Switch to single-tablet bictegravir–lenacapavir from a complex HIV regimen (ARTISTRY-1): a randomised, open-label, phase 3 clinical trial

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Summary

Background Single-tablet regimens (STRs) revolutionised HIV-1 treatment, improving adherence and clinical outcomes; however, many people cannot take these due to resistance, contraindications, or drug–drug interactions, instead relying on complex multi-tablet regimens. Novel STRs are therefore needed. We aimed to evaluate the efficacy and safety of a novel STR, bictegravir–lenacapavir, in people with HIV-1.

Methods ARTISTRY-1 was a randomised, open-label, active-controlled, non-inferiority phase 3 trial conducted at hospitals and clinics across 15 countries that enrolled people with HIV-1 with virological suppression on complex regimens. Participants were randomly assigned (using interactive technology, 2:1, stratified by geographical region) to switch to once-daily oral bictegravir–lenacapavir 75 mg/50 mg STR or continued complex regimen. The primary outcome was the proportion of participants with an HIV-1 RNA viral load of 50 copies per mL or higher at week 48 (US Food and Drug Administration Snapshot algorithm), assessed in all randomly assigned participants who received any dose of assigned treatment. This trial (active; enrolment complete) was registered with ClinicalTrials.gov (NCT05502341).

Findings Between Jan 29 and Sept 26, 2024, 729 participants were screened; 557 were randomly assigned and treated (bictegravir–lenacapavir n=371; complex regimen n=186). At baseline, median age was 60 years (range 22–84), HIV treatment duration was 28 years (IQR 22–32); participants were taking a median of three antiretroviral pills per day (range 2–11). At week 48, an HIV-1 RNA viral load of 50 copies per mL or higher was observed in three (1%) participants receiving bictegravir–lenacapavir and two (1%) receiving a complex regimen (difference −0·3%; 95·002% CI −2·3 to 1·8), meeting the non-inferiority margin of 4%. No resistance emerged. Adverse event rates were similar between groups. Six (2%) participants discontinued bictegravir–lenacapavir and one (1%) discontinued their complex regimen due to adverse events. There were five deaths in the bictegravir–lenacapavir group, none of which were deemed related to study drug. Participants reported increased treatment satisfaction after switching to bictegravir–lenacapavir.

Interpretation Bictegravir–lenacapavir STR demonstrated non-inferior efficacy to complex regimens, with a similar safety profile and increased treatment satisfaction. Bictegravir–lenacapavir offers new opportunities for HIV-1 treatment optimisation for people taking complex regimens.

Funding Gilead Sciences.

Introduction

People with HIV taking complex multi-tablet antiretroviral therapy regimens face a substantial unmet treatment need, often experiencing significant pill burden, adherence challenges, and difficulties with long-term HIV management.[1] These individuals—often older adults diagnosed early during the HIV-1 epidemic or people born with HIV-1, with decades of antiretroviral therapy experience and a higher likelihood of resistance—continue to rely on regimens consisting of multiple pills and/or doses per day.[2] These regimens usually require the use of pharmacological boosting agents and can result in higher drug concentrations.[3]

Single-tablet regimens (STRs) have been standard of care for people with HIV-1[2,4] for almost two decades,[5] offering simplicity, reduced pill burden, improved adherence, and better clinical outcomes compared with complex multi-tablet regimens.[6–8] A novel STR combining bictegravir, a global guideline-recommended integrase strand-transfer inhibitor (INSTI) with a high resistance barrier,[2,4,9–11] and lenacapavir, a first-in-class capsid inhibitor with no documented de novo resistance in the absence of previous exposure,[12–14] offers a promising treatment optimisation option for people with HIV-1 with virological suppression on a complex regimen who are unable to use currently available STRs. The phase 2/3

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Research in context

Evidence before this study

We searched PubMed on Feb 12, 2026, using the terms "bictegravir AND lenacapavir" without language or date restrictions. 16 articles were identified. None of these studies compared a single-tablet regimen of bictegravir–lenacapavir with complex regimens for treatment of HIV-1, with the exception of the phase 2 portion of the current trial. There is a need for additional treatment options for people with HIV-1 who are unable to benefit from available single-tablet regimens due to resistance, intolerance, contraindications, or drug–drug interactions. Instead, these individuals—often older adults with multiple comorbidities, decades of antiretroviral therapy experience, and a higher likelihood of resistance—rely on complex antiretroviral regimens, and frequently experience significant pill burden, adherence challenges, and difficulties with long-term HIV management. A novel single-tablet regimen of bictegravir and lenacapavir could offer a new treatment option for this population. The open-label, randomised phase 2/3 ARTISTRY-1 trial evaluated the efficacy and safety of switching to bictegravir–lenacapavir in people with HIV-1 with virological suppression on a complex regimen. Two previously published phase 2 articles reported that bictegravir and lenacapavir maintained virological suppression through 48 weeks and were well tolerated, including in people with a history of antiretroviral resistance. Here we report phase 3 data from ARTISTRY-1.

Added value of this study

Phase 3 ARTISTRY-1 is the first randomised trial to investigate the novel single-tablet regimen of bictegravir–lenacapavir for treatment of HIV-1. It included the oldest study population enrolled in a registrational programme for HIV treatment to date, with a median participant age of 60 years. At baseline, most participants had at least one comorbidity (54% had two or more select comorbidities) and 61% were taking two or more select concomitant medications. Median duration of HIV treatment was 28 years, and a large percentage of participants (81%) were on a complex regimen due to antiretroviral resistance, demonstrating the treatment challenges faced by this underserved population.
Once-daily oral bictegravir–lenacapavir single-tablet regimen demonstrated non-inferior efficacy to complex regimens, with an HIV-1 RNA viral load of 50 copies per mL or higher in 1% of participants receiving bictegravir–lenacapavir and 1% of participants receiving a complex regimen at week 48 (difference −0·3%; 95·002% CI −2·3% to 1·8%). No resistance emerged. There were similar rates of adverse events in both treatment groups despite the open-label trial design, and participants who switched to bictegravir–lenacapavir reported greater treatment satisfaction than those continuing a complex regimen.

Implications of all the available evidence

These findings support the use of bictegravir–lenacapavir as a new, optimised treatment option to maintain virological suppression in people with HIV-1 on complex regimens who have not benefitted from available single-tablet regimens due to antiretroviral resistance or other reasons. In particular, bictegravir–lenacapavir could offer a more suitable long-term treatment option for an ageing population with comorbidities and a greater risk of polypharmacy.

See Online for appendix

ARTISTRY-1 trial evaluated the efficacy and safety of switching to bictegravir–lenacapavir STR in people with HIV-1 with virological suppression on complex regimens. In phase 2, bictegravir and lenacapavir were well tolerated and maintained virological suppression through 48 weeks in participants, most of whom had a history of antiretroviral resistance.[15] Here, we aimed to evaluate the 48-week efficacy and safety of bictegravir–lenacapavir STR in people with HIV who switched from complex regimens in the phase 3 study.

Methods

Study design

ARTISTRY-1 was a randomised, open-label, active-controlled, non-inferiority phase 3 trial (GS-US-621-6289; ClinicalTrials.gov number NCT05502341), conducted at 90 hospitals and clinics across 15 countries or territories (Australia, Argentina, Canada, Dominican Republic, France, Germany, Italy, Japan, Puerto Rico, South Africa, South Korea, Spain, Taiwan, UK, and USA). The trial was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by an institutional review board or ethics committee at each trial site (trial investigators and ethics approvals are listed in the appendix [pp 3–5]). The protocol and statistical analysis plan are provided in the appendix (p 25). A summary of important protocol amendments is also provided in the appendix (pp 6–7). The trial is active and closed to new participants.

Participants

Eligible participants were aged 18 years or older, with plasma HIV-1 RNA concentrations below 50 copies per mL for at least 6 months before and at screening, and on a complex regimen for at least 6 months due to previous antiretroviral resistance, intolerance, or contraindication to existing STRs, with no resistance to bictegravir or previous exposure to lenacapavir. A complex regimen was defined as (1) containing a boosted protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) plus one or more other third agent from a class other than nucleos(t)ide reverse transcriptase inhibitor (NRTI), or (2) requiring two or more pills per day or one drug requiring more than once-daily dosing, or (3) containing a parenteral agent(s) as well as oral agents (excluding a complete long-acting injectable

regimen). Participants were required to have an estimated glomerular filtration rate (eGFR) by Cockroft–Gault equation of at least 15 mL/min and not be on renal replacement therapy. Those with chronic hepatitis B virus (HBV) infection, decompensated liver cirrhosis, or active tuberculosis infection were excluded. A complete list of eligibility criteria is provided in the appendix (pp 8–9).

People with HIV were screened and recruited by clinical investigators at hospitals and clinics. All participants provided written consent. Demographic data on sex at birth (male or female), gender (cisgender, transgender, non-binary or third gender, other, not disclosed), race (American Indian or Alaska Native, Asian, Black, Native Hawaiian or Pacific Islander, White, Other, not permitted), and ethnicity (Hispanic or Latine, not Hispanic or Latine, not permitted) were collected through self-reporting by study participants.

Randomisation and masking

Following confirmation of eligibility, the investigator or an appropriately trained designee randomly assigned each participant to a treatment group using an interactive response system (IXRS) in a 2:1 ratio stratified by geographical region (appendix p 10). The randomisation sequence was obtained using block number and treatment allocation provided at each trial site by the interactive response system. There was no blinding of treatment allocation in this trial.

Procedures

Eligible participants were randomly assigned in a 2:1 ratio either to switch to oral bictegravir–lenacapavir 75 mg/50 mg STR once daily, regardless of food intake, or continue their complex regimen (figure 1A). Participants in the bictegravir–lenacapavir group received an oral pharmacokinetic loading dose of 600 mg lenacapavir on days 1 and 2 in addition to bictegravir–lenacapavir.

Blood samples drawn for laboratory analyses, HIV-1 RNA, CD4 cell counts, and adverse event assessments were performed at day 1, weeks 4 and 12, and every 12 weeks thereafter.

Resistance analysis was performed in confirmed cases of virological rebound (HIV-1 RNA ≥50 copies per mL at any visit after day 1 followed by HIV-1 RNA ≥200 copies per mL at the subsequent scheduled or unscheduled visit) or when a participant had an HIV-1 RNA viral load of 200 copies per mL or higher at the last on-treatment visit through week 48 (including early discontinuation or loss to follow-up).

Treatment satisfaction was assessed using HIV Treatment Satisfaction Questionnaire status version (HIVTSQs; at day 1 and weeks 4, 12, 24, and 48) and change version (HIVTSQc; at week 48; see appendix pp 11–14 for copies of the questionnaires).

Outcomes

The primary endpoint was the proportion of participants with an HIV-1 RNA viral load of 50 copies per mL or higher at week 48, as determined by the US Food and Drug Administration (FDA) Snapshot algorithm.[16] Secondary endpoints included the proportion of participants with an

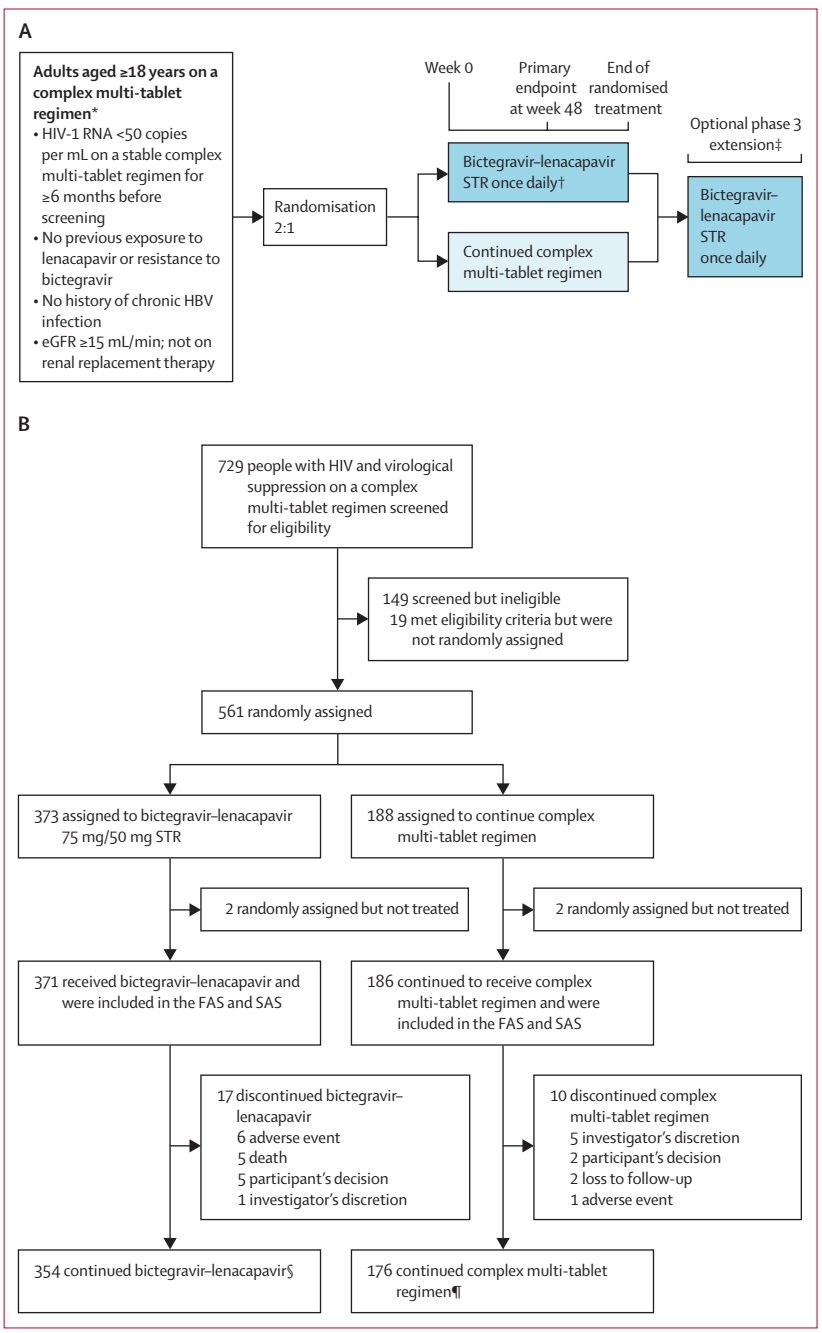

Figure 1: **Study design and trial profile**

eGFR=estimated glomerular filtration rate. FAS=full analysis set. HBV=hepatitis B virus. SAS=safety analysis set. STR=single-tablet regimen. *Due to antiretroviral resistance, intolerance, drug–drug interactions, or contraindication to existing STRs. †Participants received an oral loading dose of lenacapavir 600 mg on days 1 and 2 of treatment. ‡Participants who switch from a complex regimen in the extension phase will take the oral loading doses of lenacapavir. §Study was ongoing in 358 participants in the bictegravir–lenacapavir group; 13 participants discontinued the study (due to adverse event [n=6], death [n=5], or consent withdrawal [n=2]). ¶Study was ongoing in 177 participants in the complex regimen group; nine participants discontinued the study (due to consent withdrawal [n=3], investigator's discretion [n=3], loss to follow-up [n=2], or adverse event [n=1]).

	Bictegravir–lenacapavir (n=371)	Complex regimen (n=186)	Total (N=557)
Age, median (range), years	60 (22–84)	60 (24–75)	60 (22–84)
Age ≥55 years	288 (78%)	139 (75%)	427 (77%)
Sex assigned at birth			
Male	307 (83%)	150 (81%)	457 (82%)
Female	64 (17%)	36 (19%)	100 (18%)
Gender identity			
Cisgender	361 (97%)	179 (96%)	540 (97%)
Transgender	3 (1%)	1 (1%)	4 (1%)
Non-binary or third gender	1 (<1%)	0	1 (<1%)
Other	2 (1%)	1 (1%)	3 (1%)
Not disclosed	4 (1%)	5 (3%)	9 (2%)
Race*			
Asian	16 (4%)	9 (5%)	25 (4%)
Black	64 (17%)	33 (18%)	97 (17%)
White	260 (70%)	124 (67%)	384 (69%)
Other†	12 (3%)	3 (2%)	15 (3%)
Ethnicity‡			
Hispanic or Latine	80 (22%)	42 (23%)	122 (22%)
Not Hispanic or Latine	270 (73%)	128 (69%)	398 (71%)
HIV-1 RNA ≥50 copies per mL§	13 (4%)	7 (4%)	20 (4%)
CD4 count, median (IQR), cells per µL	626 (457–836); n=366	579 (450–747); n=185	612 (456–809); n=551
CD4 count <200 cells per µL	12 (3%)	5 (3%)	17 (3%)
History of AIDS	43 (12%)	24 (13%)	67 (12%)
Duration of HIV treatment, median (IQR), years	28·3 (21·6–32·3); n=358	28·3 (21·4–31·8); n=183	28·3 (21·6–32·1); n=541
Historical resistance mutations¶‖			
NRTI	247 (67%)	128 (69%)	375 (67%)
NNRTI	203 (55%)	104 (56%)	307 (55%)
PI	151 (41%)	77 (41%)	228 (41%)
INSTI	1 (<1%)	2 (1%)	3 (1%)
Reasons for receiving complex regimen¶			
History of antiretroviral resistance	297 (80%)	153 (82%)	450 (81%)
Intolerance to components of STRs	89 (24%)	39 (21%)	128 (23%)
Contraindication to STRs	23 (6%)	10 (5%)	33 (6%)
Number of antiretroviral pills per day, median (range)	3·0 (2·0–11·0)	3·0 (2·0–9·0)	3·0 (2·0–11·0)
Number of antiretroviral pills per day			
2	152 (41%)	74 (40%)	226 (41%)
3	96 (26%)	48 (26%)	144 (26%)
4	40 (11%)	23 (12%)	63 (11%)
≥5	83 (22%)	41 (22%)	124 (22%)
Number of antiretrovirals in complex regimen, median (range)**	2·0 (2·0–5·0)	3·0 (2·0–6·0)	3·0 (2·0–6·0)
Highest dosing frequency			
Daily	219 (59%)	120 (65%)	339 (61%)
Twice daily	152 (41%)	66 (35%)	218 (39%)
Select comorbidities¶††			
Dyslipidaemia	244 (66%)	133 (72%)	377 (68%)
Hypertension	190 (51%)	90 (48%)	280 (50%)
Hyperglycaemia or diabetes	91 (25%)	42 (23%)	133 (24%)
Chronic kidney disease	49 (13%)	29 (16%)	78 (14%)

(Table 1 continues on next page)

HIV-1 RNA viral load of less than 50 copies per mL (US FDA Snapshot algorithm)[16] at week 48, change from baseline in CD4 cell count at week 48, and the proportion of participants experiencing treatment-emergent adverse events (TEAEs) through week 48. Vital signs (including bodyweight) and laboratory analyses (including fasting lipid concentrations) were performed throughout the study. Adverse events were coded according to the Medical Dictionary for Regulatory Activities. Adverse events and laboratory abnormalities were graded using the Division of AIDS Toxicity Grading Scale, version 2.1. Patient-reported treatment satisfaction was an exploratory endpoint.

Statistical analysis

The week-48 primary analysis was conducted after all participants either completed their week-48 visit or prematurely discontinued study treatment. For the primary endpoint, a sample size of 546 participants (randomly assigned in a 2:1 ratio to the bictegravir–lenacapavir or complex regimen group) was estimated to provide at least 90% power to detect non-inferiority, assuming that 2% of participants in both treatment groups had an HIV-1 RNA viral load of 50 copies per mL or higher at week 48, a non-inferiority margin of 4% for a 0·025 one-sided significance level. To account for multiplicity (two interim analyses for the primary endpoint were performed before this analysis), the primary efficacy endpoint analysis alpha level was adjusted to 0·04998 (95·002% CI). If the upper bound of the two-sided 95·002% CI of the treatment difference in proportion of participants with an HIV-1 RNA viral load of 50 copies per mL or higher at week 48 was less than 4%, non-inferiority of bictegravir–lenacapavir to complex regimens was established. The proportion of participants with an HIV-1 RNA viral load of 50 copies per mL or higher at week 48 was summarised by treatment group and by visit using missing=failure and missing=excluded approaches, as detailed in the appendix (p 15). Safety data were reported descriptively.

Efficacy outcomes were analysed in the full analysis set, which included all randomly assigned participants who received any dose of assigned treatment; participants were grouped according to the treatment they were assigned to. Safety outcomes were analysed in the safety analysis set, which included all randomly assigned participants who received any dose of assigned treatment; participants were grouped according to the treatment they received. Adverse events were reported throughout the study period non-systematically and were reviewed by an Independent Safety Monitoring Committee. TEAEs were summarised by the number and percentage of participants who experienced at least one TEAE. No statistical comparisons were performed for safety.

Analyses were conducted using SAS, version 9.4. Details of statistical analyses, including handling of missing data, are included in the appendix (pp 15–16).

Role of the funding source
The study sponsor, Gilead Sciences (Foster City, CA, USA), played a role in the study design; data collection, analysis, and interpretation; decision to publish; and preparation of the manuscript.

Results
Between Jan 29 and Sept 26, 2024, 729 participants were screened (figure 1B); 557 were randomly assigned and received at least one dose of study treatment: 371 switched to bictegravir–lenacapavir and 186 continued their complex regimen and were included in the full analysis set and safety analysis set. Two participants in each study group were randomly assigned but not treated and were excluded from the analysis. Baseline characteristics were balanced between groups (table 1). At baseline, median age was 60 years (range 22–84), 100 (18%) of 557 participants were assigned female at birth, 97 (17%) were Black, and 122 (22%) were Hispanic or Latine; 377 (68%) had dyslipidaemia, 280 (50%) hypertension, 133 (24%) hyperglycaemia or diabetes, and 78 (14%) chronic kidney disease; 298 (54%) had two or more of these comorbidities and 339 (61%) were taking two or more concomitant medications. Median duration of HIV treatment was 28 years (IQR 22–32). Baseline complex regimen consisted of a median of three antiretroviral pills per day (range 2–11), and 218 (39%) participants were taking antiretroviral pills twice daily. The most common reason for receiving a complex regimen was a history of resistance (450 [81%] participants), followed by intolerance to components of currently available STRs (128 [23%]) and contraindications to STRs (33 [6%]). The proportion of participants randomly assigned by country was balanced between treatment groups according to the stratification by geographical region (appendix p 18).

Participants were receiving a broad range of complex regimens at baseline (figure 2); 427 (77%) of 557 were taking a regimen that included a PI. The most common regimen was PI plus INSTI, either alone (166 [30%]) or with an NRTI (135 [24%]).

At week 48, three (1%) participants in the bictegravir–lenacapavir group and two (1%) in the complex regimen group had an HIV-1 RNA viral load of 50 copies per mL or higher (difference −0·3% [95·002% CI −2·3 to 1·8]; table 2). These results met the prespecified non-inferiority criteria for the primary endpoint. At week 48, 356 (96%) participants in the bictegravir–lenacapavir group and 174 (94%) in the complex regimen group had an HIV-1 RNA viral load of less than 50 copies per mL. Data were not available in the week-48 analysis window for a total of 12 (3%) participants in the bictegravir–lenacapavir group and ten (5%) participants in the complex regimen group. Of these, seven (2%) participants in the bictegravir–lenacapavir group and one (1%) participant in the complex regimen group discontinued study drug due to adverse events or death (two deaths in the bictegravir–lenacapavir group contributed to this category; neither were deemed related to study drug; the one discontinuation in the complex regimen group in this category was due to an adverse event); five (1%) participants in the bictegravir–lenacapavir group and eight (4%) participants in the complex regimen group also discontinued due to other reasons but with last available HIV-1 RNA viral load below 50 copies per mL; one participant in the complex regimen group had missing data during the analysis window but was still on study drug. Results were consistent when using missing=excluded and missing=failure analyses (table 2). CD4 cell count remained stable in both groups; median change in CD4 count from baseline to week 48 was +18 cells per µL (IQR −72 to 98) in the bictegravir–lenacapavir group and −12 (−82 to 93) in the complex regimen group (difference in change +19·0 [95% CI −11·6 to 49·5]; p=0·22; appendix p 19).

	Bictegravir–lenacapavir (n=371)	Complex regimen (n=186)	Total (N=557)
(Continued from previous page)			
Number of select comorbidities			
1	95 (26%)	53 (28%)	148 (27%)
≥2	202 (54%)	96 (52%)	298 (54%)
Select concomitant medications‡‡			
Antidiabetic agents	84 (23%)	44 (24%)	128 (23%)
Antihypertensive agents	203 (55%)	101 (54%)	304 (55%)
Lipid-lowering agents	262 (71%)	134 (72%)	396 (71%)
Antidiabetic and antihypertensive agents	58 (16%)	36 (19%)	94 (17%)
Antidiabetic, antihypertensive, and lipid-lowering agents	50 (13%)	32 (17%)	82 (15%)
Number of select concomitant medications			
1	62 (17%)	50 (27%)	112 (20%)
≥2	237 (64%)	102 (55%)	339 (61%)
Creatinine clearance, median (IQR), mL/min	82·9 (66·4–103·2)	82·4 (65·4–100·2)	82·8 (66·0–102·6)
>15 to ≤30	3 (1%)	3 (2%)	6 (1%)
>30 to <60	56 (15%)	26 (14%)	82 (15%)
≥60	312 (84%)	157 (84%)	469 (84%)

Data are n (%) unless otherwise specified. ATC=Anatomical Therapeutic Chemical Medical Class Level. INSTI=integrase strand-transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleos(t)ide reverse transcriptase inhibitor. PI=protease inhibitor. STR=single-tablet regimen. *Local regulators did not allow the collection of race information for 36 participants (19 in the bictegravir–lenacapavir group and 17 in the complex regimen group). †Category includes American Indian or Alaska Native, Native Hawaiian, Pacific Islander, and other. ‡Local regulators did not allow the collection of ethnicity information for 37 participants (21 in the bictegravir–lenacapavir group and 16 in the complex regimen group). §Participants had screening HIV-1 RNA <50 copies per mL, but baseline HIV-1 RNA ≥50 copies per mL. ¶Categories are not mutually exclusive. ||Investigators were asked to document previous resistance data from available historical HIV-1 genotype and/or phenotype reports. No resistance testing was performed at baseline; NRTI, NNRTI, PI, and INSTI data were not available for 75, 79, 78, and 197 participants in the bictegravir–lenacapavir group, and 44, 46, 50, and 100 participants in the complex regimen group, respectively. **Multiple reported antiretroviral therapies were counted only once per participant for each drug name and each drug class. ††Grouped terms on standardised Medical Dictionary for Regulatory Activities query narrow search. ‡‡Antidiabetic agents included drugs with WHO ATC2 "drugs used in diabetes"; antihypertensive agents included drugs with WHO ATC2 "agents acting on the renin–angiotensin system", "antihypertensives" (excluding ATC3 "other antihypertensives"), "beta-blocking agents", "calcium channel blockers", or "diuretics"; lipid-lowering agents included drugs with WHO ATC2 "drugs used in diabetes".

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

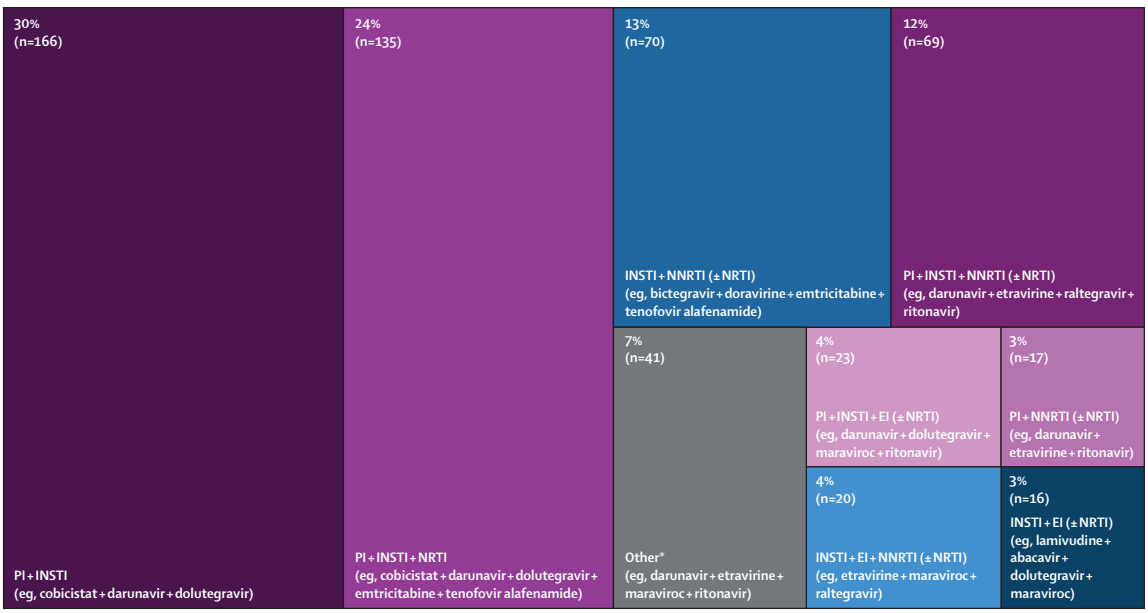

Figure 2: **Diversity of complex regimens at baseline (safety analysis set)**
Most commonly used regimen is noted in parentheses. EI=entry inhibitor. INSTI=integrase strand-transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleos(t)ide reverse transcriptase inhibitor. PI=protease inhibitor. *List of regimens comprising "Other" category is provided in the appendix (p 17).

	Bictegravir–lenacapavir (n=371)	Complex regimen (n=186)	Difference for bictegravir–lenacapavir *vs* complex regimen (95·002% CI)	Difference for bictegravir–lenacapavir *vs* complex regimen (95% CI)
US Food and Drug Administration Snapshot algorithm (full analysis set)*				
HIV-1 RNA ≥50 copies per mL	3 (1%)	2 (1%)	−0·3% (−2·3 to 1·8)	..
HIV-1 RNA <50 copies per mL	356 (96%)	174 (94%)	2·4% (−1·8 to 6·6)	..
No virological data	12 (3%)	10 (5%)	..	..
Discontinued due to adverse event or death	7 (2%)†	1 (1%)‡	..	..
Discontinued study due to other reasons§ and last available HIV-1 RNA was <50 copies per mL	5 (1%)	8 (4%)	..	..
Had missing data during the analysis window but was still on study drug	0	1 (1%)	..	..
Missing=excluded analysis (full analysis set with non-missing HIV-1 RNA value at week-48 visit, while on treatment)*				
HIV-1 RNA <50 copies per mL	356/359 (99%)	174/176 (99%)	..	0·3% (−1·9 to 2·5)
HIV-1 RNA ≥50 copies per mL	3/359 (1%)	2/176 (1%)	..	..
50 to <200 copies per mL	2/359 (1%)	1/176 (1%)	..	..
200 to <1000 copies per mL	1/359 (<1%)	1/176 (1%)	..	..
Missing=failure analysis (full analysis set, while on treatment)*				
HIV-1 RNA <50 copies per mL	356/371 (96%)	174/186 (94%)	..	2·4% (−1·8 to 6·6)
HIV-1 RNA ≥50 copies per mL	3/371 (1%)	2/186 (1%)	..	..
50 to <200 copies per mL	2/371 (1%)	1/186 (1%)	..	..
200 to <1000 copies per mL	1/371 (<1%)	1/186 (1%)	..	..
Missing data	12/371 (3%)	10/186 (5%)	..	..

Data are n (%) or n/N (%) unless otherwise specified. *Differences in percentages of participants between treatment groups (bictegravir–lenacapavir minus complex regimen) and two-sided CIs were constructed based on Mantel–Haenszel stratum weights and Koch variance estimator and adjusted by geographical region (USA *vs* non-USA). †Category included two deaths (neither were related to study drug) and five adverse events. ‡Category included one adverse event. §Other reasons included discontinuation of study drug due to investigator's discretion, participant's decision, loss to follow-up, non-compliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

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

Of the three participants in the bictegravir–lenacapavir group and two in the complex regimen group with a confirmed HIV-1 RNA viral load of 50 copies per mL or higher by week 48, two had a viral load below 200 copies per mL and did not qualify for resistance testing. Three met the criteria for protocol-defined confirmed virological rebound (two in the bictegravir–lenacapavir group and one in the complex regimen group) and qualified for resistance testing. No treatment-emergent resistance mutations to study drugs were detected in either treatment group.

Treatment satisfaction at baseline was similar between groups (mean HIVTSQs total score at baseline was 55 [SD 10·4] in the bictegravir–lenacapavir group and 55 [9·4] in the complex regimen group; available range 0 to 66; appendix p 20). At week 48, participants in the bictegravir–lenacapavir group reported improvement from baseline in treatment satisfaction (mean change in HIVTSQs total score, +7 [SD 10·6]), while those in the complex regimen group reported no change (0 [9·6]; appendix p 20). After switching to bictegravir–lenacapavir, mean HIVTSQc total score at week 48 was +27 (SD 9·1; available range –33 to 33).

Overall, the incidence of adverse events was similar in both groups (bictegravir–lenacapavir: 305 [82%] of 371; complex regimen: 157 [84%] of 186), with the majority being mild or moderate in severity (grade 1 or 2; table 3). 51 (14%) participants in the bictegravir–lenacapavir group and 26 (14%) in the complex regimen group experienced a grade 3 or worse adverse event. Drug-related adverse events (DRAEs) were reported by 53 (14%) participants in the bictegravir–lenacapavir group and three (2%) participants in the complex regimen group (table 3 and appendix p 21). Of these, two (1%) and zero participants, respectively, reported grade 3 or worse DRAEs. One participant in the bictegravir–lenacapavir group with high fasting concentrations of glucose and lipase, and grade 1 triglyceride concentration, at baseline, experienced a serious DRAE of newly diagnosed diabetes. This participant had switched from efavirenz plus ritonavir-boosted darunavir; the event resolved after switching back to original treatment regimen. Six (2%) participants discontinued bictegravir–lenacapavir due to adverse events; one participant experienced nausea, dizziness, headache, alopecia, and worsening fatigue; one experienced headache and hypoaesthesia; one experienced erectile dysfunction and worsening hypertension; and one experienced each of the following: cerebrovascular accident, diabetes (same participant as above), and HBV viraemia; all except the cerebrovascular accident, HBV viraemia, and hypoaesthesia were deemed related to study drug. One (1%) participant discontinued their complex regimen due to an adverse event of pulmonary embolism (due to interaction of boosted PI component of regimen with anticoagulants); this was not deemed related to the complex regimen. Five deaths occurred during the study in the bictegravir–lenacapavir group (one due to each of the following: liver failure secondary to metastatic cancer, sudden cardiac arrest, and oropharyngeal cell carcinoma; two due to unknown cause); none were deemed related to bictegravir–lenacapavir. No difference in the overall safety profile was observed for participants by level of renal function, and renal-related adverse events were infrequent (appendix p 22).

	Bictegravir–lenacapavir (n=371)	Complex regimen (n=186)
Adverse event—any grade	305 (82%)	157 (84%)
Grade ≥3 adverse event	51 (14%)	26 (14%)
DRAE—any grade	53 (14%)	3 (2%)
Grade ≥3 DRAE	2 (1%)*	0
Serious adverse event	52 (14%)	22 (12%)
Serious DRAE	1 (<1%)†	0
Adverse event leading to discontinuation of study drug	6 (2%)‡	1 (1%)§
Adverse event occurring in ≥5% of participants in either group		
Upper respiratory tract infection	34 (9%)	24 (13%)
Nasopharyngitis	26 (7%)	17 (9%)
Diarrhoea	22 (6%)	11 (6%)
Headache	28 (8%)	4 (2%)
Cough	18 (5%)	11 (6%)
Arthralgia	19 (5%)	8 (4%)
Hypertension	21 (6%)	6 (3%)
COVID-19	20 (5%)	6 (3%)
Death¶	5 (1%)‖	0

Data are n (%). Median duration of exposure was 65·9 weeks (IQR 56·6–74·0) for the bictegravir–lenacapavir group and 65·9 weeks (55·6–73·9) for the complex regimen group. Includes all randomly assigned participants who received any dose of assigned treatment grouped according to the treatment they received. DRAE=drug-related adverse event. HBV=hepatitis B virus. *Diabetes and maculopapular rash. †Newly diagnosed diabetes on day 76 in a participant with a high baseline fasting glucose concentration (100 mg/dL); resolved on day 173 after switching back to baseline regimen of efavirenz plus ritonavir-boosted darunavir on day 103. ‡One participant experienced nausea, dizziness, headache, alopecia, and worsening fatigue; one participant experienced headache and hypoaesthesia; one participant experienced erectile dysfunction and worsening hypertension; and one participant experienced each of the following: cerebrovascular accident, diabetes, and HBV viraemia; all but hypoaesthesia, HBV viraemia, and cerebrovascular accident were deemed related to study drug. §Due to pulmonary embolism; this was not deemed related to study drug. ¶Includes any that occurred during the study. ‖Due to unknown cause (n=2; one participant had a history of arterial hypertension and one a history of hypercholesterolaemia; no autopsy was performed on these participants), cardiac arrest (n=1), metastatic neoplasm (n=1), and respiratory failure (n=1); no deaths were deemed related to study drug.

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

Laboratory abnormalities occurred in 341 (92%) of 371 participants in the bictegravir–lenacapavir group and 178 (96%) of 186 participants in the complex regimen group (appendix p 23); most were grade 1 or 2 in severity. The most common grade 3 or worse abnormalities in both groups were decreased creatinine clearance and increased direct bilirubin concentration, which were mostly transient and not clinically relevant. Vital signs were unchanged through 48 weeks.

At week 48, fasting total cholesterol, triglyceride, and LDL cholesterol concentrations, and total cholesterol:HDL cholesterol ratio improved from baseline in the bictegravir–lenacapavir versus the complex regimen group. Median changes from baseline to week 48 in the

bictegravir–lenacapavir versus complex regimen groups were: total cholesterol, –15 mg/dL versus +2 mg/dL (nominal p<0·0001); LDL cholesterol, –9 mg/dL versus +2 mg/dL (nominal p<0·0001); triglycerides, –15 mg/dL versus +4 mg/dL (nominal p=0·0008); total cholesterol:HDL cholesterol ratio, –0·3 mg/dL versus 0 mg/dL (nominal p<0·0001). HDL cholesterol remained stable in both groups (appendix p 24). Reductions in total cholesterol, LDL cholesterol, and triglyceride concentrations, and total cholesterol:HDL cholesterol ratio, with bictegravir–lenacapavir compared with complex regimens were observed from the first assessment at week 12 onwards. Bodyweight remained stable in both treatment groups through 48 weeks (median change from baseline +0·6 kg [IQR –1·1 to 2·6] and 0·0 kg [–2·0 to 2·4] in the bictegravir–lenacapavir and complex regimens groups, respectively).

Discussion

Treatment optimisation is widely recognised as the best way to ensure adherence and treatment success when managing chronic conditions such as HIV. For two decades, this has remained an unmet need for people not suitable for currently available STRs due to antiretroviral resistance. Here, we show that once-daily oral bictegravir–lenacapavir was non-inferior to complex regimens in maintaining virological suppression through 48 weeks, with similarly high suppression rates, similar adverse event rates in both groups, and increased treatment satisfaction through 48 weeks. Hence, the novel STR of bictegravir–lenacapavir offers an alternative treatment option for people on complex regimens.

With a median participant age of 60 years, this is the oldest study population ever enrolled in a registrational programme for HIV treatment.[17–20] This is particularly relevant given that advances in antiretroviral therapy have allowed people with HIV to have near-normal life expectancies; consequently, most people with HIV in high-resource countries are aged 50 years or older.[2,21] The median treatment duration of 28 years, high level of historical antiretroviral resistance (67% with NRTI resistance), and high proportion of participants on a complex regimen because of antiretroviral resistance (81%) is consistent with their extensive HIV-1 treatment experience and underscores why optimisation to currently available STRs has not been possible thus far. In addition, the study population was generally representative of people with HIV receiving complex regimens in routine care, reflecting the diverse race and ethnicity of the participating countries.

Most participants had at least one comorbidity at baseline (14% had chronic kidney disease and 50% had hypertension), 81% were taking concomitant medications for these comorbidities, three-quarters were on a complex regimen that included a PI, and a third were taking four or more antiretroviral tablets per day, all contributing to an increased risk of clinically significant drug–drug interactions and requiring active management. Additionally, the lenient eGFR cutoff of 15 mL/min (six [1%] had eGFR ≤30 mL/min and 88 [16%] had eGFR <60 mL/min) provides confidence in bictegravir–lenacapavir for those with chronic kidney disease.

Bictegravir–lenacapavir was well tolerated, and similar numbers of adverse events and serious adverse events were reported in both groups. Although the frequency of DRAEs was higher in the bictegravir–lenacapavir group than in the complex regimen group, this is consistent with an open-label trial design involving switching away from a long-standing familiar regimen.[19,22,23] Moreover, only one serious adverse event was considered related to bictegravir–lenacapavir, a newly diagnosed case of diabetes in a participant with hyperglycaemia at baseline. Only two DRAEs in the bictegravir–lenacapavir group were grade 3 or worse; rates of discontinuation due to adverse events were low overall. Switching to bictegravir–lenacapavir improved fasting lipid concentrations in a population in whom approximately 70% had a diagnosis of dyslipidaemia at baseline and over half of participants had two or more comorbidities associated with increased cardiovascular risk. These observations might indicate a potential beneficial effect of bictegravir–lenacapavir in people with HIV and metabolic or cardiovascular risk factors.

Participants who switched to bictegravir–lenacapavir from a complex regimen reported greater treatment satisfaction than those continuing a complex regimen. This confirms that participants found multi-tablet treatment regimens more challenging. These challenges could over time jeopardise adherence (enhanced adherence has been reported with STRs)[2,6–8] and retention in care, which are both necessary to maintain virological suppression and avoid emergent resistance. Switching to bictegravir–lenacapavir STR reduced the pill burden (a third of participants were taking four or more antiretroviral pills per day, with a maximum of 11 pills per day) and thereby the risk of drug–drug interactions. Taken together, this highlights the importance of continuing to optimise treatment in the face of previous resistance, comorbidities, and preferences.

This trial had limitations. This was an open-label trial, but, given the wide range of antiretrovirals included in the complex regimens and the importance of patient satisfaction for regimen optimisation, a blinded design was impractical. A separate blinded phase 3 trial (NCT06333808) comparing outcomes after switching from bictegravir–emtricitabine–tenofovir alafenamide to bictegravir–lenacapavir is ongoing. Longer-term efficacy and safety outcomes of bictegravir–lenacapavir will be assessed through continued follow-up. However, bictegravir has an established safety profile in both clinical and real-world studies with bictegravir–emtricitabine–tenofovir alafenamide[10,24–27] and lenacapavir has been studied extensively in individuals receiving pre-exposure prophylaxis.[28,29] Of note, participants with

previous or chronic HBV infection were excluded; vaccination and routine surveillance should be conducted according to current guidelines for individuals without HBV immunity.[2,4,11] Future work might be required to study how different approaches to delivery of clinical care (eg, across different health-care systems) have impacted these findings.

In this phase 3 trial, once-daily oral bictegravir–lenacapavir was non-inferior to complex regimens in maintaining HIV-1 suppression. Bictegravir–lenacapavir was generally well tolerated, led to improvement in the lipid profile, and provided greater treatment satisfaction among participants who switched from a complex regimen. This STR could present the first opportunity to optimise treatment while maintaining virological suppression in people taking complex regimens who have not benefitted from available STRs due to antiretroviral resistance or other reasons. In particular, bictegravir–lenacapavir could offer a more suitable long-term treatment option for an ageing population with cardiometabolic comorbidities, declining GFR, and a greater risk of polypharmacy.

Contributors

CO, PJR, MH, CG, MHL, BT, TL, MO, MB, JS, MRa, SS, KM, H-CT, JSB, and PC contributed to data collection. JMM-R and PS contributed to study design and data analysis or interpretation. CO, XZ, KA, KP, NM, and MRh contributed to data analysis or interpretation. All authors contributed to drafting or revising of the manuscript, approved the final version for submission, and agree to be accountable for all aspects of the work. CO, XZ, KA, JMM-R, and PS directly accessed and verified the study data. All authors had full access to the study data and shared final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

CO received grants (paid to her institution) from Gilead Sciences, MSD, and ViiV Healthcare; received consulting fees for advisory boards and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Bavarian Nordic, Gilead Sciences, GSK, MSD, and ViiV Healthcare; received support for attending meetings and/or travel from Bavarian Nordic, Gilead Sciences, and ViiV Healthcare; and is a governing council member of the International AIDS Society (unpaid). PJR received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Gilead Sciences and ViiV Healthcare. MH received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events, and support for attending meetings and/or travel from, and participated on advisory boards for, Gilead Sciences, Merck, and ViiV Healthcare. CG received consulting fees from Gilead Sciences, Merck, and ViiV Healthcare; and received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Gilead Sciences and ViiV Healthcare. MHL received research grants (paid to his institution) from Gilead Sciences, and participated on advisory boards for Gilead Sciences and ViiV Healthcare. BT received consulting fees, payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events, and support for attending meetings and/or travel, from Gilead Sciences and ViiV Healthcare. TL received grants or contracts from AbbVie, Charité Berlin, Deutsche Leberstiftung, Gilead Sciences, GSK/ViiV Healthcare, Immuno Therapeutics Heidelberg, Janssen, Moderna, and MSD. MO received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Gilead Sciences; received support for attending meetings and/or travel from Gilead Sciences, Janssen, and ViiV Healthcare; participated on a data safety monitoring or advisory board for Gilead Sciences; and is an unpaid member of ASHM Board and Australian ARV Guidelines Committee. MB received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Gilead Sciences, GSK, and ViiV Healthcare; received support for attending meetings and/or travel from Gilead Sciences and ViiV Healthcare; and participated on data safety monitoring or advisory boards for Gilead Sciences, GSK, and ViiV Healthcare. JS received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Gilead Sciences, Merck, Thera, and ViiV Healthcare. MRa received consulting fees from Gilead Sciences, Shionogi, and ViiV Healthcare; and received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AbbVie, Gilead Sciences, and ViiV Healthcare. SS received research grants and support for clinical trials (paid to her institution) from Janssen, Merck, and the South African Medical Research Council; received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from ViiV Healthcare; received support for attending meetings and/or travel from Merck; received a drug donation to her institution from ViiV Healthcare; and participated on an advisory board for AbbVie. KM received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from, and served on an advisory board for, Epividian, Gilead Sciences, Janssen, Merck, and ViiV Healthcare. H-CT received honoraria for a lecture at an international congress, and travel and registration support for attending an international meeting, from Gilead Sciences. JSB received research grants or contracts from Chem Bio Diagnostics, Gilead Sciences, and Moderna; and consulting fees and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AbbVie. XZ, KA, KP, NM, JMM-R, PS, and MRh are employees of Gilead Sciences and own employee stock grants. PC received research grants and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from ViiV Healthcare; and consulting fees from Gilead Sciences, Merck, and ViiV Healthcare.

Data sharing

Gilead Sciences shares 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 must also include a statistician. Approval of such requests is at Gilead Sciences' discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to DataSharing@gilead.com. The clinical study protocol and statistical analysis plan are provided in the appendix available with the online version of the article.

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