir alafenamide group died due to coronary artery disease.

Interpretation Bictegravir–lenacapavir has the potential to be a novel single-tablet antiretroviral regimen option for virologically suppressed people with HIV-1.

Funding Gilead Sciences.

Introduction

Single-tablet regimens have transformed the HIV-1 treatment landscape, improving clinical outcomes, medication adherence, treatment satisfaction, and quality of life for people with HIV-1.[1,2] There is a continued need to expand the repertoire of safe and effective single-tablet regimens that can help to address the needs and preferences in this population throughout a lifetime of

Research in context

Evidence before this study

Two oral, single-tablet, two-drug antiretroviral regimens are approved for the treatment of people with HIV-1: dolutegravir–lamivudine and dolutegravir–rilpivirine. We searched PubMed for articles on non-inferiority clinical trials published between Jan 1, 2010, and March 27, 2026, using the search terms "([dolutegravir AND lamivudine] OR [dolutegravir AND rilpivirine] OR [bictegravir AND lenacapavir AND noninferiority])", without language restrictions. We identified 98 articles and of those, six articles reported primary analyses from five phase 3 non-inferiority trials in adults with HIV-1 who were virologically suppressed when switching to these regimens. Only primary publications were included, and phase 4 studies were excluded. The SALSA and TANGO trials showed that switching to dolutegravir–lamivudine was non-inferior to continuing a three-drug or four-drug regimen for maintaining virological suppression at week 48, with the TANGO trial showing durable efficacy until week 196. In the SWORD-1 and SWORD-2 trials, switching to dolutegravir–rilpivirine was non-inferior to continuing the current antiretroviral regimen in maintaining virological suppression at week 48, with virological suppression sustained at week 100. The ARTISTRY-1 trial showed non-inferiority in maintaining virological suppression of HIV-1 when switching to bictegravir–lenacapavir compared with continuing complex multitablet regimens over 48 weeks. There were no trials comparing a single-tablet regimen of bictegravir–lenacapavir with another coformulated single-tablet regimen for the treatment of people with HIV-1.

Added value of this study

To our knowledge, ARTISTRY-2 is the first double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial to compare the safety and efficacy of bictegravir–lenacapavir with the approved single-tablet regimen of bictegravir–emtricitabine–tenofovir alafenamide. In addition to ARTISTRY-1, this study is the second trial to assess the use of oral lenacapavir as part of an HIV-1 treatment regimen without concomitant administration of subcutaneous lenacapavir.

Implications of all the available evidence

This trial builds on the evidence from ARTISTRY-1 and shows that the single-tablet regimen of bictegravir–lenacapavir is a safe and effective treatment option for virologically suppressed people with HIV-1, including older individuals and those with multiple medical comorbidities. Long-term efficacy and safety outcomes of bictegravir–lenacapavir will be assessed during continued follow-up in the ongoing open-label phase of the ARTISTRY-1 and ARTISTRY-2 trials.

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See **Online** for appendix

taking antiretroviral therapy (ART).[3] A potential new regimen of coformulated bictegravir–lenacapavir combines bictegravir (an integrase strand-transfer inhibitor [INSTI] with a high barrier to resistance)[4] and lenacapavir (a first-in-class capsid inhibitor).[5,6] Bictegravir is widely used clinically as a component of the single-tablet regimen bictegravir–emtricitabine–tenofovir alafenamide, which is recommended by global guidelines as one of the preferred first-line standard of care antiretroviral therapies[7–9] with an established efficacy and safety profile.[10–14] Injectable long-acting lenacapavir has been approved as a subcutaneous injection administered every 6 months for HIV-1 pre-exposure prophylaxis[15–17] and HIV-1 treatment in combination with other antiretrovirals in people with multidrug-resistant HIV-1 for whom constructing a suppressive antiviral regimen is not otherwise possible.[18,19] Furthermore, in vitro studies showed that bictegravir plus lenacapavir had synergistic anti-HIV-1 activity with no antagonism and a robust resistance barrier.[20] Together, these findings prompted interest in evaluating a coformulation of bictegravir–lenacapavir as a possible new daily, oral single-tablet regimen for HIV-1 treatment.

The randomised, open-label ARTISTRY-1 trial compared switching to the once-a-day oral bictegravir–lenacapavir single-tablet regimen versus continuing complex baseline regimens in people with HIV-1 who required multiple daily tablets or a combination of parenteral and oral agents to maintain HIV-1 virological suppression.[21] Switching to bictegravir–lenacapavir was non-inferior to continuing complex regimens at maintaining high rates of virological suppression up to and including week 48 in a population that was predominantly older than 55 years and had a high prevalence of comorbidities, polypharmacy, and previous resistance.[21]

In this ARTISTRY-2 trial, we aimed to evaluate the safety and efficacy of switching to single-tablet bictegravir–lenacapavir compared with continuing the bictegravir–emtricitabine–tenofovir alafenamide single-tablet regimen over 48 weeks in people with HIV-1 who are virologically suppressed on bictegravir–emtricitabine–tenofovir alafenamide.

Methods

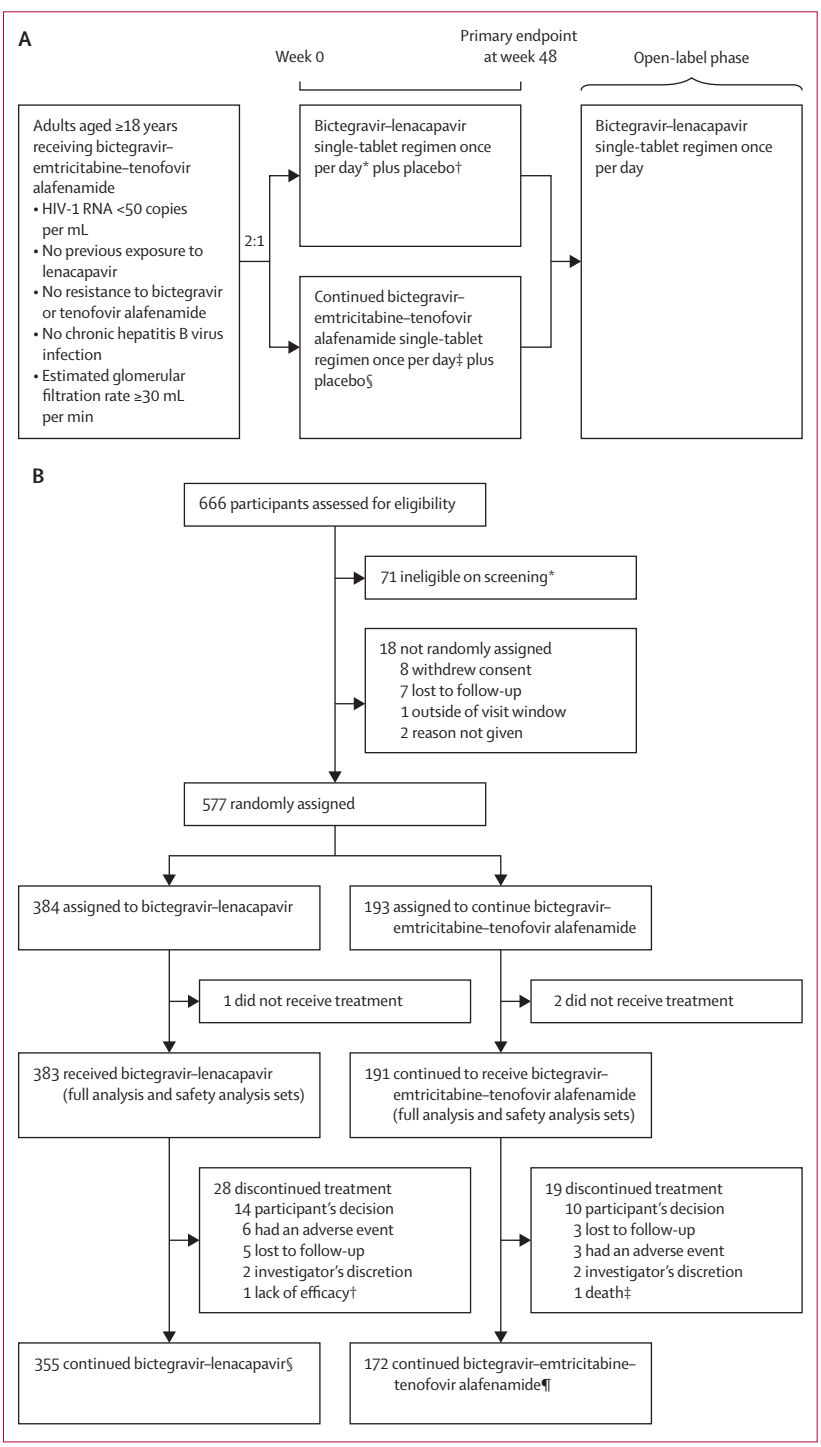
Study design

This double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial was conducted in 100 hospitals and HIV clinics across 14 countries and territories (Argentina, Australia, Canada, Dominican Republic, Germany, Italy, Japan, Mexico, Puerto Rico, South Korea, Spain, Taiwan, the UK, and the USA). Clinical investigators screened and recruited people with HIV-1 at hospitals and clinics. We conducted the study in accordance with the Declaration of Helsinki and an institutional review board or ethics committee from each study site approved the protocol (appendix pp 3–5). The protocol and statistical analysis plan are provided in the appendix (p 18). A

summary of key protocol amendments is also provided in the appendix (pp 6–7). This trial is registered with ClinicalTrials.gov, NCT06333808 (active, not recruiting).

Participants

Eligible participants were aged 18 years or older, currently receiving bictegravir–emtricitabine–tenofovir alafenamide for at least 6 months, virologically suppressed (HIV-1 RNA <50 copies per mL) for at least 6 months before screening, had no known or suspected resistance to bictegravir or tenofovir alafenamide, no previous exposure to lenacapavir, and an estimated glomerular filtration rate of 30 mL per min or higher (calculated using the Cockcroft–Gault formula) in accordance with prescribing information for bictegravir–emtricitabine–tenofovir alafenamide.[22] The key exclusion criteria were chronic hepatitis B virus (HBV) infection (a positive hepatitis B surface antigen or an isolated positive hepatitis B core antibody combined with a negative hepatitis B surface antibody), decompensated liver cirrhosis, and active tuberculosis infection. Full inclusion and exclusion criteria are listed in the appendix (pp 8–9). Participants in ARTISTRY-2 had similar demographic characteristics to those who participated in trials that evaluated the efficacy and safety of bictegravir–emtricitabine–tenofovir alafenamide.[10,12,13,23] All participants provided written informed consent. Participants self-reported data on sex at birth (male or female), gender (cisgender, transgender, non-binary, other, or not disclosed), race (Asian, Black, White, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other, or not permitted), and ethnicity (Hispanic or Latinx, not Hispanic or Latinx, or not permitted).



Randomisation and masking

We randomly assigned participants (2:1) to switch to bictegravir–lenacapavir or continue bictegravir–emtricitabine–tenofovir alafenamide (figure A). Randomisation was stratified by geographical region (Asia, Central and South America, Europe, North America, and Oceania; appendix p 9). We obtained the randomisation sequence using block number and treatment allocation provided at each trial site by an interactive response system. Participants and personnel directly involved in the study conduct were masked to treatment assignment, except for the unmasked pharmacist at each site. We used matching placebo tablets identical in size, shape, colour, and appearance to the study treatments.

Procedures

Participants received bictegravir–lenacapavir (75–50 mg) or bictegravir–emtricitabine–tenofovir alafenamide

Figure: **Study design and trial profile**
(A) Study design. *Participants received an oral loading dose of lenacapavir 600 mg on days 1 and 2 of treatment. †Placebo to match bictegravir–emtricitabine–tenofovir alafenamide. ‡Placebo to match lenacapavir on days 1 and 2 of treatment. §Placebo to match bictegravir–lenacapavir. (B) Trial profile. *Reasons for ineligibility on screening are shown in the appendix (p 12). †An investigator-chosen reason for study discontinuation. ‡Death due to coronary artery disease. §Study ongoing for 359 participants in the bictegravir–lenacapavir group and 24 discontinued the study (due to consent withdrawal [n=13], an adverse event [n=5], loss to follow-up [n=5], or investigator's discretion [n=1]). ¶Study ongoing for 173 participants in the bictegravir–emtricitabine–tenofovir alafenamide group and 18 discontinued the study (due to consent withdrawal [n=9], an adverse event [n=3], loss to follow-up [n=3], investigator's discretion [n=2], or death [n=1]).

(50–200–25 mg), as per previous trials,[10,12,13,23] and corresponding placebo orally once a day as single-tablet regimens, without regard to food, for 48 weeks (each participant received two tablets a day [one placebo and one active drug] during the randomisation phase). Participants in the bictegravir–lenacapavir group received a 2-day oral loading dose of lenacapavir 600 mg to expeditiously attain therapeutic concentrations and those in the bictegravir–emtricitabine–tenofovir alafenamide group received matched placebo tablets. Study visits occurred on day 1; day 2 (virtual or in person); weeks 4, 12, 24, 36, and 48; then every 12 weeks until the end-of-blinded-treatment visit, which was scheduled after all participants completed week 48 and after the primary endpoint analysis.

We collected blood samples for laboratory analyses to assess HIV-1 RNA concentrations, CD4 cell counts, safety, and laboratory adverse events in participants who attended all on-treatment visits until week 48. Virological failure was defined as confirmed virological rebound (HIV-1 RNA ≥50 copies per mL at any visit after day 1, if confirmed at the following visit) or HIV-1 RNA of 50 copies per mL or higher at the last on-treatment study visit (including in participants with early study drug discontinuation or loss to follow-up before week 48). At any visit after screening, if the HIV-1 RNA viral load was 50–200 copies per mL, we conducted a reflex HIV-1 RNA repeat test on a stored plasma sample. If the repeat measurement was lower than 50 copies per mL, participants resumed scheduled study visits, and if the repeat measurement was 50 copies per mL or higher, we asked participants to return to the clinic for a scheduled or unscheduled blood draw within 2–4 weeks for confirmation of virological rebound.

We performed resistance testing for participants who had virological failure and HIV-1 RNA of 200 copies per mL or higher, which included prespecified HIV-1 genotypic and phenotypic analyses of the viral capsid, protease, reverse transcriptase, and integrase.

Outcomes

The primary endpoint was the proportion of participants with HIV-1 RNA of 50 copies per mL or higher at week 48 as determined by the US Food and Drug Administration (FDA) Snapshot algorithm, assessed in the full analysis set (defined as all randomly assigned participants who received any dose of the study drug).[24]

Secondary endpoints were the proportion of participants with HIV-1 RNA of lower than 50 copies per mL (US FDA Snapshot algorithm),[24] change from baseline in CD4 cell count, and the proportion of participants with adverse events, all assessed at week 48. We coded clinical and laboratory adverse events according to the Medical Dictionary for Regulatory Activities (version 28.0) and graded the severity according to the Division of AIDS Toxicity Grading Scale (version 2.1). We also analysed virological outcomes at week 48 using prespecified missing=excluded and missing=failure approaches (appendix p 9). These outcomes were similar to those in previous trials that evaluated the efficacy and safety of bictegravir–emtricitabine–tenofovir alafenamide.[10,12,13,23]

Statistical analysis

We performed the primary analysis after all enrolled participants completed week-48 visits or discontinued study treatment. Efficacy analysis was done on the full analysis set. For the primary endpoint, we estimated that a sample size of 546 participants would provide 90% power to detect non-inferiority, assuming that 2% of participants in both treatment groups would have HIV-1 RNA of 50 copies per mL or higher at week 48. The non-inferiority margin was set at 4% (based on US FDA requirements) for a 0·025 significance level of a one-sided test. The data monitoring committee performed two planned interim analyses before the primary analysis, applying an α penalty of 0·00001 for each analysis to account for multiplicity. The significance level for the two-sided non-inferiority test at week 48 was 0·04998 (corresponding to a 95·002% CI).

A non-inferiority study design was used because effective and well tolerated treatments for people with HIV-1 are available. Bictegravir–lenacapavir would be deemed non-inferior to bictegravir–emtricitabine–tenofovir alafenamide if the upper bound of the two-sided 95·002% CI of the treatment difference in the primary endpoint was less than 4%. This margin was prespecified based on previous studies of bictegravir–emtricitabine–tenofovir alafenamide, the number of participants in ARTISTRY-2, and the randomisation ratio.[10,12] We constructed the two-sided 95·002% CIs based on stratum-adjusted Mantel–Haenszel method, adjusted by geographical region (USA *vs* non-USA). We used the same method to analyse a secondary endpoint (proportion of participants with HIV-1 RNA <50 copies per mL at week 48). We performed prespecified analyses of the proportion of participants with HIV-1 RNA of 50 copies per mL or higher at week 48 in subgroups by age (<55 years and ≥55 years), sex at birth (male and female), race (White and non-White), ethnicity (Hispanic or Latinx and non-Hispanic or Latinx), and geographical region (USA *vs* non-USA). The difference in percentages between treatment groups and 95% CIs were calculated based on an unconditional exact method using two inverted one-sided tests. We summarised CD4 cell counts using observed on-treatment data for participants in the full analysis set. We estimated the difference in least-squares mean change from baseline in CD4 cell count between treatment groups using an ANCOVA model that included baseline CD4 cell count and geographical region as covariates and study treatment as a fixed effect.

Safety outcomes were analysed in the safety analysis set (defined as all participants who received any dose of the study drug). Adverse events were reported throughout the study period non-systematically and reviewed by an

independent safety monitoring committee. We summarised adverse events by the number and proportion of participants who had at least one event. No statistical comparisons were performed for safety. All analyses were done using SAS (version 9.4). Full details of the statistical analyses, including handling of missing data, are shown in the appendix (pp 9–10).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

	Bictegravir–lenacapavir group (n=383)	Bictegravir–emtricitabine–tenofovir alafenamide group (n=191)	Total (n=574)
Age, years*	47 (38–58)	51 (41–59)	49 (39–58)
Age ≥55 years	135 (35%)	70 (37%)	205 (36%)
Sex assigned at birth			
Male	314 (82%)	149 (78%)	463 (81%)
Female	69 (18%)	42 (22%)	111 (19%)
BMI, kg/m²	26·8 (24·2–30·3)	27·1 (24·1–31·2)	26·8 (24·1–30·5)
Gender			
Cisgender	380 (99%)	187 (98%)	567 (99%)
Transgender woman	2 (1%)	1 (1%)	3 (1%)
Non-binary	1 (<1%)	0	1 (<1%)
Missing data	0	3 (2%)	3 (1%)
Race			
American Indian or Alaska Native	1 (<1%)	1 (1%)	2 (<1%)
Asian	51 (13%)	26 (14%)	77 (13%)
Black	113 (30%)	44 (23%)	157 (27%)
Native Hawaiian or Pacific Islander	1 (<1%)	0	1 (<1%)
White	199 (52%)	111 (58%)	310 (54%)
Other	18 (5%)	9 (5%)	27 (5%)
Ethnicity			
Hispanic or Latinx	106 (28%)	49 (26%)	155 (27%)
Not Hispanic or Latinx	277 (72%)	141 (74%)	418 (73%)
Not permitted†	0	1 (1%)	1 (<1%)
Geographical region			
North America	272 (71%)	131 (69%)	403 (70%)
Asia	49 (13%)	24 (13%)	73 (13%)
Europe	46 (12%)	23 (12%)	69 (12%)
Central and South America	5 (1%)	4 (2%)	9 (2%)
Oceania	11 (3%)	9 (5%)	20 (3%)
HIV-1 RNA ≥50 copies per mL‡	7 (2%)	1 (1%)	8 (1%)
CD4 count, cells per µL	711 (547–914)	663 (522–873)	695 (541–902)
CD4 count <200 cells per µL	1 (<1%)	2 (1%)	3 (1%)
History of an AIDS diagnosis	15 (4%)	8 (4%)	23 (4%)
Duration of HIV-1 treatment from diagnosis, years	12·6 (6·7–20·7)	14·8 (8·3–23·4)	13·8 (7·4–21·8)
Duration of HIV-1 treatment, years	11·3 (6·4–18·4)	13·6 (7·1–19·6)	12·0 (6·5–18·7)
Number of select comorbidities			
1	94 (25%)	57 (30%)	151 (26%)
≥2	121 (32%)	52 (27%)	173 (30%)

(Table 1 continues on next page)

Results

Between March 25 and Oct 30, 2024, 666 people with HIV-1 were assessed for eligibility (figure B). Of those, 89 participants were ineligible and 577 were randomly assigned (384 to bictegravir–lenacapavir and 193 to continue bictegravir–emtricitabine–tenofovir alafenamide). Three participants did not receive treatment. 574 participants received at least one dose of study treatment (full and safety analysis sets).

Baseline demographic and clinical characteristics were similar and balanced between the treatment groups (table 1). The types of previously used antiretroviral regimens were similar between the treatment groups at baseline (appendix p 14).

At week 48, five (1·3%) of 383 participants in the bictegravir–lenacapavir group and two (1·0%) of 191 in the bictegravir–emtricitabine–tenofovir alafenamide group had HIV-1 RNA of 50 copies per mL or higher with a percentage difference of 0·3% (95·002% CI –1·9 to 2·4), meeting the non-inferiority criteria for the primary endpoint (table 2). One of five participants in the bictegravir–lenacapavir group with HIV-1 RNA of 50 copies per mL or higher in the Snapshot analysis had a viral load of 10700 copies per mL and resuppressed after a change of regimen at investigator's discretion (bictegravir–emtricitabine–tenofovir alafenamide then darunavir–cobicistat–emtricitabine–tenofovir alafenamide). The other four participants had HIV-1 RNA of 56, 64, 146, and 147 copies per mL; one continued bictegravir–lenacapavir and resuppressed by week 60, one was lost to follow-up after day 33, and two switched regimens (one switched to darunavir–cobicistat–emtricitabine–tenofovir alafenamide and the other switched to bictegravir–emtricitabine–tenofovir alafenamide). Of two participants in the bictegravir–emtricitabine–tenofovir alafenamide group with HIV-1 RNA of 50 copies per mL or higher in the Snapshot analysis, one had a viral load of 291 copies per mL and was lost to follow-up; the other had a viral load of 839 copies per mL, discontinued bictegravir–emtricitabine–tenofovir alafenamide at day 93 (participant's decision), and received bictegravir–emtricitabine–tenofovir alafenamide plus darunavir–cobicistat for 6 weeks before switching back to bictegravir–emtricitabine–tenofovir alafenamide and resuppressed by week 24. 20 (5%) participants in the bictegravir–lenacapavir group and 16 (8%) in the bictegravir–emtricitabine–tenofovir alafenamide group had no virological data available in the week-48 analysis window (table 2).

358 (93%) participants in the bictegravir–lenacapavir group versus 173 (91%) in the bictegravir–emtricitabine–tenofovir alafenamide group had HIV-1 RNA of lower than 50 copies per mL at week 48 (US FDA Snapshot algorithm; table 2); these proportions were the same in the missing=failure analysis, whereas in the missing=excluded analysis, these proportions were 358 (99%) versus 173 (100%).

Two participants in each treatment group met criteria for resistance testing (virological failure and HIV-1 RNA ≥200 copies per mL). One participant in the bictegravir–lenacapavir group and two in the bictegravir–emtricitabine–tenofovir alafenamide group had no treatment-emergent resistance. One participant in the bictegravir–lenacapavir group had an isolated treatment-emergent R263K integrase substitution detected at week 36 and no capsid mutations. The R263K isolate remained phenotypically susceptible to bictegravir. This participant had a history of previous exposure to raltegravir and dolutegravir and had polymorphic secondary mutations in integrase detected before study entry (M50I and S119P detected in plasma in 2015 and in proviral DNA in 2019). The participant had a maximum HIV-1 RNA of 208 copies per mL at week 36 (146 copies per mL at week 48) and switched to darunavir–cobicistat–emtricitabine–tenofovir alafenamide at week 48.

The proportion of participants with HIV-1 RNA of 50 copies per mL or higher at week 48 were similar between the treatment groups in all subgroups (stratified by age, sex, race, ethnicity, and geographical region), ranging from 0–3% across subgroups, and 95% CIs for the percentage difference showed no difference between

	Bictegravir–lenacapavir group (n=383)	Bictegravir–emtricitabine–tenofovir alafenamide group (n=191)	Total (n=574)
(Cntinued from previous page)			
Select comorbidities§¶			
Dyslipidaemia	158 (41%)	79 (41%)	237 (41%)
Hypertension	141 (37%)	63 (33%)	204 (36%)
Hyperglycaemia or diabetes	68 (18%)	31 (16%)	99 (17%)
Chronic kidney disease	20 (5%)	12 (6%)	32 (6%)
Historical primary resistance mutations§||			
NNRTI	25 (17%)	14 (18%)	39 (17%)
NRTI	14 (10%)	15 (19%)	29 (13%)
Protease inhibitor	7 (5%)	7 (9%)	14 (6%)
INSTI	0	0	0

Data are n (%) or median (IQR). INSTI=integrase strand-transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleos(t)ide reverse transcriptase inhibitor. *The age range was 23–77 years in the bictegravir–lenacapavir group and 26–77 years in the bictegravir–emtricitabine–tenofovir alafenamide group. †Local regulators did not allow the collection of ethnicity information. ‡Participants had screening HIV-1 RNA of lower than 50 copies per mL, but baseline HIV-1 RNA of 50 copies per mL or higher. §Categories are not mutually exclusive. ¶Grouped terms on the standardised Medical Dictionary for Regulatory Activities queries narrow search. ||Investigators were asked to document previous resistance data from available historical HIV-1 genotype and phenotype reports. The numbers of participants with available resistance data were 144 for NNRTI, 144 for NRTI, 144 for protease inhibitor, and 83 for INSTI in the bictegravir–lenacapavir group versus 80, 80, 79, and 41, respectively, in the bictegravir–emtricitabine–tenofovir alafenamide group.

Table 1: **Demographic and clinical characteristics of participants at baseline (safety analysis set)**

	Bictegravir–lenacapavir group	Bictegravir–emtricitabine–tenofovir alafenamide group	Percentage difference (95·002% CI)*
US Food and Drug Administration Snapshot algorithm†			
HIV-1 RNA ≥50 copies per mL (primary endpoint)	5/383 (1%)	2/191 (1%)	0·3% (−1·9 to 2·4)
HIV-1 RNA ≥50 copies per mL in week-48 window	2/383 (1%)	0	..
Discontinued study drug due to other reasons (with last available HIV-1 RNA ≥50 copies per mL)‡	3/383 (1%)	2/191 (1%)	..
HIV-1 RNA <50 copies per mL	358/383 (93%)	173/191 (91%)	3·1% (−1·8 to 8·0)
No virological data in week-48 analysis window	20/383 (5%)	16/191 (8%)	..
Discontinued study drug due to adverse event or death	6/383 (2%)§	4/191 (2%)¶	..
Discontinued study drug due to other reasons (with last available HIV-1 RNA <50 copies per mL)‡	14/383 (4%)	12/191 (6%)	..
Missing=excluded analysis||			
HIV-1 RNA <50 copies per mL	358/360 (99%)	173/173 (100%)	−0·6% (−2·1 to 0·9)*
HIV-1 RNA ≥50 copies per mL	2/360 (1%)	0	..
50 to <200 copies per mL	2/360 (1%)	0	..
≥200 copies per mL	0	0	..
Missing=failure analysis**			
HIV-1 RNA <50 copies per mL	358/383 (93%)	173/191 (91%)	3·1% (−1·8 to 8·0)*
HIV-1 RNA ≥50 copies per mL	2/383 (1%)	0	..
50 to <200 copies per mL	2/383 (1%)	0	..
≥200 copies per mL	0	0	..
Missing data	23/383 (6%)	18/191 (9%)	..

Data are n/N (%), unless stated otherwise. *Differences in percentages between the two study groups and two-sided 95·002% CIs (95% CIs for missing=excluded and missing=failure analyses) were constructed based on Mantel–Haenszel stratum weights and Koch variance estimator and adjusted by geographical region (USA *vs* non-USA). †Full analysis set. ‡Other reasons included discontinuation of study drug due to investigator's discretion, participant's decision, loss to follow-up, non-compliance with the study drug, participant never received the study drug, protocol violation, pregnancy, and study termination by the sponsor. §Six discontinuations due to adverse events: colon cancer (n=1), anxiety (n=1), intracranial mass and encephalopathy (n=1), and libido decreased (n=1), which were deemed unrelated to the study treatment, and trismus, rash, and restless legs syndrome (n=1), and fatigue and alopecia (n=1), which were deemed related to the study treatment. ¶One discontinuation due to death (coronary artery disease deemed unrelated to the study treatment) and three discontinuations due to adverse events: road traffic accident (n=1) and abdominal discomfort (n=1), which were deemed unrelated to the study treatment, and dry mouth (n=1) deemed related to the study treatment. ||Full analysis set with non-missing HIV-1 RNA value at week-48 visit during treatment. **Full analysis set during treatment.

Table 2: **Virological outcomes at week 48**

treatment groups (appendix p 13). CD4 cell counts remained stable throughout 48 weeks in both treatment groups (appendix p 15). Median change from baseline to week 48 in CD4 count was –7 cells per µL (IQR –111 to 88) in the bictegravir–lenacapavir group and 6 cells per µL (–87 to 95) in the bictegravir–emtricitabine–tenofovir alafenamide group (least-squares mean difference –8·4 [95% CI –39·8 to 22·9]).

288 (75%) participants in the bictegravir–lenacapavir group and 141 (74%) in the bictegravir–emtricitabine–tenofovir alafenamide group had adverse events (table 3). The most common adverse events (occurring in ≥5% of participants) with bictegravir–lenacapavir were diarrhoea (31 [8%]), nasopharyngitis (30 [8%]), and upper respiratory tract infection (29 [8%]); and with bictegravir–emtricitabine–tenofovir alafenamide were nasopharyngitis (13 [7%]), nausea (11 [6%]), and COVID-19 (10 [5%]). Most adverse events were mild or moderate in severity (grades 1 or 2 in 376 [88%] of 429 participants). 38 (10%) participants in the bictegravir–lenacapavir group and 15 (8%) in the bictegravir–emtricitabine–tenofovir alafenamide group had an adverse event of grade 3 or higher. One participant in the bictegravir–lenacapavir group had drug-related grade 3 rhabdomyolysis starting on day 17 but continued treatment, and this adverse event resolved after 12 days (asymptomatic and revised to grade 1 after data cutoff; table 3; appendix p 11).

	Bictegravir–lenacapavir group (n=383)	Bictegravir–emtricitabine–tenofovir alafenamide group (n=191)
All adverse events		
Adverse events of any grade	288 (75%)	141 (74%)
Adverse events of grade 3 or higher	38 (10%)	15 (8%)
Drug-related adverse events of any grade	40 (10%)	23 (12%)
Drug-related adverse events of grade 3 or higher	1 (<1%)†	0
Serious adverse events	27 (7%)	13 (7%)
Serious drug-related adverse events	0	0
Adverse events leading to study drug discontinuation	6 (2%)‡	3 (2%)§
Drug-related adverse events leading to study drug discontinuation	2 (<1%)	1 (<1%)
Adverse events occurring in ≥5% of participants in either group		
Diarrhoea	31 (8%)	9 (5%)
Nasopharyngitis	30 (8%)	13 (7%)
Upper respiratory tract infection	29 (8%)	9 (5%)
Nausea	20 (5%)	11 (6%)
Headache	22 (6%)	6 (3%)
COVID-19	5 (1%)	10 (5%)
Deaths		
Total deaths	0	1 (<1%)¶

Data are n (%). Median exposure was 60·6 weeks (IQR 53·0–69·0) in the bictegravir–lenacapavir group and 59·9 weeks (52·0–67·9) in the bictegravir–emtricitabine–tenofovir alafenamide group. *Adverse events beginning on or after the study drug start date and up to 60 days after permanent discontinuation of bictegravir–lenacapavir or on or after the study drug start date and up to 30 days after permanent discontinuation of bictegravir–emtricitabine–tenofovir alafenamide, or leading to premature study drug discontinuation. †Grade 3 rhabdomyolysis revised to grade 1 after data cutoff (appendix p 11). ‡Deemed unrelated to the study treatment (colon cancer [n=1], anxiety [n=1], intracranial mass and encephalopathy [n=1], and libido decreased [n=1]). Deemed related to the study treatment (trismus, rash, and restless legs syndrome [n=1] and fatigue and alopecia [n=1]). §Deemed unrelated to the study treatment (road traffic accident [n=1] and abdominal discomfort [n=1]). Deemed related to the study treatment (dry mouth [n=1]). ¶Death due to coronary artery disease deemed unrelated to the study treatment.

Table 3: **Safety outcomes (safety analysis set)***

Drug-related adverse events occurred in 40 (10%) participants in the bictegravir–lenacapavir group versus 23 (12%) in the bictegravir–emtricitabine–tenofovir alafenamide group; serious adverse events occurred in 27 (7%) versus 13 (7%), with none deemed related to treatment. Adverse events leading to discontinuation of the study drug occurred in six (2%) participants in the bictegravir–lenacapavir group versus three (2%) in the bictegravir–emtricitabine–tenofovir alafenamide group; whereas two (<1%) versus one (<1%) participants had drug-related adverse events leading to study drug discontinuation (table 3).

One participant in the bictegravir–emtricitabine–tenofovir alafenamide group died during the study due to coronary artery disease, which was deemed unrelated to the study treatment. We detected no new HBV infections or reactivations. Four pregnancies occurred during the study (three in the bictegravir–lenacapavir group and one in the bictegravir–emtricitabine–tenofovir alafenamide group). Of three pregnancies in the bictegravir–lenacapavir group, two resulted in elective induced abortions and one in a spontaneous abortion, which was deemed unrelated to the study treatment.

Laboratory abnormalities of grade 3 or higher occurred in 93 (24%) of 382 participants in the bictegravir–lenacapavir group and 44 (23%) of 190 in the bictegravir–emtricitabine–tenofovir alafenamide group. The most frequent grade 3 or higher laboratory abnormalities were decreased creatinine clearance (23 [6%] in the bictegravir–lenacapavir group *vs* 21 [11%] in the bictegravir–emtricitabine–tenofovir alafenamide group) and increased direct bilirubin concentration (36 [9%] *vs* seven [4%]; appendix p 16). Fasting total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and total cholesterol to HDL cholesterol ratio remained stable at week 48 compared with baseline in both treatment groups (table 4). Bodyweight also remained stable up to and including week 48 in both treatment groups (median change –0·2 kg [IQR –2·5 to 1·8] in the bictegravir–lenacapavir group *vs* 0·0 kg [–2·2 to 2·3] in the bictegravir–emtricitabine–tenofovir alafenamide group).

Discussion

This phase 3 ARTISTRY-2 trial met the primary endpoint of non-inferiority using the US FDA Snapshot algorithm. The proportion of participants with HIV-1 RNA of 50 copies per mL or higher at 48 weeks was 1% in both the bictegravir–lenacapavir group and the bictegravir–emtricitabine–tenofovir alafenamide group. Maintenance of virological suppression (HIV-1 RNA <50 copies per mL) was high (>90%), and CD4 cell counts

were stable over 48 weeks in both treatment groups. No differences in the proportions of participants with HIV-1 RNA of 50 copies per mL or higher at week 48 were observed across subgroups by age, sex, race, ethnicity, or geographical region. The trial population included a high number of participants with comorbidities at baseline (including dyslipidaemia, hypertension, and hyperglycaemia or diabetes) and there were no observed increases in bodyweight or worsening of fasting lipid profiles with the switch to bictegravir–lenacapavir over 48 weeks.

Participants in this trial were demographically diverse, with a broad range of ages (23–77 years) and other characteristics represented. Bictegravir–lenacapavir was well tolerated in this population, with a similar proportion of participants in each treatment group having adverse events (approximately 75%). The incidence of grade 3 or higher adverse events and drug-related adverse events were similar between treatment groups. Serious adverse events and adverse events leading to treatment discontinuation were infrequent and occurred in a similar proportion of participants in both treatment groups. No serious adverse events were deemed related to the study treatment.

Treatment-emergent resistance was rare, showing the robust resistance barrier of bictegravir–lenacapavir. We detected no capsid mutations in the two participants in the bictegravir–lenacapavir group who were not suppressed at week 48 and met criteria for resistance analysis. A single integrase mutation (R263K) was detected in the bictegravir–lenacapavir group, which was not associated with phenotypic resistance. This participant had a history of previous exposure to raltegravir and dolutegravir and although the mutation was not found in samples obtained before study entry, there is a possibility that the mutation was pre-existing. The development of R263K during virological failure on bictegravir-based therapy is rare but has been observed in clinical trials and real-world settings.[25,26]

The results of this trial complement the findings of ARTISTRY-1; together, these phase 3 studies provide a balanced overview of the safety and efficacy of the single-tablet regimen bictegravir–lenacapavir for the treatment of people with HIV-1 who are virologically suppressed on their current regimen. The open-label ARTISTRY-1 trial showed that bictegravir–lenacapavir was non-inferior to complex regimens in maintaining high levels of virological suppression, with increased treatment satisfaction and no emergence of resistance.[21] In ARTISTRY-1, there were higher rates of drug-related adverse events with bictegravir–lenacapavir versus complex regimens (53 [14%] of 371 *vs* three [2%] of 186).[21] These data, however, must be evaluated in the context of the open-label design of ARTISTRY-1, which introduces the possibility of reporting bias[27] against the novel regimen in participants who, despite receiving a more complex ART regimen, had been stable on that treatment.

	Bictegravir–lenacapavir group	Bictegravir–emtricitabine–tenofovir alafenamide group
Total cholesterol, mg/dL	174 (147 to 197); 355	174 (153 to 200); 165
Change from baseline	0 (–16 to 17); 343	1 (–11 to 18); 162
HDL cholesterol, mg/dL	49 (41 to 59); 354	46 (39 to 57); 165
Change from baseline	0 (–4 to 5); 341	0 (–3 to 5); 162
LDL cholesterol, mg/dL	100 (81 to 127); 355	104 (85 to 125); 165
Change from baseline	1 (–12 to 15); 343	3 (–8 to 16); 162
Triglycerides, mg/dL	99 (71 to 139); 354	102 (80 to 148); 165
Change from baseline	0 (–29 to 25); 341	–5 (–27 to 23); 162
Total cholesterol to HDL cholesterol ratio	3·4 (2·8 to 4·3); 354	3·6 (3·0 to 4·5); 165
Change from baseline	–0·1 (–0·4 to 0·3); 341	0·0 (–0·3 to 0·3); 162

Data are median (IQR); n.

Table 4: **Fasting lipid parameters at week 48 (safety analysis set)**

A blinded design standardises participant expectations between treatment groups; therefore, ARTISTRY-2 enabled a robust evaluation of the safety of bictegravir–lenacapavir versus bictegravir–emtricitabine–tenofovir alafenamide.

Unlike bictegravir–emtricitabine–tenofovir alafenamide, bictegravir–lenacapavir does not contain any HBV-active medications. Evaluation and management of HBV in this study was consistent with clinical guidelines for HBV screening for all individuals starting a regimen that does not contain a nucleos(t)ide reverse transcriptase inhibitor (NRTI),[7,8] as participants with chronic HBV infection were excluded from the study, and vaccination was encouraged for those who were susceptible to HBV. In our study, there were no observed acute HBV infections or HBV reactivations through week 48. The potential for HBV acquisition or reactivation remains an important consideration for people with HIV-1 considering a two-drug regimen that does not have the antiHBV activity provided by a tenofovir-based treatment.[28]

There are currently two single-tablet, two-drug regimens approved and recommended for some people with HIV-1,[7–9] both include the INSTI dolutegravir combined with rilpivirine (a non-nucleoside reverse transcriptase inhibitor) or lamivudine (an NRTI). These regimens were assessed in non-inferiority trials in virologically suppressed people with HIV-1 who switched from their current ART regimen. Participants switching to dolutegravir–rilpivirine had non-inferior maintenance of virological suppression compared with those continuing to receive their current ART regimen over 48 weeks in two identically designed open-label studies.[29] Trials of participants switching to dolutegravir–lamivudine showed non-inferior maintenance of virological suppression compared with continuing three-drug or four-drug ART regimens over 48 weeks[30,31] or continuing bictegravir–emtricitabine–tenofovir alafenamide over this timeframe.[32] Similar to ARTISTRY-1, these studies had open-label designs and rates of drug-related adverse events or discontinuations due to adverse events were

generally higher in the dual-regimen groups than the groups continuing current treatment. When ARTISTRY-2 is considered in the context of these previous trials, bictegravir–lenacapavir has the potential to offer a new two-drug single-tablet regimen treatment option for people with HIV-1 who are virologically suppressed, including those receiving more complex regimens containing three or more active agents.

One limitation of our study is that some geographical regions with the highest prevalence of HIV-1 were not represented, because bictegravir–emtricitabine–tenofovir alafenamide is not routinely accessible in African countries (aside from South Africa), meaning that participants from these regions would have been unable to meet trial eligibility criteria. In addition, the proportion of participants assigned female sex at birth was low (19%) relative to the estimated worldwide prevalence of HIV-1 in women and girls (53%).[33] Nevertheless, the primary endpoint results were consistent across sex subgroups, providing some confidence in the applicability of these findings. The 48-week duration of our analysis is another limitation; however, long-term efficacy and safety outcomes will be assessed in an ongoing open-label extension phase, in which participants receiving bictegravir–lenacapavir will be followed-up for at least 144 weeks. If approved, the real-world effectiveness of bictegravir–lenacapavir should be evaluated outside of a clinical trial setting.

In conclusion, although there are multiple safe and effective treatment options for people with HIV-1, the needs of this population are diverse over a lifetime of taking ART. The evaluation of bictegravir–lenacapavir versus complex regimens (ARTISTRY-1) and versus bictegravir–emtricitabine–tenofovir alafenamide (ARTISTRY-2) supports the potential for bictegravir–lenacapavir to be a safe and effective novel two-drug single-tablet regimen with clinical utility in broad populations of virologically suppressed people with HIV-1, including older people with comorbidities, those receiving complex or multitablet regimens, those with previous resistance, or those seeking a novel treatment option.

Contributors

EGM, MoR, PJR, WS, GC, J-PR, CB, ED, CTM, MT, YY, MO, SL, SS, JIL-M, BC, and C-CH contributed to the data collection. JMM-R and PS contributed to the study design and data analysis or interpretation. EGM, KA, MLD, HH, KM, and MaR contributed to the data analysis or interpretation. All authors contributed to drafting or revising the manuscript. All authors had access to the study data and had final responsibility for the decision to submit the manuscript for publication. EGM, KA, HH, KM, JMM-R, PS, and MaR accessed and verified the data underlying the study.

Declaration of interests

EGM received research grants and chaired an independent data monitoring committee for ViiV Healthcare. MoR received consulting fees from Gilead Sciences, Shionogi, and ViiV Healthcare; and payment or honoraria for speaker engagements from AbbVie, Gilead Sciences, and ViiV Healthcare. PJR received payment or honoraria for speaker engagements from Gilead Sciences and ViiV Healthcare. GC received research grants from Gilead Sciences, Merck, Pfizer, and ViiV Healthcare. J-PR received grants or contracts from AbbVie, the Canadian Institute of Health Research, and Fonds de recherche du Québec-Santé; consulting fees from AbbVie, Gilead Sciences, Merck, and ViiV Healthcare; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events and payment for expert testimony from Gilead Sciences, Merck, and ViiV Healthcare; support for attending meetings or travel (or both) from Gilead Sciences and ViiV Healthcare; participated on a data safety monitoring board or advisory board for AbbVie, Gilead Sciences, and ViiV Healthcare; and received equipment, materials, drugs, medical writing, gifts, or other services from Merck. CB received payment or honoraria for participation in speakers bureaus from Gilead Sciences; and support for attending meetings or travel (or both) related to clinical research activities from Gilead Sciences, Merck, and Viking Therapeutics. ED received research grants from Gilead Sciences and ViiV Healthcare. CTM received research grants from AbbVie, Gilead Sciences, and ViiV Healthcare; and payment or honoraria for speaker engagements from Gilead Sciences, Theratechnologies, and ViiV Healthcare. MT received grants or contracts from MSD; and payment or honoraria for speaker engagements from Gilead Sciences. YY received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Chugai, Denka, Gilead Sciences, Janssen, MSD, Roche Diagnostics, and ViiV Healthcare; and is a member of the Second Committee on Drugs, Pharmaceutical Affairs and Food Sanitation Council and the Review Committee on Adverse Drug Reactions, Pharmaceuticals, and Medical Devices Agency. MO received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Gilead Sciences; support for attending meetings or travel (or both) from Gilead Sciences, Janssen, and ViiV Healthcare; participated on a data safety monitoring board or advisory board for Gilead Sciences; and is a member of the Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine and Australian Antiretroviral Guidelines Committee. SL received grants or contracts from GSK and Merck; consulting fees from GSK; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Gador and GSK. SS received consulting fees for advisory boards from AbbVie, Gilead Sciences, Janssen-Cilag, MSD, Novavax, Pfizer, Sanofi, Theratechnologies, and ViiV Healthcare; payment or honoraria for lectures and presentations from AbbVie, Gilead Sciences, Janssen-Cilag, MSD, Pfizer, Sanofi, Theratechnologies, and ViiV Healthcare; and support for attending meetings or travel (or both) from Gilead Sciences. BC received consulting fees from Gilead Sciences; payment or honoraria for lectures from Gilead Sciences, GSK, Handok, ViiV Healthcare, and Yuhan; support for attending meetings or travel (or both) from, and participated on a data safety monitoring board or advisory board for, Gilead Sciences, GSK, and ViiV Healthcare. C-CH received research grants, consulting fees, and honoraria for lectures, speakers bureaus, or educational events from Gilead Sciences. KA, MLD, HH, KM, JMM-R, PS, and MaR are employees of and hold stocks in Gilead Sciences. WS and JIL-M declare no competing interests.

Data sharing

Gilead Sciences will share anonymised individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal also needs to include a statistician. Approval of such requests is at the discretion of Gilead Sciences and is dependent on the nature of the request, merit of the research proposed, availability of data, and the intended use of data. Data requests should be sent to datasharing@gilead.com. The protocol and statistical analysis plan are provided in the appendix (p 19).

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