Safety of teropavimab and zinlirvimab with lenacapavir once every 6 months for HIV treatment: a phase 1b, randomised, proof-of-concept study

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Summary

Background Long-acting treatment for HIV has potential to improve adherence, provide durable viral suppression, and have long-term individual and public health benefits. We evaluated treatment with two antibodies that broadly and potently neutralise HIV (broadly neutralising antibodies; bNAbs), combined with lenacapavir, a long-acting capsid inhibitor, as a long-acting regimen.

Methods This ongoing, randomised, blind, phase 1b proof-of-concept study conducted at 11 HIV treatment centres in the USA included adults with a plasma HIV-1 RNA concentration below 50 copies per mL who had at least 18 months on oral antiretroviral therapy (ART), CD4 counts of at least 500 cells per µL, and protocol-defined susceptibility to bNAbs teropavimab (3BNC117-LS) and zinlirvimab (10-1074-LS). Participants stopped oral ART and were randomly assigned (1:1) to one dose of 927 mg subcutaneous lenacapavir plus an oral loading dose, 30 mg/kg intravenous teropavimab, and 10 mg/kg or 30 mg/kg intravenous zinlirvimab on day 1. Investigational site personnel and participants were masked to treatment assignment throughout the randomised period. The primary endpoint was incidence of serious adverse events until week 26 in all randomly assigned participants who received one dose or more of any study drug. This study is registered with ClinicalTrials.gov, NCT04811040.

Findings Between June 29 and Dec 8, 2021, 21 participants were randomly assigned, ten in each group received the complete study regimen and one withdrew before completing the regimen on day 1. 18 (86%) of 21 participants were male; participants ranged in age from 25 years to 61 years and had a median CD4 cell count of 909 (IQR 687–1270) cells per µL at study entry. No serious adverse events occurred. Two grade 3 adverse events occurred (lenacapavir injection-site erythaema and injection-site cellulitis), which had both resolved. The most common adverse events were symptoms of injection-site reactions, reported in 17 (85%) of 20 participants who received subcutaneous lenacapavir; 12 (60%) of 20 were grade 1. One (10%; 95% CI 0–45) participant had viral rebound (confirmed HIV-1 RNA concentration of ≥50 copies per mL) in the zinlirvimab 10 mg/kg group, which was resuppressed on ART, and one participant in the zinlirvimab 30 mg/kg group withdrew at week 12 with HIV RNA <50 copies per mL.

Interpretation Lenacapavir with teropavimab and zinlirvimab 10 mg/kg or 30 mg/kg was generally well tolerated with no serious adverse events. HIV-1 suppression for at least 26 weeks is feasible with this regimen at either zinlirvimab dose in selected people with HIV-1.

Funding Gilead Sciences.

Introduction

Daily combination oral antiretroviral therapy (ART) for HIV-1 infection is the global standard-of-care.[1] ART results in viral suppression, return to good health, and elimination of HIV transmission risk; however, most treatment requires lifelong daily adherence with no cure.[1] Long-acting therapies have the potential to improve adherence and have corresponding benefits of persistent viral suppression and reduced transmission for some people with HIV.[2] Widespread benefits from long-acting antiretroviral regimens have not yet been realised. Realisation of these benefits will require therapies that are as safe, effective, and available as current oral regimens without the requirement for daily adherence. Progress towards long-acting therapy has been made with the approval of an ART regimen consisting of cabotegravir and rilpivirine that can be injected intramuscularly monthly or every 2 months;[3] however, injection-site reactions are common and virological failure can result in cross-resistance to integrase strand-transfer inhibitors and non-nucleoside reverse transcriptase inhibitors. Therefore, therapy with a longer interval between treatment and without risk of resistance to widely used antiretroviral classes might be preferable.

After years of infection with HIV-1, some people develop highly potent antibodies against HIV envelope

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Research in context

Evidence before this study

We searched PubMed from database inception to April 4, 2023, using the terms "HIV" and "subcutaneous" or "intramuscular" or "intravenous" or "neutralising antibody(ies)" for clinical trials of long-acting HIV-1 infection treatment; there were no language restrictions. After excluding irrelevant studies and duplicates, we found 34 reports of clinical studies with long dosing intervals. Nine reports on trial results were for the integrase inhibitor cabotegravir, with the non-nucleoside reverse transcriptase inhibitor rilpivirine, which is the only approved long-acting regimen, administered as intramuscular injections every 4 or 8 weeks and has potential for cross-resistance with major antiretroviral classes. We found four studies of lenacapavir, a first-in-class HIV-1 capsid inhibitor, which provided rapid reductions in HIV-1 viral load and sustained therapeutic plasma concentrations for more than 6 months in phase 1 studies. Oral lenacapavir significantly reduced HIV-1 viral load versus placebo in participants with multidrug-resistant HIV and suppression was reached by more than 80% of participants with HIV after 6 months of lenacapavir in addition to optimised background therapy. Neither this study, nor a study of participants who were treatment-naive initiating antiretroviral therapy (ART) with lenacapavir every 26 weeks combined with other oral antiretrovirals, described a complete long-acting treatment regimen. In clinical studies, lenacapavir resistance developed in participants who had no fully active agents in the background regimen, who had emergent resistance to a background agent, or who had inconsistent adherence to background agents. In 16 studies, inadequate potency and breadth of neutralisation limited development of several therapeutic broadly neutralising antibodies (bNAbs) and highlighted the need for bNAb combinations. A triple combination targeting V2 glycans (PGDM1400), V3 glycans (PGT121), and CD4-binding site (VRC07-523LS) did not achieve or maintain suppression and emergent resistance to two of the bNAbs was observed. A combination of bNAbs targeting the CD4-binding site (3BNC117) and V3 glycan supersite (10-1074) on the Env protein have shown rapid reductions in viraemia with effects persisting for approximately 4 weeks when studied as monotherapy. Infusions of 3BNC117 and 10-1074 during analytic treatment interruption maintained HIV-1 viral suppression in most participants with HIV that was suspectable to 3BNC117 and 10-1074 for up to 6 months in the study with the longest duration of repeat infusions. However, approximately one in four participants across four trials of multiple 3BNC117 and 10-1074 doses had virological rebound while antibody concentrations were high, suggesting that the two bNAbs alone are not sufficient for controlling HIV.

Added value of this study

Subcutaneous lenacapavir combined with two of the most promising bNAbs, 3BNC117 (teropavimab) and 10-1074 (zinlirvimab), modified to extend half-life, might provide a complete regimen with dosing every 6 months. In this phase 1b study, we show that people with bNAb-sensitive HIV-1 who were virologically suppressed and on stable ART for at least 2 years were able to replace their baseline oral daily ART with the long-acting combination of subcutaneous lenacapavir, intravenous teropavimab, and one of two doses of intravenous zinlirvimab and maintain viral suppression for at least 26 weeks after one administration of the triple combination. The study regimen was generally safe and the most common adverse events were expected mild-to-moderate injection-site reactions related to lenacapavir administration.

Implications of all the available evidence

This study provides proof-of-concept that lenacapavir, teropavimab, and zinlirvimab could provide long-acting ART with twice yearly dosing for appropriately selected people with HIV. The efficacy and safety results support further clinical development of this combination that might provide an option for people who prefer less frequent dosing, have adherence challenges, suffer from stigma associated with daily oral pills, or are experiencing side-effects with current ART options.

glycoproteins that can neutralise a wide variety of HIV strains.[4,5] A few broadly neutralising antibodies (bNAbs) have been isolated and are being explored as potential novel, long-acting agents for HIV treatment and prevention.[5–7] Two such bNAbs, 3BNC117 targeting the CD4-binding site and 10-1074 targeting the V3 glycan loop on the HIV envelope protein gp120, were well tolerated in single-agent, dose-escalation studies and demonstrated a rapid, direct antiviral effect at doses of 30 mg/kg (3BNC117) and 10 mg/kg or 30 mg/kg (10-1074).[6,7] Four infusions of 3BNC117 (30 mg/kg) were administered every 2 weeks while ART was interrupted, delaying viral rebound by an average of 9·9 weeks.[8] However, single bNAbs are limited by incomplete neutralisation activity against diverse HIV variants, resulting in viral breakthroughs.[6–9] Combining potent bNAbs targeting non-overlapping epitopes on the HIV envelope improved the breadth of viruses neutralised and the duration of viral suppression when participants were not taking ART.[10–13] In one study, individuals with viral suppression on oral ART who stopped oral ART and received seven infusions of 30 mg/kg 3BNC117 and 10-1074 over 20 weeks maintained viral suppression for a median of 12 weeks after the last infusion; however, four of 17 study participants had viral rebound and resumed oral ART before completing bNAb treatment.[10] Combining two bNAbs with another antiviral agent might provide greater breadth of antiviral activity and potentially result in a complete therapeutic regimen for HIV treatment.

Teropavimab (formerly 3BNC117-LS or GS-5423) and zinlirvimab (formerly 10-1074-LS or GS-2872) are bNAbs with HIV envelope targets identical to 3BNC117 and 10-1074, modified to extend their half-life with pharmacokinetics modelling that supported dosing every 6 months.[14] Lenacapavir is a first-in-class, HIV capsid inhibitor, with high potency and long half-life, administered subcutaneously every 6 months,[15] which is compatible with the potential dosing interval for teropavimab and zinlirvimab due to the extended half-life. In clinical trials, lenacapavir demonstrated potent antiviral activity alone and clinical efficacy in combination with other oral antiretroviral agents.[15–17] Lenacapavir is approved in the EU and USA for heavily treatment-experienced adults with HIV with multidrug-resistant HIV who have not responded to treatment due to resistance, intolerance, or safety. Because virological rebound with resistance has been shown for each of these agents in the setting of monotherapy or functional monotherapy,[10,11,18] this phase 1b, proof-of-concept study assessed whether a combination of lenacapavir, teropavimab, and zinlirvimab is safe, tolerable, and able to maintain HIV suppression when dosed every 6 months.

Methods

Study design and participants

This phase 1b, randomised, blinded, proof-of-concept trial included adults with HIV-1 that was virologically suppressed by ART. Eligible participants were aged 18–65 years with documented plasma HIV-1 RNA concentration below 50 copies per mL for 18 months or more, a CD4 count nadir of 350 cells per µL or more, a current CD4 count of 500 cells per µL or more, have been taking first-line ART for 2 years or more, and with proviral phenotypic susceptibility to both teropavimab and zinlirvimab defined as 90% inhibitory concentration (IC_{90}) of 2 µg/mL or more for each antibody. Exclusion criteria included having previously received any anti-HIV-1 monoclonal antibodies, immunosuppressive treatment (corticosteroids, immunoglobulins, and other immune-based or cytokine-based therapies), or chemotherapy within 4 weeks of enrolment; documented historical resistance to any component of the current ART regimen; co-infection with hepatitis C (antibody positive and hepatitis C RNA detectable) or hepatitis B virus (positive hepatitis B virus surface antigen and negative surface antibody, regardless of core antibody status, or positive core antibody and negative surface antibody, regardless of surface antigen status) at the screening visit; or co-infection with other serious active infections requiring systemic antibiotic or antifungal treatment within 42 days before study day 1 (appendix pp 187–189). The study was conducted in 11 HIV treatment centres in the USA.

The trial was approved by the institutional review board or ethics committee at each study site and was done in accordance with International Council for Harmonisation Good Clinical Practice guidelines and with laws and guidelines regarding clinical trials. All participants provided written informed consent. The study protocol is provided in the appendix (pp pp 227–231).

Randomisation and masking

We randomly assigned participants 1:1 to two treatment groups that differed in the dose of zinlirvimab (either 10 mg/kg or 30 mg/kg intravenously). Both groups also received teropavimab 30 mg/kg and lenacapavir 927 mg in a non-masked way. Once eligibility was determined on day 1, participants were assigned a unique participant number and randomly assigned by the investigator using an interactive response technology system. The interactive response technology system assigned a study drug bottle or vials at the day 1 visit for each participant. Randomisation was unstratified. Investigational site personnel and participants were masked to treatment assignment throughout the randomised period and unmasked after baseline ART was resumed. Sponsor personnel and site pharmacists remained unmasked throughout the trial period. The zinlirvimab dose of 10 mg/kg or 30 mg/kg was prepared for infusion in 5% dextrose by a pharmacist not masked to treatment assignment and administered to the participant by masked study personnel. Teropavimab and lenacapavir doses were identical for both treatment groups and were not masked.

Procedures

We assessed plasma HIV-1 RNA viral load by the Roche TaqMan 2.0 assay (Covance, Indianapolis, IN, USA) with a lower limit of detection of 20 copies per mL. We conducted teropavimab and zinlirvimab susceptibility testing using the PhenoSense Monoclonal Antibody assay from Monogram Biosciences (South San Francisco, CA, USA).[19,20] We isolated archived proviral DNA from peripheral blood mononuclear cells, and proviral HIV-1 envelope and capsid genes were sequenced at study entry at Seq-IT (Kaiserslautern, Germany) using MiSeq next-generation sequencing at a mutation detection threshold of 1% for proviral HIV-1 envelope and 2% for proviral HIV-1 capsid.

We selected doses of bNAbs based on published pharmacokinetic and pharmacodynamic data with the parent bNAbs (3BNC117 and 10-1074)[6,7,11] and preliminary pharmacokinetic data with teropavimab and zinlirvimab (unpublished). A dose of 30 mg/kg teropavimab and 10 mg/kg zinlirvimab was expected to maintain their serum concentration above the proposed minimal therapeutic concentration (>10 µg/mL), described in previous studies during the dosing interval of 26 weeks. Considering that zinlirvimab and 10-1074 have also been studied previously at doses up to 30 mg/kg with an acceptable safety profile, we also included a higher zinlirvimab dose of 30 mg/kg to assess the potential dose–response relationship of zinlirvimab in

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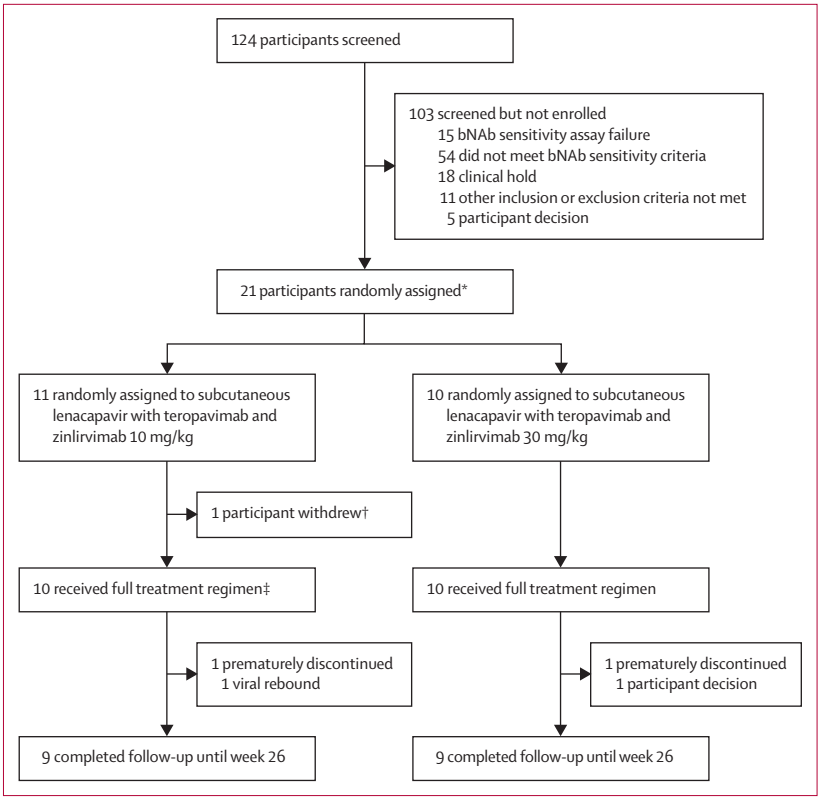

Figure 1: **Trial profile**
ART=antiretroviral therapy. bNAb=broadly neutralising antibody.*All randomly assigned individuals were included in the safety analysis (n=21). †Participant received oral lenacapavir and then withdrew before receiving the complete study regimen. The participant continued baseline ART and was included in the safety analysis but not the efficacy analysis. ‡All participants who received the complete study regimens were included in the efficacy analyses (n=20).

combination with teropavimab and lenacapavir. The antibodies were administered intravenously on day 1 and 927 mg lenacapavir was administered subcutaneously on day 1, with 600 mg lenacapavir administered orally for pharmacological loading on days 1 and 2.

We defined virological rebound as a confirmed post-day 1 plasma HIV-1 RNA concentration of 50 copies per mL or more or an HIV-1 RNA concentration of 50 copies per mL or more at study discontinuation or at week 26. Resistance testing of rebound plasma viruses was done at Monogram Biosciences with genotypic and phenotypic analyses of HIV-1 envelope and capsid (GenoSure HIV Envelope RNA, PhenoSense Monoclonal Antibody RNA, GenoSure Gag-Pro, and PhenoSense Gag-Pro assays, Monogram Biosciences, South San Francisco, CA, USA).[19,21,22] The GenoSure HIV Envelope RNA and GenoSure Gag-Pro assays use next-generation sequencing to detect codon variants present at a frequency greater than 1% and 10%, respectively. The primary endpoint was measured at week 26, after which participants restarted oral ART.

Follow-up visits occurred at weeks 4, 8, 12, 16, 20, 24, 26, 38, and 52 and included assessment of plasma HIV-1 RNA concentration, with additional visits at weeks 30, 34, 42, and 46 for pharmacokinetics sampling. We conducted physical examinations, vital signs, weight, complete blood counts, CD4 cell counts, and blood chemistry profiles at day 1 and weeks 4, 12, 26, 38, and 52. Electrocardiograms were done at day 1 and weeks 26 and 52. We collected serum or plasma pharmacokinetic samples pre-dose, within 5 min of first infusion and within 5 min of the second infusion on day 1 and then at each follow-up and pharmacokinetics sampling visit. Serum pharmacokinetics samples were analysed by validated sandwich electrochemiluminescence immunoassay methods, with lower limit of quantitation of 100 ng/mL to quantify teropavimab and zinlirvimab concentrations. Plasma pharmacokinetic samples were analysed by liquid chromatography-mass spectrometry (lower limit of quantitation 0·5 ng/mL) to quantify lenacapavir concentrations. We collected serum for assessment of anti-teropavimab and anti-zinlirvimab anti-drug antibodies (ADAs) at day 1 and weeks 4, 12, 26, 38, and 52. Serum ADA samples were analysed by a three-tiered (screen, confirmatory, and titration assay) ADA assay method developed and validated in accordance with the current regulatory agency guidance[23] to detect the presence of anti-teropavimab and anti-zinlirvimab ADAs.

Outcomes

The primary endpoint was safety, measured as the incidence of treatment-emergent serious adverse events until week 26. Adverse events were graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July, 2017). Secondary endpoints included efficacy assessed as the proportion of participants with a plasma HIV-1 RNA concentration of 50 copies per mL or more and with below 50 copies per mL at week 26, as defined by the US Food and Drug Administration Snapshot algorithm; change from baseline CD4 cell counts at week 26; treatment-emergent resistance to study drugs until week 26; proportion of participants with positive anti-teropavimab or anti-zinlirvimab antibodies; treatment-emergent adverse events until week 26; and pharmacokinetics of lenacapavir, teropavimab, and zinlirvimab.

Statistical analysis

The trial sample size was based on practical considerations and experience with similar types of studies and was not powered for between-group comparisons. We originally designed the trial to enrol 50 participants with a second dose of study regimen at 26 weeks and follow-up for a secondary endpoint at 52 weeks; however, the trial was truncated during a period of temporary regulatory hold on lenacapavir. The safety analysis (primary outcome) included all randomly assigned participants who received one dose

or more of any study drug. The efficacy analyses included all randomly assigned participants who received one dose or more of complete study regimen (lenacapavir, teropavimab, and zinlirvimab). We summarised safety and efficacy data by treatment group and total and we calculated descriptive statistics including frequency counts and percentages. No formal statistical comparisons between zinlirvimab dose groups were prespecified or conducted. For efficacy endpoints, including the proportion of participants with HIV-1 RNA concentrations of 50 copies per mL or more or below 50 copies per mL defined by the US Food and Drug Administration Snapshot algorithm at week 26, we calculated the 95% CI by treatment group and total using the Clopper-Pearson exact method. Pharmacokinetic analysis included all randomly assigned participants who received at least one dose of any study drug and had at least one non-missing concentration value. We summarised concentration data and pharmacokinetic parameters using descriptive statistics. Immunogenicity analysis included all randomly assigned participants who received at least one dose of any study drug and had at least one non-missing value for each immunogenicity evaluation (eg, anti-teropavimab or anti-zinlirvimab). We summarised the numbers and percentages of participants with treatment-emergent ADAs to one or both bNAbs by treatment group and total. We also present ADA titres. In this Article, we report data until week 26. This study is ongoing and registered with ClinicalTrials.gov, NCT04811040.

Role of the funding source

The trial was designed and conducted by the sponsor (Gilead Sciences) in collaboration with the investigators. The sponsor collected the data, monitored trial conduct, and performed the statistical analyses.

Results

Between June 29 and Dec 8, 2021, we screened a total of 124 participants and 21 were enrolled at 11 HIV treatment sites in the USA (appendix p 2; figure 1). For enrolled participants, geometric mean IC_{90} was 0·48 (range 0·08–1·79) µg/mL for teropavimab and 0·19 (0·03–1·05) µg/mL for zinlirvimab (appendix p 7).

One participant received oral lenacapavir only on day 1 and then withdrew. Ten participants received the full lenacapavir, teropavimab, and zinlirvimab 10 mg/kg regimen and ten participants received the full lenacapavir, teropavimab, and zinlirvimab 30 mg/kg regimen. 18 participants completed follow-up on the study regimen until week 26 (data cutoff date for the 26-week analysis was June 10, 2022). One participant in the zinlirvimab 30 mg/kg group withdrew from study participation at week 12 and one in the zinlirvimab 10 mg/kg group resumed ART before week 26 because of viral rebound.

18 (86%) of 21 participants were male. Participants ranged in age from 25 years to 61 years and median age was 44 years. Most enrolled participants were White men and all participants were cisgender. People of Black, Asian, or mixed race or who declined to state race comprised nine people and seven identified as Hispanic or Latino (table 1; appendix p 3). Median BMI was 30·2 (range 21·6–54·1) kg/m². Median CD4 cell count was 909 (range 547–1644; IQR 687–1270) cells per µL. Median self-reported time since HIV diagnosis was 8·2 (range 2·6–26·3) years and 16 (76%) of 21 reported starting ART within 1 year of diagnosis. 14 participants were receiving a combination of integrase inhibitor and nucleoside reverse transcriptase inhibitors as the baseline regimen; five were receiving non-nucleoside reverse transcriptase inhibitors combined with nucleoside reverse transcriptase inhibitors, one received a protease inhibitor and nucleoside reverse transcriptase inhibitor combination, and one received an integrase inhibitor and non-nucleoside reverse transcriptase inhibitor combination (table 1). Median duration of the baseline ART regimen was 2·6 (range 2·0–5·5) years.

	Subcutaneous lenacapavir, teropavimab, zinlirvimab 10 mg/kg (n=11)	Subcutaneous lenacapavir, teropavimab, zinlirvimab 30 mg/kg (n=10)	Total (n=21)
Age, years	46 (31–61)	37 (25–59)	44 (25–61)
Sex at birth			
Male	11	7	18
Female	0	3	3
Race			
Asian	2	1	3
Black	1	2	3
White	7	5	12
Other	1	2	3
Hispanic or Latino ethnicity	4	3	7
Weight, kg	90·2 (58·9–150·0)	92·9 (60·2–143·0)	90·2 (58·9–150·0)
BMI, kg/m²	30·2 (21·6–42·9)	30·2 (21·6–54·1)	30·2 (21·6–54·1)
CD4 count, cells per µL	778 (547–1391)	1024 (667–1644)	909 (547–1644)
CD4/CD8 ratio	0·87 (0·58–1·98)	1·21 (0·86–2·29)	1·09 (0·58–2·29)
Duration of baseline ART, years	3·6 (2·4–4·8)	2·6 (2·0–5·5)	2·6 (2·0–5·5)
Time since HIV diagnosis, years	12·4 (6·4–26·3)	5·3 (2·6–22·4)	8·2 (2·6–26·3)
HIV-1 RNA <50 copies per mL	11	10	21
Teropavimab IC_{90}, µg/mL	..	..	0·48 (0·08–1·79)
Zinlirvimab IC_{90}, µg/mL	..	..	0·21 (0·03–1·05)
Baseline antiretroviral therapy			
INSTI + NRTI	6	8	14
NNRTI + NRTI	4	1	5
Protease inhibitor + NRTI	1	0	1
INSTI + NNRTI	0	1	1

Data are median (range) or number. ART=antiretroviral therapy. IC_{90}=90% inhibitory concentration. INSTI=integrase strand-transfer inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Table 1: **Participant characteristics at baseline**

	Subcutaneous lenacapavir, teropavimab, zinlirvimab 10 mg/kg (n=11)	Subcutaneous lenacapavir, teropavimab, zinlirvimab 30 mg/kg (n=10)	Total (n=21)
Participants with any treatment-emergent serious adverse	9	10	19
Injection-site pain	5	5	10
Injection-site erythaema	4	3	7
Injection-site induration	2	4	6
Injection-site nodule	4	2	6
Injection-site mass	3	1	4
COVID-19	3	0	3
Upper respiratory tract infection	3	0	3
Abdominal pain upper	2	0	2
Arthralgia	2	0	2
Back pain	0	2	2
Cough	1	1	2
Dermatitis	1	1	2
Diarrhoea	1	1	2
Fatigue	1	1	2
Gastroenteritis	2	0	2
Injection-site discolouration	1	1	2
Injection-site reaction	1	1	2
Insomnia	1	1	2
Lower respiratory tract congestion	0	2	2
Lymphadenopathy	0	2	2
Urinalysis abnormal	1	1	2
Abdominal distension	0	1	1
Abdominal pain	1	0	1
Abdominal tenderness	1	0	1
Abnormal faeces	1	0	1
Anxiety	1	0	1
Aphthous ulcer	1	0	1
Bacterial vulvovaginitis	0	1	1
Bladder discomfort	1	0	1
Depression	0	1	1
Dermatitis allergic	0	1	1
Dermatitis contact	0	1	1
Erectile dysfunction	0	1	1
Fall	1	0	1
Folliculitis	0	1	1
Foot fracture	0	1	1
Gastroenteritis *Escherichia coli*	1	0	1
Genital herpes simplex	0	1	1
Genital lesion	1	0	1
Glossitis	1	0	1
Headache	1	0	1
Hordeolum	1	0	1
Hyperglycaemia	1	0	1
Hypothyroidism	1	0	1
Influenza-like illness	1	0	1
Injection-site bruising	0	1	1
Injection-site cellulitis	0	1	1

(Table 2 continues on next page)

There were no serious adverse events, no adverse events that led to study drug discontinuation, and no deaths. 19 participants reported an adverse event. Most adverse events were grade 1 or 2, two were grade 3, and none were grade 4 or higher. One participant had grade 3 injection-site cellulitis that resolved with one dose of antibiotics by intramuscular injection plus oral antibiotic treatment and one participant had injection-site erythaema that was grade 3 based on size (>10 cm) without other DAIDS-defined clinical features and resolved without intervention.

Overall, the most common adverse events were injection-site reactions due to subcutaneous injection of lenacapavir (table 2), consistent with what has been previously reported.[17] Injection-site reactions were reported in 17 of 20 participants who received lenacapavir injection. 12 participants had grade 1, three had grade 2, and two had grade 3 injection-site reactions. Excluding injection-site reactions, the most common adverse events occurring in more than one participant were COVID-19 (three participants) and upper respiratory tract infections (three participants), all occurring in the zinlirvimab 10 mg/kg group. One participant in the zinlirvimab 10 mg/kg group had an infusion-related reaction of grade 1 pyrexia with flushing after completing administration of both bNAbs, which resolved without treatment.

Two participants had treatment-emergent laboratory abnormalities with post-baseline value of grade 3 or higher (appendix p 5), one in the 10 mg/kg group with a graded increase in serum creatinine concentration despite having absolute serum creatinine values in the normal range and one in the 30 mg/kg group with a transient increase in lipase concentration and subsequent normal lipase on repeat testing. Neither treatment-emergent laboratory abnormality was judged to be clinically significant by the investigator.

At week 26, 18 (90%; 95% CI 68–99) of 20 participants who received the complete study regimen had an HIV-1 RNA concentration that was lower than 50 copies per mL (table 3). One (10%; 95% CI 0–45) of ten participants had viral rebound with plasma HIV-1 RNA concentration of 155 copies per mL at week 16 (repeat test was 534 copies per mL) in the 10 mg/kg group, and no participants had viral rebound in the 30 mg/kg group. One participant in the zinlirvimab 30 mg/kg group had no data in the analysis window because they withdrew consent at week 12 and had HIV-1 RNA concentrations of below 50 copies per mL at that time.

The participant who had virological rebound restarted baseline ART (emtricitabine, rilpivirine, and tenofovir alafenamide) with the week 16 visit and had resuppressed viral load (HIV-1 RNA <50 copies per mL) at the following week 20 visit. No pre-existing lenacapavir resistance-associated substitutions (including Leu56Ile, Met66Ile, Gln67His, Lys70Asn/Ser/Arg, Asn74Asp/Ser, Ala105Thr,

and Thr107Asn)[24] were detected in HIV-1 capsid from proviral HIV DNA at screening. Genotypic and phenotypic testing for resistance to study drugs was unsuccessful at the time of virological rebound (attributed to low plasma viral load). Plasma concentration of lenacapavir and serum concentrations of teropavimab and zinlirvimab for this participant were within the range of other participants in the same dose group (appendix p 8).

No clinically meaningful changes from baseline in CD4 counts were observed at weeks 4 or 12. At week 26, median change in CD4 cell counts from baseline was an increase of 61 (IQR –54 to 112) cells per µL: an increase of 61 (–32 to 118) cells per µL in the zinlirvimab 10 mg/kg group and an increase of 36 (–54 to 96) cells per µL in the zinlirvimab 30 mg/kg group (appendix p 10). Median change from baseline in CD4/CD8 cell count ratio at week 26 was an increase of 0·06 (–0·07 to 0·21): an increase of 0·06 (–0·05 to 0·35) in the zinlirvimab 10 mg/kg group and an increase of 0·04 (–0·22 to 0·14) in the zinlirvimab 30 mg/kg group.

Median concentration-over-time profiles of lenacapavir match what has been previously observed,[15] and profiles for teropavimab and zinlirvimab 10 mg/kg and 30 mg/kg align with profiles in a previous phase 1 study (figure 2).[25] Difference in zinlirvimab concentration between the 10 mg/kg and 30 mg/kg dose was approximately dose-proportional. Mean week 26 teropavimab concentration was 40·5 mg/mL (SD 6·4; range 28·1–50·8) following a single intravenous dose of 30 mg/kg. Mean week 26 zinlirvimab concentrations were 27·2 mg/mL (6·4; 18·9–38·2) in the 10 mg/kg group and 84·6 mg/mL (27·1; 51·9–124·0) following single intravenous doses, which were more than 20-fold higher than the highest in vitro IC_{90} values for teropavimab and zinlirvimab, suggesting that therapeutic concentrations of the bNAbs were maintained in all participants for at least 26 weeks. Mean week 26 lenacapavir concentration was 24·9 mg/mL (SD 16·8; range 4·83–57·2), which was comparable to that in previous phase 2 and phase 3 clinical studies of lenacapavir.[26]

By the week 26 primary analysis cutoff, six (30%) of 20 participants developed treatment-emergent ADAs against teropavimab and six (30%) developed treatment-emergent ADAs against zinlirvimab (appendix p 6); one participant did not receive either antibody. Among them, four participants developed treatment-emergent ADAs against both bNAbs, including the participant with virological rebound at week 16 who developed low-titre ADAs against zinlirvimab at week 12 and against teropavimab at week 26. ADAs detected were generally low in titres and did not seem to increase with time in all participants within the 26-week period reported in this Article (appendix p 11). We found no clinically significant effect of ADAs on participant safety or the pharmacokinetic profile of teropavimab and zinlirvimab.

	Subcutaneous lenacapavir, teropavimab, zinlirvimab 10 mg/kg (n=11)	Subcutaneous lenacapavir, teropavimab, zinlirvimab 30 mg/kg (n=10)	Total (n=21)
(Continued from previous page)			
Injection-site inflammation	0	1	1
Injection-site oedema	1	0	1
Injection-site paraesthesia	1	0	1
Injection-site pruritus	1	0	1
Libido decreased	0	1	1
Migraine	1	0	1
Myokymia	1	0	1
Night sweats	1	0	1
Onychomycosis	1	0	1
Oral herpes	0	1	1
Oropharyngeal pain	0	1	1
Peripheral swelling	1	0	1
Pharyngitis	1	0	1
Pharyngitis streptococcal	0	1	1
Proteinuria	0	1	1
Pyrexia	1	0	1
Rhinitis	1	0	1
Seasonal allergy	1	0	1
Sleep disorder	1	0	1
Tension headache	1	0	1
Tooth abscess	1	0	1
Toothache	1	0	1
Vaccination complication	1	0	1
Weight decreased	1	0	1

Data are n. With the exception of lenacapavir injection-site reactions, treatment-related adverse events occurred in three participants: diarrhoea (grade 2, n=1), headache (grade 1, n=1), and pyrexia (grade 1, n=1).

Table 2: **Treatment-emergent adverse events**

	Subcutaneous lenacapavir, teropavimab, zinlirvimab 10 mg/kg (n=10)	Subcutaneous lenacapavir, teropavimab, zinlirvimab 30 mg/kg (n=10)	Total (n=20)
HIV-1 RNA ≥50 copies per mL, n (%; 95% CI)	1 (10%; 0–45)	0 (0; 0–31)	1 (5%; 0–25)
HIV-1 RNA <50 copies per mL, n (%; 95% CI)	9 (90%; 56–100)	9 (90%; 56–100)	18 (90%; 68–99)
Discontinued study treatment and last available HIV-1 RNA <50 copies per mL, n	0	1	1

Table 3: **Virological efficacy outcomes at week 26 by US Food and Drug Administration Snapshot**

Discussion

In this study, we provide preliminary evidence of the potential for a new regimen for HIV treatment that incorporates novel, long-acting classes of agents: two potent bNAbs that target distinct binding sites on the HIV-1 envelope and lenacapavir, which is a first-in-class HIV capsid inhibitor approved for multidrug-resistant HIV. The results serve as proof-of-principle that this regimen can sustain viral suppression for 6 months

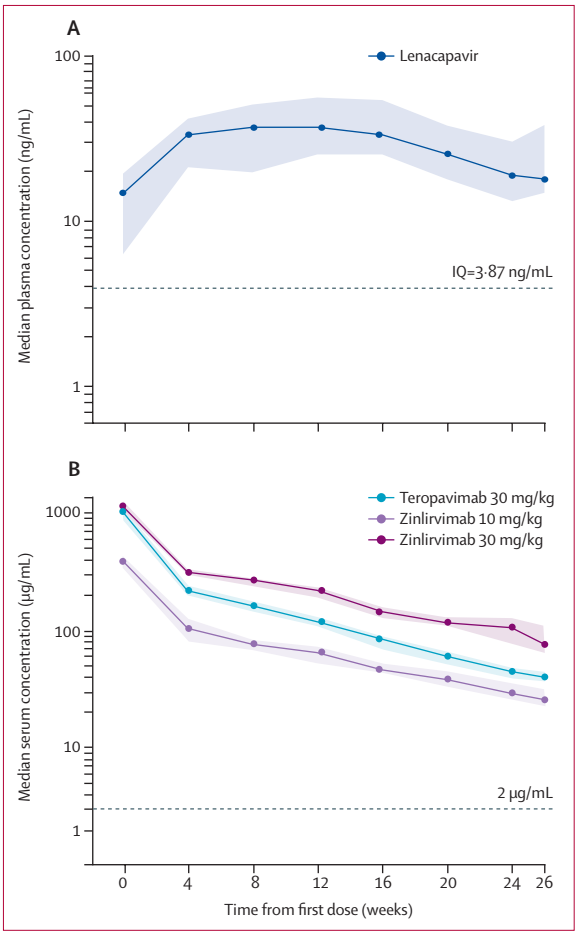

Figure 2: **Median concentration *vs* time curve for the long-acting regimen**
The shaded area indicates IQR. (A) Lenacapavir. (B) Teropavimab and zinlirvimab. An in-vitro IC_{90} level of ≤2 µg/mL was used to define sensitivity in the screening assay. IC_{90}=90% inhibitory concentration. IQ=inhibitory quotient.

in select participants, allowing additional investigation of a treatment regimen with twice yearly dosing.

Like other therapeutic antibodies targeting viruses, bNAbs have had an excellent safety profile;[10,13,27] the novel combination with lenacapavir was generally well tolerated, with no serious adverse events or adverse events that led to treatment discontinuation. Expected injection-site reactions to lenacapavir were observed and experience from larger studies suggests that these reactions are manageable, generally mild-to-moderate, and do not result in treatment discontinuation.[16,17] In the current study, two grade 3 injection-site reactions were observed; one (erythaema) resolved without intervention and the other was managed with antibiotics and resolved. Neither grade 3 injection-site reactions led to participant discontinuation. The long-term side-effects of lenacapavir combined with bNAbs are unknown and whether the regimen might have decreased risk of the types of long-term toxicity associated with some oral ART regimens remains to be seen.[28]

One virological breakthrough occurred in a participant who received the lower dose of zinlirvimab. In this individual, no resistance to any of the three agents was detected at baseline and concentrations of all study drugs were maintained at levels predicted to be therapeutic.[10,11,16] A low level of ADAs to zinlirvimab developed before virological rebound but did not alter antibody concentration relative to other participants. Phenotypic susceptibility testing of bNAbs on HIV DNA, as was done in this study, might help identify people who will respond to treatment but is not widely available and resulted in more than 50% of participants screened being ineligible, either due to assay failure or susceptibility above our cutoff for one or both antibodies. Different groups are working on assay optimisation or alternative screening methods that can lower the rate of assay failure. In addition, there are limited data on the performance of the available methods to predict clinical outcomes and optimal interpretation criteria (eg, an IC_{90} threshold) have not been established. Whether susceptibility to both antibodies is required for success or whether a clinically validated cutoff can be established will require additional research. Importantly, individuals with a viral rebound on this novel regimen can resume oral ART without risk of cross-resistance to one or more established standard-of-care antiretroviral classes.[3,29] In addition to direct antiviral activity, bNAbs engage immune effector cells and can produce targeted killing of HIV-infected cells, which are mechanisms that have led to the investigation of bNAbs in HIV cure research.[30–32] Whether the regimen of lenacapavir, teropavimab, and zinlirvimab results in measurable changes in the HIV-specific immune responses or effects on the HIV-1 viral reservoir is currently being explored.

Limitations include the small sample size of this study and, due to the study length, the risk of viral rebound after 26 weeks with repeated dosing and the optimal dose of zinlirvimab could not be assessed. Participants were healthy, had long-term use of ART, with preserved CD4 cell counts appropriate for a novel regimen in a phase 1 study, and results might not be generalisable to all people with HIV.

Long-acting ART has been heralded for people with HIV who are unable to adhere to daily pills as a way to improve viral suppression, to reduce onward transmission, and potentially to reduce stigma, protect disclosure of HIV status, and provide convenience.[2,33] Short of a cure, progress on innovative, long-acting treatments for HIV that enable infrequent dosing could provide better persistence on therapy, resulting in individual and public health benefits for both HIV disease and transmission. The results of this study provide evidence that HIV-1 suppression for at least 26 weeks can be safely achieved with a novel combination of lenacapavir, teropavimab, and zinlirvimab in appropriately selected people with HIV.

Contributors

LAV, YZ, HH, SEC, JMB, and MC contributed to study conception and design. JJE, SJL, GC, PC, PJR, DJ, ED, AM, SEW, MR, and LG contributed to data acquisition. All authors contributed to data analysis or interpretation. JJE, HH, and SEC directly accessed and verified the underlying data. All authors were involved in the writing, review, and editing of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Gilead Sciences shares anonymised individual participant data on 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 the discretion of Gilead Sciences 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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