Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial

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Summary

Background Antiretroviral agents with novel mechanisms and dosing intervals could expand treatment options for people with HIV. Lenacapavir, an inhibitor of capsid protein that makes use of a unique mechanism, can be administered orally or subcutaneously. We sought to explore the efficacy of lenacapavir in various combination regimens as initial and maintenance therapy for HIV.

Methods In a phase 2, randomised, open-label, ongoing study at 41 investigational sites in the USA and Dominican Republic, we randomly assigned adults with HIV who had not previously received antiretrovirals to four groups (2:2:2:1). Randomisation was stratified by plasma HIV-1 RNA load (≤100 000 or >100 000 copies per mL) at screening. Groups 1 and 2 both received lenacapavir (927 mg) subcutaneously every 26 weeks (after 2 weeks of oral loading [600 mg on days 1 and 2, followed by 300 mg on day 8]) with oral daily emtricitabine (200 mg) and tenofovir alafenamide (25 mg) for 28 weeks followed by subcutaneous lenacapavir (927 mg) plus oral daily tenofovir alafenamide (25 mg, group 1) or bictegravir (75 mg, group 2). Group 3 received oral daily lenacapavir (600 mg on days 1 and 2, followed by 50 mg daily) with emtricitabine (200 mg) and tenofovir alafenamide (25 mg). Group 4 received oral daily bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg). Participants and investigators were not masked to group assignment. The primary endpoint was the percentage of participants with virological suppression (HIV-1 RNA <50 copies per mL) at week 54, analysed in the full analysis set (all randomly assigned participants who received at least one dose of study drug) using only on-treatment data. The safety outcome measures were incidences of treatment-emergent adverse events and graded laboratory abnormalities, analysed in the full analysis set. This study is registered at ClinicalTrials.gov, NCT04143594.

Findings Between Nov 22, 2019, and Aug 27, 2020, 249 people with HIV were screened, 183 participants were randomly assigned and 182 received a dose of antiretroviral drugs (52 in group 1, 53 in group 2, 52 in group 3, and 25 in group 4). 22 participants did not complete the full study course (five in group 1, 12 in group 2, four in group 3, and one in group 4). At week 54, virological suppression was 90% (47 of 52 patients) for group 1 (difference *vs* group 4: –2·6%, 95% CI –18·4 to 13·2), 85% (45 of 53) for group 2 (–7·1%, –23·4 to 9·3), 85% (44 of 52) for group 3 (–7·2%, –23·5 to 9·1), and 92% (23 of 25) for group 4. The most frequent non-injection-site adverse events with lenacapavir (subcutaneous or oral) were headache (13%, 21 of 157) and nausea (13%, 21 of 157). The most common lenacapavir-related injection-site reactions were erythema (27%, 28 of 105), swelling (23%, 24 of 105), and pain (19%, 20 of 105), which were generally mild or moderate. No serious adverse event related to study treatment occurred. Three participants discontinued subcutaneous lenacapavir because of grade 1 injection-site reactions (two for induration and one for erythema or swelling).

Interpretation Lenacapavir warrants further investigation as a potential antiretroviral used orally and as injection in combination with other antiretroviral drugs.

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Introduction

Worldwide, approximately 38 million people have HIV.[1] Standard-of-care HIV treatment, with a combination of antiretroviral agents, suppresses viral replication to below detectable limits. Successful antiretroviral therapy increases CD4 cell counts, prolongs lifespans, and prevents transmission.[2,3] Although combination antiretroviral therapy is effective and well tolerated, life-long daily adherence can be difficult to maintain, and selection of viral resistance poses a risk to sustained successful therapy.[4,5] Novel antiretroviral agents and dosing intervals could improve long-term treatment

Research in context

Evidence before this study

We searched PubMed for publications of randomised clinical trials of injectable HIV treatment from Jan 1, 2015, to Aug 15, 2022, with the search terms: "HIV" AND "treatment" AND ("subcutaneous" or "intramuscular" or "intravenous") AND "randomized". The search was limited to trials published in English. Our search yielded 339 published articles, with 15 in treatment-naive populations (generated by adding AND "NAÏVE" to the original search). Our search did not yield any publications based on clinical trials evaluating long-acting injectable agents in treatment-naive populations with HIV. Of the 15 articles, three were based on two randomised clinical trials evaluating the combination of intramuscular cabotegravir (an integrase transfer inhibitor) and rilpivirine (a non-nucleoside reverse transcriptase inhibitor) as a maintenance regimen in participants with HIV who were virologically suppressed. The remaining 12 articles were not relevant because they were not based on randomised clinical trials, they did not study people with HIV, or the investigational agents were administered orally once daily. Efficacy and safety of lenacapavir with optimised background regimen in viraemic people with multidrug-resistant HIV infection have been investigated, and treatment leads to a high rate of virological suppression with a clinically meaningful increase in the CD4 cell count.

Added value of this study

Lenacapavir is a multistage, selective inhibitor of the HIV capsid protein that makes use of a unique mechanism and it is flexible in terms of route of administration (oral or injectable) and dosing interval (daily or every 6 months). The efficacy and safety of lenacapavir in people with HIV who are initiating antiretroviral treatment is unknown. This is the first active-controlled trial comparing lenacapavir in combination with other antiretrovirals with the current standard-of-care regimen in treatment-naive individuals. We show that subcutaneous lenacapavir every 26 weeks or oral daily lenacapavir administered with emtricitabine and tenofovir alafenamide for 28 weeks had similar virological suppression as treatment with bictegravir, emtricitabine, and tenofovir alafenamide. After 28 weeks, for individuals with virological suppression, the two-drug combination of subcutaneous lenacapavir with either tenofovir alafenamide or bictegravir maintained virological suppression through to 54 weeks.

Implications of all the available evidence

This phase 2 study was designed to generate exploratory clinical data of lenacapavir-containing regimens, either as part of three-drug or two-drug regimens. The efficacy and safety results from this study support future development of lenacapavir-containing regimens. Lenacapavir can meet the diverse needs of people with HIV with its flexible route of administration (injectable or oral) and dosing interval (daily or every 26 weeks).

adherence and expand treatment options for people with HIV.

Lenacapavir is a novel, multistage, selective inhibitor of the HIV capsid protein that makes use of a unique mechanism. By binding to neighbouring capsid subunits, lenacapavir disrupts multiple phases of the viral replication cycle.[6,7] Lenacapavir is highly potent, with a low clearance and slow-release kinetics, allowing oral dosing daily to weekly or subcutaneous dosing as infrequently as every 6 months.[7–10] In people who are highly treatment experienced, with multi-drug resistant HIV-1, subcutaneous lenacapavir in combination with other antiretroviral agents led to a high rate of virological suppression and was well tolerated.[11]

See Online for appendix

We designed the CALIBRATE phase 2 trial to generate exploratory clinical data to support the future development of lenacapavir-containing regimens. We assessed the efficacy and safety of subcutaneous and oral lenacapavir in combination with oral antiretroviral agents as initial antiretroviral therapy for people with HIV.

Methods

Study design

We did a randomised, open-label, active-controlled, induction-maintenance study at 41 investigational sites in the USA and Dominican Republic. The trial was approved by the institutional review board or ethics committee at all sites and was conducted in compliance with international laws and guidelines. Duration of treatment is at least 80 weeks; the present analysis includes efficacy and safety data up to week 54 (Oct 27, 2021).

Participants

We screened and enrolled participants at the selected investigational sites. Eligible individuals (appendix p 3) had not previously taken antiretroviral therapy for HIV treatment and were older than 18 years with plasma HIV-1 RNA of at least 200 copies per mL and CD4 cell counts of at least 200 cells per µL without hepatitis B or C infection. All participants provided written informed consent.

Randomisation and masking

Using an interactive web response system, the investigator or designee randomly assigned participants (2:2:2:1) to four treatment groups (figure 1) before or during the day 1 visit. Randomisation was stratified by plasma HIV-1 RNA load at screening (≤100 000 or >100 000 copies per mL). Participants and investigators were not masked to group assignment.

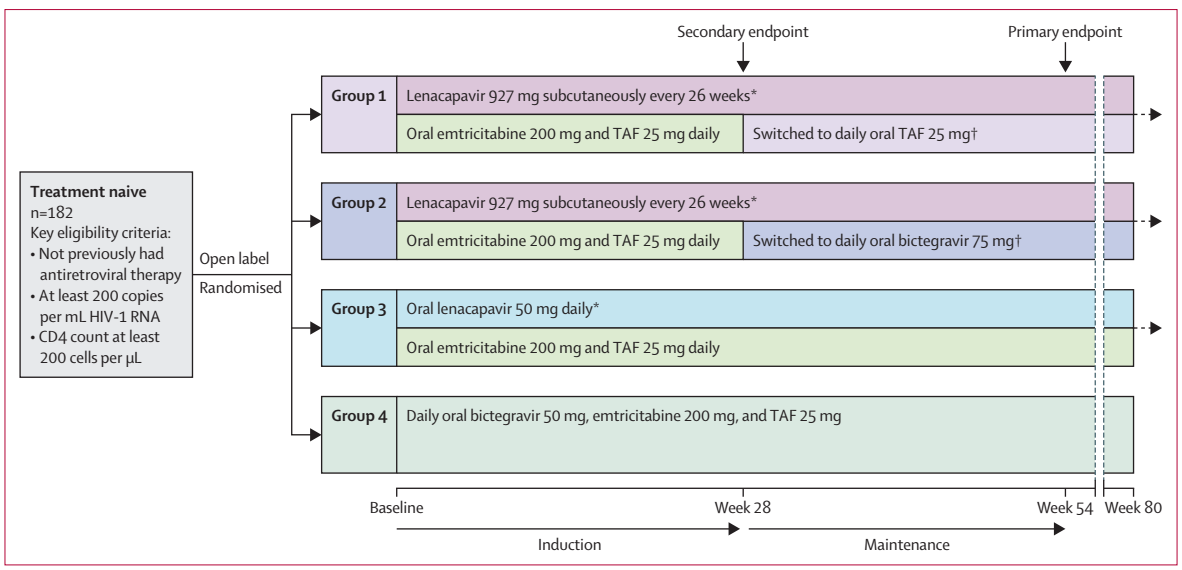

Figure 1: **Overall study design**
TAF=tenofovir alafenamide. *Following an oral loading dose. †Participants in groups 1 and 2 needed HIV-1 RNA results of less than 50 copies per mL at weeks 16 and 22 to continue in the study; those with 50 copies per mL or more of HIV-1 RNA discontinued the study before or at week 28.

Procedures

At screening, laboratory analyses (ie, haematology, chemistry, and urinalysis; and serum pregnancy test for women), HIV-1 RNA, CD4 cell count, vital signs, electrocardiogram, complete physical examination, and estimated glomerular filtration rate were done, and hepatitis B virus and hepatitis C virus serologies were analysed. Analysis of the participant's HIV-1 resistance to support eligibility was also completed.

Groups 1 and 2 had oral loading of lenacapavir 600 mg (2×300 mg tablets) on days 1 and 2 and 300 mg on day 8. Both groups received oral emtricitabine (200 mg) and tenofovir alafenamide (25 mg) daily from day 1 to week 27 and subcutaneous lenacapavir (927 mg; 309 mg per mL; 2×1·5 mL) every 26 weeks from day 15. The oral loading before subcutaneous lenacapavir was necessary to rapidly reach therapeutic concentrations. After the initial 28-week induction period, those with less than 50 copies per mL HIV-1 RNA at week 16 and week 22 switched at week 28 from emtricitabine and tenofovir alafenamide to just tenofovir alafenamide (25 mg oral daily, group 1) or to bictegravir (75 mg oral daily, group 2), while continuing lenacapavir. The efficacy and safety of bictegravir (75 mg) as a single agent in combination with emtricitabine and tenofovir alafenamide was previously evaluated in a phase 2 study, and the exposure of bictegravir (75 mg) as a single agent was confirmed to be similar to that of combined bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) in a phase 3 study.[12,13] Group 3 received 600 mg oral lenacapavir on days 1 and 2 and 50 mg daily from day 3 to week 54 with oral emtricitabine (200 mg) and tenofovir alafenamide (25 mg) daily from day 1 to week 54. Group 4 received oral bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) daily for 54 weeks, for comparison of lenacapavir-containing regimens against standard-of-care daily oral therapy.

Participants in groups 1, 2, and 3 only had visits on day 1; day 2; day 5 (within 1 day; if possible); day 8; and day 15. All participants had a week 4 visit and attended study visits every 6 weeks until week 28. At each visit, adverse events and concomitant medications were recorded and laboratory tests and physical examinations were done.

After week 28, participant study visits occurred or will occur at weeks 38, 54, 64, and 80. After week 80, participants in group 4 will complete the study, and participants in groups 1, 2, and 3 will be given the option to receive further treatment and continue to attend visits alternating between every 10 weeks and every 16 weeks.

Outcomes

The primary efficacy endpoint was the percentage of participants with virological suppression (HIV-1 RNA <50 copies per mL) at week 54 (between days 323 and 413) as determined by the US Food and Drug Administration snapshot algorithm.[14] Secondary endpoints were the proportion of participants with less than 50 copies per mL of HIV-1 RNA at weeks 28, 38, and 80; and the change from baseline in $\log_{10}$ HIV-1 RNA and in CD4 cell counts at weeks 28, 38, 54, and 80. Change in CD4 cell counts at week 54 is provided in this Article, but changes at weeks 28 and 38 are not. Week 80 data for all endpoints are not available at this time as the trial is ongoing.

There were three virological failure criteria. The first criterion was suboptimal virological response, defined as

having two consecutive visits with HIV-1 RNA of 50 copies per mL or more and a decline of less than 1 $\log_{10}$ at week 10. Second was virological rebound, defined as having two consecutive visits with HIV-1 RNA of 50 copies per mL or more after reaching less than 50 copies per mL, or two consecutive visits with an increase from nadir of more than 1 $\log_{10}$. Third was 50 copies per mL of HIV-1 RNA or more at study discontinuation.

For all participants, baseline resistance in HIV protease, reverse transcriptase, and integrase were assessed at screening by population genotyping using GenoSure MG, GenoSure Integrase, or GeneSeq Integrase assays (Monogram Biosciences, South San Francisco, CA, USA). HIV-1 capsid genotypic and phenotypic data at study entry were identified using the GenoSure Gag-Pro and PhenoSense Gag-Pro assays (Monogram Biosciences). The GenoSure Gag-Pro assay uses next-generation sequencing to detect codon variants present at a frequency greater than 10%. Subsequent resistance testing was done at Monogram Biosciences and consisted of genotypic and phenotypic analyses of HIV capsid, protease and reverse transcriptase (PhenoSense GT assay), and integrase (PhenoSense IN and GeneSeq IN assays) at the virological failure timepoints. In incidents of assay failure or for exploratory analyses, genotyping was tested at Seq-IT (Kaiserslautern, Germany), at a mutation detection threshold of at least 2%. Among participants who experienced virological failure, capsid resistance development was analysed in samples from either the initial or confirmation visit, whereas protease, reverse transcriptase, and integrase resistance development were analysed in confirmation visit samples.

Concentrations of lenacapavir, tenofovir alafenamide, tenofovir, and bictegravir in plasma samples and concentrations of tenofovir diphosphate in human peripheral blood mononuclear cells were identified with fully validated high-performance

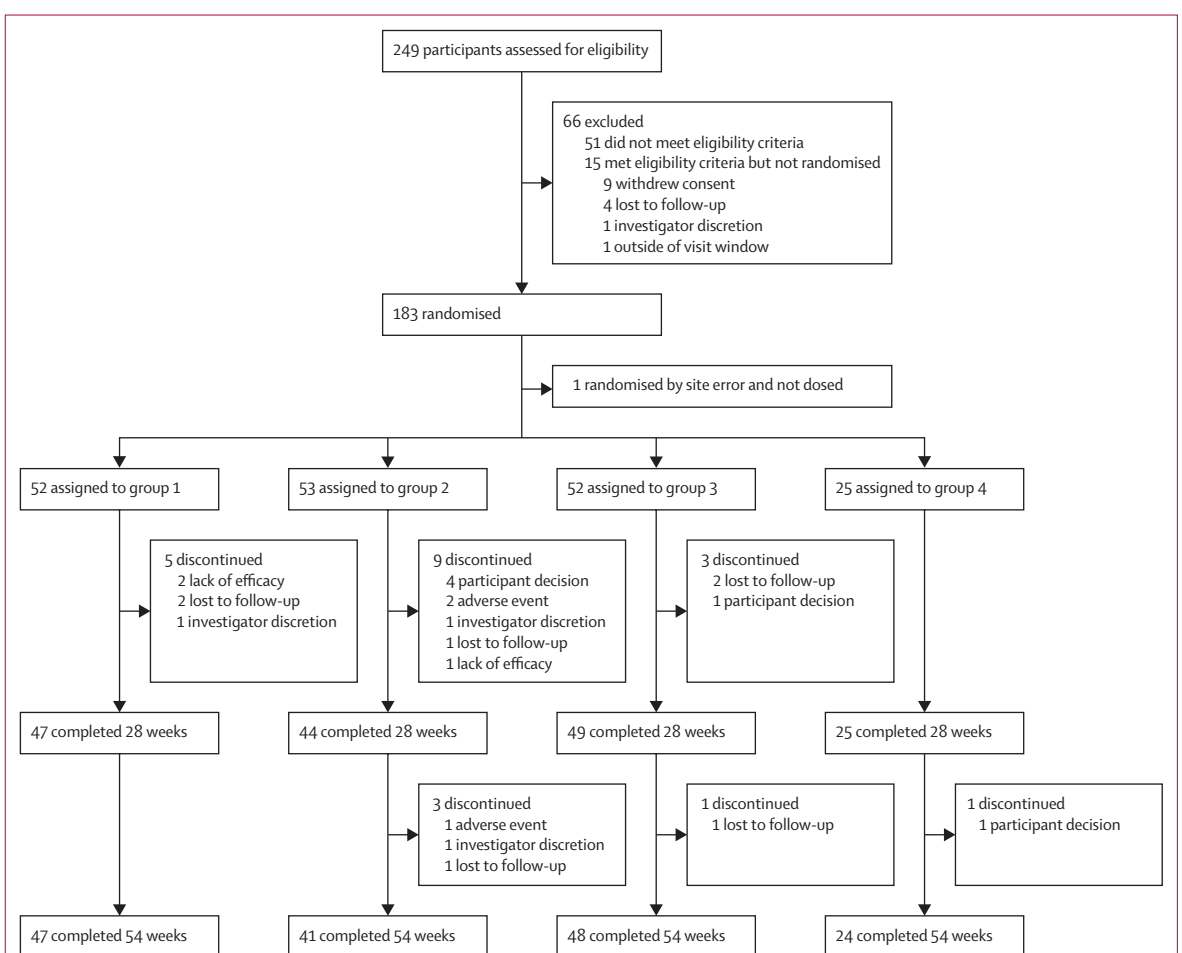

Figure 2: **Trial profile**
Participants in group 1 started subcutaneous lenacapavir with emtricitabine and tenofovir alafenamine and went on to continue tenofovir alafenamide; participants in group 2 started subcutaneous lenacapavir with emtricitabine and tenofovir alafenamine and went on to have bictegravir; participants in group 3 received oral lenacapavir with emtricitabine and tenofovir alafenamine; and participants in group 4 received bictegravir, emtricitabine, and tenofovir alafenamide.

liquid chromatography-tandem mass spectroscopy bioanalytical methods.

The safety secondary endpoints were incidences of treatment-emergent adverse events and graded laboratory abnormalities. Safety assessments included monitoring of adverse events and concomitant medications, clinical laboratory analyses, vital sign measurements, electrocardiograms, and physical examinations. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 23.1).

Statistical analysis

A sample size of 50 participants for each lenacapavir-containing regimen (groups 1 to 3) was chosen to estimate the response rate of HIV RNA of less than 50 copies per mL at week 54. Given the exploratory nature of this phase 2 trial, the sample size was chosen on the basis of practical consideration and past experience for similar studies. We included twice as many participants in each group receiving lenacapavir as were in the control group to generate more safety data for lenacapavir.

For the difference in response rates between the lenacapavir-containing regimens (groups 1 to 3) and the bictegravir, emtricitabine, and tenofovir alafenamide group (group 4), point estimates and 95% CIs were obtained with SAS software (version 9.4) by use of the normal approximation method, stratified by baseline HIV-1 RNA level (≤100 000 or >100 000 copies per mL).

Analyses of the primary efficacy endpoint were based on the full analysis set, which includes all participants who were randomly assigned and received at least one dose of study drug and uses only on-treatment data (ie, data collected up to 1 day after the last study dose date). For the missing equals failure analysis, missing data were treated as virological failure. Analyses of the safety outcome measures also included the full analysis set.

	Group 1 (n=52)	Group 2 (n=53)	Group 3 (n=52)	Group 4 (n=25)	Total (N=182)
Age (years)	31 (26–40)	28 (24–33)	28 (24–36)	29 (26–33)	29 (24–36)
Sex					
Female	5 (10%)	1 (2%)	6 (12%)	0 (0%)	12 (7%)
Male	47 (90%)	52 (98%)	46 (89%)	25 (100%)	170 (93%)
Race					
American Indian or Alaska Native	1 (2%)	0	0	0	1 (1%)
Asian	1 (2%)	0	1 (2%)	0	2 (1%)
Black	24 (46%)	24 (45%)	31 (60%)	16 (64%)	95 (52%)
Native Hawaiian or Pacific Islander	1 (2%)	1 (2%)	0	0	2 (1%)
White	23 (44%)	28 (53%)	19 (37%)	8 (32%)	78 (43%)
Other	2 (4%)	0	1 (2%)	1 (4%)	4 (2%)
Latinx ethnicity	25 (48%)	21 (40%)	24 (46%)	12 (48%)	82 (45%)
Gender identity					
Cisgender	50 (96%)	50 (94%)	45 (87%)	24 (96%)	169 (93%)
Transgender	1 (2%)	1 (2%)	1 (2%)	0	3 (2%)
Prefer not to disclose	1 (2%)	2 (4%)	6 (12%)	1 (4%)	10 (6%)
Weight (kg)	78 (64–97)	77 (67–90)	77 (68–94)	80 (72–99)	78 (66–95)
BMI (kg/m^2)	26 (21–30)	25 (22–29)	26 (22–30)	27 (23–31)	26 (22–30)
HIV-1 RNA					
$\log_{10}$ copies per mL	4·3 (3·8–4·6)	4·3 (4·0–4·7)	4·5 (3·8–4·8)	4·4 (4·1–4·8)	4·4 (3·9–4·7)
>100 000 copies per mL	5 (10%)	9 (17%)	9 (17%)	4 (16%)	27 (15%)
CD4 count					
Cells per µL	404 (320–599)	450 (332–599)	409 (301–600)	482 (393–527)	437 (332–599)
Distribution					
<50 cells per µL	0	0	0	0	0
≥50 to <200 cells per µL	0	1 (2%)	3 (6%)	0	4 (2%)
≥200 to <350 cells per µL	17 (33%)	15 (28%)	16 (31%)	4 (16%)	52 (29%)
≥350 to <500 cells per µL	17 (33%)	15 (28%)	15 (29%)	11 (44%)	58 (32%)
≥500 cells per µL	18 (35%)	22 (42%)	18 (35%)	10 (40%)	68 (37%)

Data are median (IQR) or n (%). Patients in group 1 received subcutaneous lenacapavir with emtricitabine and tenofovir alafenamide followed by tenofovir alafenamide; patients in group 2 received subcutaneous lenacapavir with emtricitabine and tenofovir alafenamide followed by bictegravir; patients in group 3 received oral lenacapavir with emtricitabine and tenofovir alafenamide; and patients in group 4 received bictegravir, emtricitabine, and tenofovir alafenamide.

Table 1: **Baseline characteristics**

This trial is registered at ClinicalTrials.gov, NCT04143594.

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.

Results

Between Nov 22, 2019, and Aug 27, 2020, 249 people with HIV were screened, and 183 were randomly assigned (figure 2). A total of 182 participants received at least one dose of the study drug; one participant was randomly assigned by site error and did not receive a dose. At baseline, the four groups were balanced in demographic and disease characteristics (table 1). Most participants were male, and just over half were Black. Overall, the median age was 29 years (range 19–72 years). 85% of participants had HIV-1 RNA of 100 000 copies per mL or less. 69% had CD4 counts of at least 350 cells per µL.

22 (12%) participants prematurely discontinued study drug before week 54: 17 (16%) of 105 receiving subcutaneous lenacapavir with emtricitabine and tenofovir alafenamide followed by tenofovir alafenamide or bictegravir, four (8%) of 52 receiving oral lenacapavir with emtricitabine and tenofovir alafenamide, and one (4%) of 25 receiving bictegravir, emtricitabine, and tenofovir alafenamide (figure 2 and appendix p 5). The last participant visit for the primary endpoint occurred on Oct 5, 2021.

Participants rapidly reached virological suppression (HIV-1 RNA <50 copies per mL), within weeks of starting study drug (appendix p 7). Virological suppression at week 28 was 94% (49 of 52 participants) in group 1, 93% (49 of 53) in group 2, 94% (49 of 52) in group 3, and 100% (25 of 25) in group 4 (appendix p 22). In the pooled lenacapavir group (receiving either subcutaneous or oral lenacapavir in combination with emtricitabine and tenofovir alafenamide), 94% (147 of 157) had less than 50 copies per mL of HIV-1 RNA by week 28. The viral kinetics of the lenacapavir-containing regimens and combination bictegravir, emtricitabine, and tenofovir alafenamide were also similar among the groups (figure 3A).

For the primary endpoint of percentage of participants with virological suppression at week 54, rates of virological suppression at week 54 were 90% (47 of 52) in group 1, 85% (45 of 53) in group 2, 85% (44 of 52 in group 3, and 92% (23 of 25) in group 4 (figure 3B, appendix p 8). Differences in the percentage of participants with virological suppression compared with group 4 were –2·6% (95% CI –18·4 to 13·2) for group 1, –7·1% (–23·4 to 9·3) for group 2, and –7·2% (–23·5 to 9·1) for group 3. The estimated difference in percentages between all lenacapavir-containing regimens and bictegravir, emtricitabine, and tenofovir alafenamide was –5·6% (–19·5 to 8·4). Among those with less than 50 copies per mL of HIV-1 RNA at week 28 in groups 1 and 2, 94% (46 of 49) in group 1 and 92% (45 of 49) in group 2 maintained their less than 50 copies per mL of HIV-1 RNA status at week 54. When missing data were excluded, rates of virological suppression at week 54 were high in all groups: 100% (47 of 47) in group 1; 100% (45 of 45) in group 2; 94% (44 of 47) in group 3; and 100% (23 of 23) in group 4.

Among participants receiving lenacapavir who did not have virological suppression at week 54, most (13 of 14) had discontinued study drug before then, and one had missing data while on the study drug. Two of three participants who received oral lenacapavir with emtricitabine and tenofovir alafenamide had more than 50 copies per mL of HIV-1 RNA at week 54, and had viriological suppression at a later visit.

At week 54, CD4 counts increased by a median of 219 cells per µL (IQR 102–318) among participants receiving lenacapavir compared with 177 (30–290) in those receiving bictegravir, emtricitabine, and tenofovir alafenamide. The estimated difference between the two groups was 21 cells per µL (95% CI –60 to 102).

Six participants met the protocol-defined virological failure criteria and were tested for resistance: two (2%) of 105 receiving subcutaneous lenacapavir with

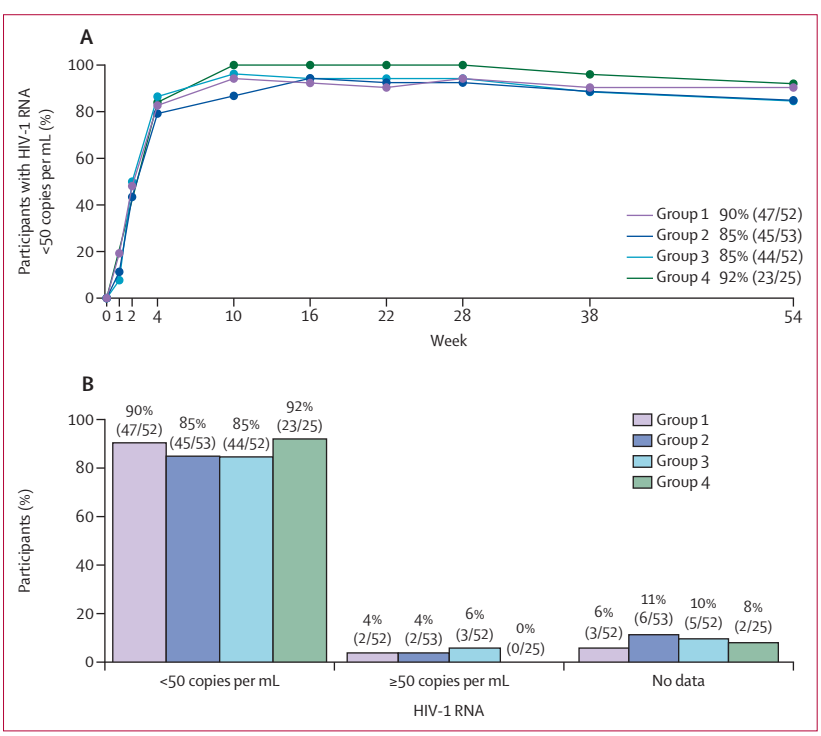

Figure 3: **Efficacy of subcutaneous and oral lenacapavir in combination with other antiretroviral agents versus bictegravir, emtricitabine, and tenofovir alafenamide**

(A) Participants with HIV-1 RNA <50 copies per mL by visit. Missing data were treated as virological failure. (B) Viral suppression at week 54. Three participants (two in treatment group 1 and one in treatment group 2) discontinued due to not meeting the protocol criteria of having HIV-1 RNA <50 copies mL before or at week 28. One participant in group 2 discontinued on day 2. Two of the three participants with HIV-1 RNA ≥50 copies per mL in group three at week 54 had viral suppression in subsequent visits.

emtricitabine and tenofovir alafenamide followed by tenofovir alafenamide or bictegravir, three (6%) of 52 receiving oral lenacapavir with emtricitabine and tenofovir alafenamide, and one (4%) of 25 receiving bictegravir, emtricitabine, and tenofovir alafenamide. Four of these six participants had viral rebound, then later resuppressed without changing treatment regimens; none developed resistance. Emergent resistance was found in two participants (one in group 2 and one in group 3). In the participant from group 2, the lenacapavir-associated capsid substitutions Gln67His and Lys70Arg and the Met184Met/Ile reverse transcriptase mutation were detected at week 10 (appendix p 9). Plasma concentrations of lenacapavir were in the target range, and those of emtricitabine and tenofovir were consistent with expected pharmacokinetics. Additional exploratory deep sequencing analyses subsequently detected Met184Ile/Val substitutions in reverse transcriptase at week 2, whereas the Gln67His mutation in capsid was first detected at week 4.[15] In the participant from group 3, virological rebound occurred at week 54 with emergent resistance to lenacapavir (Gln67His; appendix p 9); plasma drug concentrations (lenacapavir and tenofovir alafenamide) suggested inconsistent adherence to all components of the regimen at the time of resistance emergence.

95 (91%) of 105 participants receiving subcutaneous lenacapavir with emtricitabine and tenofovir alafenamide followed by tenofovir alafenamide or bictegravir had at least one adverse event (groups 1 and 2), as did 43 (83%) of 52 receiving oral lenacapavir with emtricitabine and tenofovir alafenamide (group 3) and 21 (84%) of 25 receiving bictegravir, emtricitabine, and tenofovir alafenamide (group 3). Among participants who received subcutaneous lenacapavir with emtricitabine and tenofovir alafenamide followed by tenofovir alafenamide or bictegravir, the most frequently reported adverse events were injection-site reactions (table 2, appendix p 10). 57 (55%) of 103 had any injection-site reactions (table 2, appendix p 12), which were generally mild (86%, 49 of 57) to moderate (12%, seven of 57). The most common reactions were erythema (27%, 28 of 103), swelling (23%, 24 of 103), and pain (19%, 20 of 103). Median durations of reactions were short for erythema (5 days, IQR 2–11), swelling (11, 6–29), and pain (4, 1–9), but longer for nodule (195, 122–301) and induration (202, 101–361). One participant had a grade 3 injection-site nodule after the second lenacapavir dose, which was visible but did not lead to discontinuation (appendix p 15). No grade 4 injection-site reactions were reported. Among those who received oral lenacapavir, the most common adverse events were headache (14%, seven of 52), followed by nausea and lymphadenopathy (12%, six of 52 each). In the bictegravir, emtricitabine, and tenofovir alafenamide group, arthralgia and syphilis were most common (16%, four of 25); headache was observed in three (12%) of 25 participants and nausea in one (4%) of 25. A total of ten serious adverse events were reported among lenacapavir-treated participants (appendix p 17). None were considered related to treatment.

	Group 1 (n=52)	Group 2 (n=53)	All subcutaneous lenacapavir (n=105)	Group 3 (n=52)	All lenacapavir (n=157)	Group 4 (n=25)
Any adverse event	50 (96%)	45 (85%)	95 (91%)	43 (83%)	138 (88%)	21 (84%)
Any adverse event grade 3 or higher	2 (4%)	5 (9%)	7 (7%)	6 (12%)	13 (8%)	2 (8%)
Serious adverse event	3 (6%)	3 (6%)	6 (6%)	4 (8%)	10 (6%)	0
Event leading to discontinuation of treatment	0	3 (6%)	3 (3%)	0	3 (2%)	0
Events in >10% in any group						
Lenacapavir-related injection-site reactions	32 (62%)	25 (47%)	57 (54%)	NA	NA	NA
Erythema	18 (35%)	10 (19%)	28 (27%)	NA	NA	NA
Swelling	13 (25%)	11 (21%)	24 (23%)	NA	NA	NA
Pain	12 (23%)	8 (15%)	20 (19%)	NA	NA	NA
Nodule	8 (15%)	7 (13%)	15 (14%)	NA	NA	NA
Inflammation	10 (19%)	4 (8%)	14 (13%)	NA	NA	NA
Induration	8 (15%)	5 (9%)	13 (12%)	NA	NA	NA
Non-injection site reactions						
Headache	9 (17%)	5 (9%)	14 (13%)	7 (14%)	21 (13%)	3 (12%)
Nausea	10 (19%)	5 (9%)	15 (14%)	6 (12%)	21 (13%)	1 (4%)
COVID-19	5 (10%)	5 (9%)	10 (10%)	5 (10%)	15 (10%)	3 (12%)
Syphilis	5 (10%)	4 (8%)	9 (9%)	5 (10%)	14 (9%)	4 (16%)
Lymphadenopathy	4 (8%)	4 (8%)	8 (8%)	6 (12%)	14 (9%)	1 (4%)
Diarrhoea	3 (6%)	4 (8%)	7 (7%)	5 (10%)	12 (8%)	1 (4%)
Depression	1 (2%)	6 (11%)	7 (7%)	3 (6%)	10 (6%)	1 (4%)
Influenza	4 (8%)	2 (4%)	6 (6%)	5 (10%)	11 (7%)	0
Fatigue	0	6 (11%)	6 (6%)	2 (4%)	8 (5%)	1 (4%)

Data are n (%). Multiple adverse events were counted only once per participant for the highest severity grade for each preferred term. Patients in group 1 received subcutaneous lenacapavir with emtricitabine and tenofovir alafenamide followed by tenofovir alafenamide; patients in group 2 received subcutaneous lenacapavir with emtricitabine and tenofovir alafenamide followed by bictegravir; patients in group 3 received oral lenacapavir with emtricitabine and tenofovir alafenamide; and patients in group 4 received bictegravir, emtricitabine, and tenofovir alafenamide. NA=not applicable.

Table 2: **Adverse events**

Three participants discontinued because of an adverse event; all were due to injection-site reactions among participants receiving subcutaneous lenacapavir. Two had grade 1 injection-site induration after the first injection, and one had grade 1 adverse events of injection-site erythema and injection-site swelling after the second injection.

Laboratory abnormalities of grade 3 or higher occurred in 39 (25%) of 156 lenacapavir-treated participants and six (24%) of 25 bictegravir, emtricitabine, and tenofovir alafenamide-treated participants, with no pattern suggesting a specific laboratory abnormality related to lenacapavir (appendix p 19).

Changes in weight from baseline to week 54 were similar for participants receiving lenacapavir (subcutaneous or

oral; median change 2·6 kg, IQR 0·2 to 6·8) and participants receiving bictegravir, emtricitabine, and tenofovir alafenamide (median change 2·3 kg, –3·1 to 7·3; appendix p 21).

Discussion

Lenacapavir given as subcutaneous injection or orally in combination with emtricitabine and tenofovir alafenamide, followed by tenofovir alafenamide, bictegravir, or continued emtricitabine and tenofovir alafenamide, led to high rates of virological suppression for 54 weeks in people with HIV who were starting therapy. These findings suggest the potential for lenacapavir to be combined with other antiretroviral agents for the effective treatment of HIV.

Rapid virological suppression occurs with regimens containing integrase inhibitor, such as bictegravir, emtricitabine, and tenofovir alafenamide. In this study, lenacapavir-containing regimens led to early virological suppression similar to that in the bictegravir, emtricitabine, and tenofovir alafenamide group (appendix p 7). All four treatment groups achieved high virological suppression rates as early as week 4 (81–87% with lenacapavir-containing regimens *vs* 84% with bictegravir, emtricitabine, and tenofovir alafenamide), and these increased further to week 28. The rapid suppression with lenacapavir is consistent with its potent antiviral activity seen in the phase 1b proof of concept study in which a single subcutaneous dose of lenacapavir given as monotherapy led to an HIV-1 RNA decline of up to 2·3 $\log_{10}$ copies per mL.[7,10]

At the primary endpoint of week 54, virological suppression was 85% to 90% in the three lenacapavir groups, which is consistent with the results from other phase 2 studies of antiretroviral combinations for initial treatment of HIV.[12,16,17] Notably, in addition to lenacapavir in combination with emtricitabine and tenofovir alafenamide reaching and maintaining virological suppression (group 3), lenacapavir combined with either tenofovir alafenamide or bictegravir (groups 1 and 2) also maintained virological suppression after initial treatment with lenacapavir combined with emtricitabine and tenofovir alafenamide. These data suggest that lenacapavir combined with a second potent agent can be effective in maintaining virological suppression, which is consistent with previous studies of two-drug regimens.[18,19]

Lenacapavir is flexible in its route of administration and dosing intervals, with oral (daily to weekly) and injectable (up to every 6 months) dosing. When combined with other antiretroviral agents with synchronous dosing schedules, a range of dosing options could be possible for people with HIV. There are currently no phase 3 trials planned for any of the specific regimens evaluated in this study, all of which include antiretrovirals requiring daily administration. Oral lenacapavir is being investigated in an all-oral, once-weekly dual combination regimen (NCT05052996). For subcutaneous injectable lenacapavir, there are ongoing efforts to develop a long-acting partner agent that can be combined with lenacapavir as a complete synchronous regimen, offering the best potential for sustained adherence.

Emergent resistance mutations to lenacapavir were rare; they occurred in two of 157 participants who received lenacapavir, and in these two incidents emergent resistance appeared to be associated with incomplete adherence to oral daily agents. In one participant in group 2 (receiving subcutaneous lenacapavir plus oral daily emtricitabine and tenofovir alafenamide), deep sequencing analyses showed that the emtricitabine resistance mutation Met184Ile/Val emerged before lenacapavir mutations at week 4, which suggests that incomplete adherence to emtricitabine and tenofovir alafenamide preceded emergent lenacapavir resistance.[15] In the other participant, in group 3 (receiving oral daily lenacapavir plus oral daily tenofovir alafenamide), poor adherence to tenofovir alafenamide and lenacapavir was documented by plasma drug concentrations.[20]

Lenacapavir was generally well tolerated. Most adverse events, including injection-site reactions, were mild or moderate. Discontinuations due to injection-site reactions were infrequent, occurring in only three (of 53) participants receiving subcutaneous lenacapavir. Results of this study, supported by others including subcutaneous lenacapavir,[11] indicate that injection-site reactions were not an impediment to the participants in this study.

Limitations of this study include those of any phase 2 study: the small sample size and limited duration. However, the efficacy and safety results from this study, when taken together with the totality of clinical data to date,[11] are sufficient to support further investigation of lenacapavir in combination with other antiretroviral agents in large phase 3 studies. Participation by women was low. Lastly, discontinuation rates were high. However, most participants discontinued for reasons not related to efficacy or safety.

These results show that lenacapavir is well tolerated and effective in combination with other antiretroviral agents at inducing and maintaining suppression of HIV-1. A range of options for antiretroviral therapy, including oral and injectable longer-acting regimens, could help to address the needs of the diversity of people with HIV.

Contributors

SKG, MB, GC, PB, MR, JS, CM, PR, WES, AS, and EK enrolled study participants. MSR contributed to the conception and design of the study. HD-S and MSR contributed to the collection of data. LAV and S-YL analysed the data, which were reviewed and interpreted by HD-S, MSR, and JMB. SKG, HD-S, and MSR had full access to and verified all the data in the study. All authors had full access to all data and contributed to the interpretation of data and drafting or revising the manuscript. All authors had final responsibility for the decision to submit for publication and approved the final version of the manuscript.

Declaration of interests

SKG has received grant support from the National Institutes of Health and ViiV Healthcare and has participated in data safety monitoring boards or advisory boards for Gilead Sciences and ViiV Healthcare. GC has received support for the present study from Gilead Sciences.

PB has served on the speakers' bureau and advisory boards for Gilead Sciences. MR has served as a consultant for Merck, ViiV Healthcare, and Gilead Sciences and has been a member of the speakers' bureau for AbbVie, Gilead Sciences, ViiV Healthcare, and Janssen. CM has received support for the present study from Gilead Sciences and honoraria for lectures and speakers' bureau from Gilead Sciences. PR has served as an adviser to Gilead Sciences and ViiV Healthcare. LAV, HD-S, MSR, and JMB are current employees of Gilead Sciences and own stock in the company. All other authors declare no competing interests.

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 Science's 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 datarequest@gilead.com.

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