Safety, pharmacokinetics, and antiviral activity of a combination of TMB-365 and TMB-380 in people living with HIV suppressed with antiretroviral therapy in the USA: a phase 1b/2a, open-label, dose-escalation study

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Summary

Background Long-acting antibody-based regimens might reduce treatment burden for people living with HIV. We aimed to assess safety, pharmacokinetics, and antiviral activity of TMB-365, a CD4-directed monoclonal antibody, combined with TMB-380, a long-acting broadly neutralising monoclonal antibody targeting gp120 CD4-binding site.

Methods In this phase 1b/2a, open-label, dose-escalation study, virologically suppressed adults (aged 18–70 years) living with HIV on stable oral combination antiretroviral therapy (ART) were enrolled from six clinic sites in California, Florida, and Texas, in the USA. In phase 1b, participants received single intravenous doses of TMB-365 plus TMB-380 at either 2400 mg, 3200 mg, or 4800 mg and continued ART for 12–16 weeks. In phase 2a, participants discontinued ART at baseline and received 4800 mg of each antibody intravenously every 8 weeks, three times over 24 weeks, without pretreatment screening. Primary outcomes were safety and pharmacokinetics in phase 1b, and safety, pharmacokinetics, and antiviral activity in phase 2a. In phase 2a all treated participants were included in safety and efficacy analyses, except one participant inadvertently dosed after developing an acute medical condition before dosing. This trial is registered at ClinicalTrials.gov (NCT05275998) and is complete.

Findings Between July 5, 2022, and Nov 20, 2024, 30 participants (28 male and two female) were enrolled in phase 1b, and 20 male participants were enrolled in phase 2a. In phase 2a, two participants discontinued prematurely, and one was lost to follow-up. No serious or grade 3 or worse adverse events were observed. All treatment-emergent adverse events were mild or moderate. Pharmacokinetic targets were met at week 8 in the phase 1b 4800 mg group. In phase 2a, viral suppression at week 24 occurred in 16 (94%, 95% CI 71–100) of 17 participants in the per-protocol population and 16 (80%, 95% CI 56–94) of 20 participants in the intention-to-treat population. No confirmed virological failures were reported.

Interpretation TMB-365 (4800 mg) plus TMB-380 (4800 mg) every 8 weeks appears safe, might be effective as maintenance therapy in virologically suppressed people living with HIV, and merits further study.

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Introduction

Globally, in 2024, 39·9 million people were living with HIV-1 infection and 620 000 died.[1] Although combination antiretroviral therapy (ART) has markedly reduced HIV-related morbidity and mortality,[2] a life-expectancy gap of 5–13 years persists, driven by higher rates of premature mortality from non-AIDS-defining comorbidities, compared with the general population.[3,4]

However, recent changes in US public health policy threaten to reverse progress domestically and globally.[5] The treatment course for HIV-1 remains lifelong daily oral ART, except bimonthly intramuscular cabotegravir and rilpivirine. Long-acting alternatives to daily oral therapy remain of intense interest to overcome issues surrounding long-term toxic effects, pill fatigue, and adherence.[6] These alternatives include broadly neutralising monoclonal antibodies.[7]

TMB-365, a second-generation, CD4-directed, post-attachment inhibitor based on ibalizumab-uiyk,[8–11] binds an epitope on domain 2 of the CD4 receptor expressed on helper (CD4) T cells, thereby inhibiting HIV entry. TMB-365 preserves the binding specificity of ibalizumab while slightly modifying the amino acid sequence to improve antiviral activity, stability, resistance profile, and pharmacokinetics.

Initial screening of ibalizumab variants with a glycan inserted on the light chain identified LM52, which showed unprecedented antiviral activity against 118 pseudoviruses across 11 distinct HIV-1 clades, and was subsequently developed as TMB-365.[12] As resistance

Research in context

Evidence before this study

We searched PubMed on May 28, 2026, using the terms "HIV clinical trials and long acting agents"; "HIV clinical trials and broadly neutralising antibodies (bNAbs)"; and "dual and triple bNAb therapy and HIV treatment", for full-text articles published over the past 7 years, without language limitation. Eight reports in English were identified as relevant after exclusion of reviews, studies in uninfected populations, and trials of long-acting small molecules alone. A combination of 3BNC117 and 10-1074 showed that antibody combinations could transiently control viraemia after analytical treatment interruption or in individuals with low-level viraemia. Viral control lasted 33 weeks in the treatment interruption group and approximately 40 weeks in two of five individuals with viraemia. However, baseline susceptibility influenced outcomes, with reduced susceptibility to one or both antibodies. Although transient suppression occurred, durable control was not achieved despite high bNAb concentrations. A triple regimen of PGDM1400, PGT121, and VRC07-523LS also did not provide durable suppression, with rapid selection of resistant variants to PGDM1400 and PGT121. Combinations of long-acting bNAbs with small molecule antivirals improved durability, but were constrained by feasibility and tolerability. Lenacapavir plus dual bNAb, teropavimab and zinlirvimab, maintained suppression in most participants for 26 weeks, but required strict susceptibility testing, resulting in an 83% screen failure rate and frequent injection site reactions. A cabotegravir plus VRC07-523LS combination maintained suppression in 93% of participants over 24 weeks, but required restrictive entry criteria and was associated with several grade 3 adverse events. UB-421, an anti-CD4 monoclonal antibody similar in mechanism and duration of activity to ibalizumab, was given every 2 weeks as monotherapy nine times to 29 adults suppressed on combination oral therapy after analytical treatment interruption. All participants maintained HIV-1 RNA below 400 copies per mL, although 28% had low-level viral rebound between 21 copies per mL and 142 copies per mL. These findings support the potential of anti-CD4 antibodies to suppress virological rebound during treatment interruption or as maintenance therapy. Taken together, these studies show that bNAb-based or hybrid long-acting regimens can achieve short-term viral suppression, but remain limited by incomplete breadth, pre-existing resistance, and practical barriers to implementation. The need for a broadly active, well tolerated, and easily administered long-acting antibody regimen, therefore, remains unmet.

Added value of this study

This study evaluated a novel combination of TMB-365, a long-acting antibody targeting the CD4 receptor, and TMB-380 (VRC07-523LS), a potent bNAb targeting the CD4 binding site on the HIV-1 envelope. Preclinical data indicated that TMB-365 exhibits exceptional breadth and potency, including against strains resistant to existing bNAbs, supporting its development in combination with TMB-380. To the best of our knowledge, this is the first study to evaluate the fixed dose, pharmacokinetics, safety, and antiviral activity of the combination of TMB-365 and TMB-380 for maintenance therapy in adults with HIV-1 virologically suppressed on oral combination antiretroviral therapy for at least 6 months. Phase 1b showed favourable pharmacokinetics and safety supporting dosing every 8 weeks. In the phase 2a study, the regimen maintained viral suppression over 24 weeks without pretreatment susceptibility screen, supporting further investigation.

Implications of all the available evidence

This study provides the first clinical evidence that a combination of an antibody targeting a cellular receptor and a long-acting bNAb can maintain viral suppression safely and effectively for 24 weeks without pretreatment susceptibility testing. The simplified dosing, favourable tolerability, and reduced screening burden make this approach more feasible than previous long-acting regimens. These findings support the initiation of a 48-week randomised phase 2b study comparing this dual-antibody regimen with standard oral combination antiretroviral therapy, incorporating bodyweight-based dosing of TMB-365. Together, these results represent a step towards a simplified, durable, and broadly applicable long-acting antibody regimen for HIV maintenance therapy.

to ibalizumab has been associated with the loss of essential N-linked glycosylation sites in the V5 loop of HIV-1 gp120, the insertion of the glycan at the 52nd site on the light chain of ibalizumab resulted in susceptibility of ibalizumab-resistant variants.[13] Commercial testing of TMB-365 against a panel of isolates from patients with HIV-1 showed consistent activity against strains resistant to all approved antiretroviral drugs, including ibalizumab. Compared with ibalizumab, TMB-365 has a glycan insertion to improve antiviral activity, an IgG1 backbone with mutations in the Fc region that reduce effector function, paired LS substitutions in the neonatal Fc receptor binding site of the IgG1 constant region, and paired H substitutions in the variable light and heavy chain regions determinant to improve pharmacokinetics.[14] The prolonged half-life of TMB-365 compared with ibalizumab was shown in monkeys and humans (appendix p 31).

See Online for appendix

In the initial clinical study of TMB-365, single intravenous doses of 400 mg and 800 mg of TMB-365, or matching placebo, were administered to people living with HIV and those who were viraemic off ART, and a single dose of 1600 mg was administered to people living with HIV and virologically suppressed while continuing oral ART. As detailed in the study protocol (appendix pp 33–35), efficacy was shown with over 1·5 $\log_{10}$

HIV-1 RNA reduction at both 400 mg and 800 mg doses, and TMB-365 was well tolerated up to 1600 mg (unpublished).

TMB-380 (also known as VRC07-523LS and VRC-HIVMAB075-00-AB) is an engineered variant of VRC07, directed against the envelope CD4-binding site of gp120.[15,16] After licensing from the National Institute of Allergy and Infectious Diseases, TaiMed Biologics manufactured TMB-380 with similar physical, chemical, and functional properties to develop a standalone combination of TMB-380 with their own monoclonal antibodies for HIV treatment.

TMB-380 is a recombinant human IgG1-based antibody produced in the Chinese hamster ovary DG44 cell line. The clinical experience with VRC07-523LS includes around 30 clinical studies conducted in Kenya, South Africa, Tanzania, the USA, Zimbabwe, and other sponsor-designated countries. Details of these studies can be found on the WHO International Clinical Trials Registry Platform. VRC07-523LS has been administered by intravenous, subcutaneous, or intramuscular injection, either individually or in combination with other HIV drugs. Single-dose regimens of VRC07-523LS up to 40 mg/kg intravenously or 20 mg/kg subcutaneously and repeat-dose regimens of 40 mg/kg intravenously, 5 mg/kg or 10 mg/kg subcutaneously, or 2·5 mg/kg intramuscularly have been well tolerated in adults. Most reported local and systemic reactogenicity was mild to moderate in severity. There have been no serious adverse events assessed as related to VRC07-523LS in adults.[16–20] VRC07-523LS showed favourable pharmacokinetics, with a half-life of 38 days and 33 days after intravenous and subcutaneous administrations, respectively, in participants without HIV infection (n=25).[16] In people living with HIV (n=9), a single intravenous dose of VRC07-523LS at 40 mg/kg achieved a 1·7 $\log_{10}$ HIV-1 RNA reduction within 14 days.[18]

In this phase 1b/2a dose-escalation study, we evaluated the safety, pharmacokinetics, and antiviral activities of the combination of the CD4-directed monoclonal antibody, TMB-365, and the broadly neutralising monoclonal antibody, TMB-380, given intravenously to people living with HIV virologically suppressed on oral ART.

Methods

Study design and participants

We conducted a multicentre, two-part, open-label, dose-escalation, phase 1b/2a study in adults living with HIV on daily oral ART. The study was conducted and completed at six sites across California, Florida, and Texas, in the USA, including clinical research centres, specialty practices, physician offices, and community clinics. The study protocol was reviewed and approved by the US Food and Drug Administration and a Sterling institutional review board (identification number 10037) and is available in the appendix (pp 11–82). The trial is registered with ClinicalTrials.gov (NCT05275998) and has been completed.

Participants were recruited by use of institutional review board-approved media. Participants were virologically suppressed adults who were evaluated for all inclusion and exclusion criteria (appendix pp 21–23). Inclusion criteria were age 18–70 years, confirmed asymptomatic HIV-1 positive by serological test, having non-quantifiable plasma HIV-1 RNA at screening, being virologically suppressed with continuous oral ART for 6 months or more, clinically stable as measured through laboratory tests including CD4 cell count above 350 cells per mm³, and being able to understand and willing to comply with the study, including use of contraception. Exclusion criteria were not being on a stable ART regimen for 3 months, receipt of antibody for HIV treatment or prevention, virologically suppressed with cabotegravir and rilpivirine given intramuscularly, pregnant or lactating, known allergy to study drug or antibody, history of severe allergic reactions to medications, major psychiatric illness, severe illness requiring systemic treatment or hospitalisation, receipt of immunomodulatory agents, HIV vaccine, chemotherapy or investigational therapy within 180 days before dosing, medical condition interfering with study determined by investigator, lack of venous access, and experienced virological failure. Written informed consent, available in English, Spanish, or Haitian Creole, was obtained from all participants in their preferred language without specifying the potential HIV transmission risk. Data on sex (male or female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, not reported, or unknown), and ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, or unknown) were self-reported by the participants. The study was monitored, and the protocol deviations were documented, including erroneous dosing and incomplete assessments. The study had an independent data monitoring committee.

For the **WHO International Clinical Trials Registry Platform** see https://trialsearch.who.int/Default.aspx

The study consisted of the single-dose sentinel (phase 1b) and multiple-dose core (phase 2a) phases. In the sentinel phase (appendix p 5), three groups of ten participants were infused sequentially with 2400 mg, 3200 mg, or 4800 mg of each antibody and evaluated for safety and pharmacokinetics while continuing ART.

The sentinel phase results informed the subsequent core phase (appendix p 5), with trough pharmacokinetic targets for TMB-365 and TMB-380 of 0·3 µg/mL and 65·0 µg/mL, respectively. Trough pharmacokinetic targets were based on previous exposure–response data for ibalizumab (plateau above 0·3 µg/mL) and a phase 1 post-hoc analysis for TMB-380, where approximately 65 µg/mL corresponded to 90% predicted neutralisation coverage (serum concentration 100-fold greater than the

viral in-vitro inhibitory concentration 50% [IC_{50}] value).[16] These targets were not prospectively validated and were used as reference values.

During phase 2a, 20 participants discontinued oral ART on the day of the first dose and were infused every 8 weeks, for a total of three infusions with 4800 mg of each antibody, and evaluated for safety, pharmacokinetics, and antiviral activity over 24 weeks; oral ART was then restarted at week 24. Baseline susceptibility and maximum percent inhibition for TMB-365 and TMB-380 on peripheral blood mononuclear cells were not performed at screening. Participants in the core phase who discontinued prematurely due to reasons other than associated treatment-emergent adverse events or virological failure could be replaced. Unscheduled visits occurred to follow up treatment-emergent adverse events or confirm virological failure in the event of plasma HIV-1 RNA being reported as more than 50 copies per mL.

Randomisation and masking

The enrolment was sequential, beginning with the phase 1b, three-group, open-label, single-dose, sequential dose-escalation sentinel phase, then phase 2a, a single-arm core phase. No randomisation or masking was applied.

Procedures

The sentinel groups were infused with 2400 mg, 3200 mg, or 4800 mg of each antibody, mixed and diluted in one 250 mL intravenous bag of normal saline, over 60 min, with sterile technique, within 4 h after preparation. Participants were followed up for pharmacokinetics and safety every 1–2 weeks for 12–16 weeks (appendix p 5). Dose escalation was approved by the independent data monitoring committee. All infusions were performed in outpatient clinics with vital signs assessed every 15 min during infusion and up to 3–5 h post infusion. Oral suppressive ART was continued throughout the sentinel phase (appendix p 5). In both phase 1b and 2a, participants were instructed to report any changes in health status to study staff. Safety was evaluated by use of the Division of AIDS Table for Grading of Adult and Pediatric Adverse Events (version 2.1), with acute infusion reactions graded per Common Terminology Criteria for Adverse Events (version 5.0) in both phase 1b and 2a.

TMB-365 serum concentrations were measured by use of anti-idiotype capture enzyme-linked immunosorbent assay. The lower limit of quantification was 100 ng/mL. TMB-380 was quantitatively measured by use of Meso Scale Discovery electrochemiluminescence (Meso Scale Diagnostics, Rockville, MD, USA). The lower limit of quantification for TMB-380 sentinel and TMB-380 core was 31·3 ng/mL and 62·5 ng/mL, respectively. Serum samples collected from sentinel participants were used to characterise the pharmacokinetic profile. The pharmacokinetic parameters were estimated by non-compartmental analysis with Phoenix WinNonlin, version 8.5.

Receptor occupancy of CD4 by TMB-365 was measured by flow cytometry (FACSCanto II; BD Biosciences, San Jose, CA, USA) with a two-tube assay (unsaturated *vs* drug saturated). CD4 cells were identified by use of CD45, CD3, and CD4 markers. Receptor occupancy was calculated as percent saturation based on the ratio of median fluorescence intensity between sample and saturated control.

The presence of anti-TMB-365 and anti-TMB-380 antibodies was established with a tiered approach based on the Meso Scale Discovery electrochemiluminescence immunoassay.

During the core phase (appendix p 5), 4800 mg of each antibody was prepared and infused every 8 weeks, with monitoring of vital signs every 15 min during infusion and up to 60 min post infusion for 24 weeks. Participants took the last oral ART at the baseline visit in the clinic before the first infusion. Safety, pharmacokinetics, and maintenance of virological suppression were assessed at least every 4 weeks with longitudinal measurements of plasma HIV-1 RNA with a minimum turnaround time of 3 days. The antiviral activity outcome was the percentage of participants with plasma HIV-1 RNA less than 50 copies per mL at week 24 and virological failure, defined as two consecutive HIV-1 RNA values of more than 50 copies per mL at least 2 weeks apart. The confirmatory testing was triggered when the HIV-1 RNA value was more than 50 copies per mL during the study. Virological failure would result in immediate resumption of oral ART. After 24 weeks, oral ART was resumed, with one additional visit at week 28. Plasma samples for potential phenotype or genotype resistance analyses were collected and stored per protocol; because no protocol-defined virological failure occurred, resistance testing was not triggered and the archived samples were discarded after study completion. The HIV Treatment Satisfaction Questionnaire status was completed by core participants at baseline and weeks 8, 24, and 28.[21–23]

Outcomes and statistical analysis

Phase 1b explored the primary outcomes of safety and pharmacokinetics of three doses of TMB-365 plus TMB-380, which was descriptive and not intended to detect statistically significant differences between doses. Phase 2a was based on the results of phase 1b; it was designed to be descriptive and was not powered for comparisons to existing maintenance regimens. Primary outcomes were safety, pharmacokinetics, and antiviral activity (appendix p 20). The efficacy analysis was planned to include all participants who received at least one dose of TMB-365 plus TMB-380 in the intention-to-treat (ITT) population. Efficacy data were ascertained for phase 2a only (n=20) and summarised the proportion of participants with confirmed plasma HIV-1 RNA values of less than 50 copies per mL at week 24 in both the ITT

population and the per-protocol population with Clopper–Pearson 95% CIs. Exploratory objectives were immunogenicity of TMB-365 plus TMB-380 and resistance profile if virological failure was observed. All statistical analyses and data summaries were performed by use of SAS, version 9.

Role of the funding source

TaiMed Biologics funded the study, including research grants to investigators at each participating site. TaiMed Biologics, as the study sponsor, had control over the study design, data analysis, data interpretation, and writing of the report.

Results

The phase 1b/2a study was conducted between July 5, 2022, and Nov 20, 2024. 70 participants were assessed for eligibility, of whom 30 participants were enrolled in the sentinel phase, and 20 in the core phase (figure 1). Participants were predominantly male, White, and non-Hispanic (table 1). Notably, one participant in phase 1b 4800 mg group, was erroneously dosed (1600 mg TMB-365 and TMB-380). This participant was not included in the pharmacokinetics analysis because the administered dose differed from the assigned regimen and was expected to result in substantially different drug concentrations.

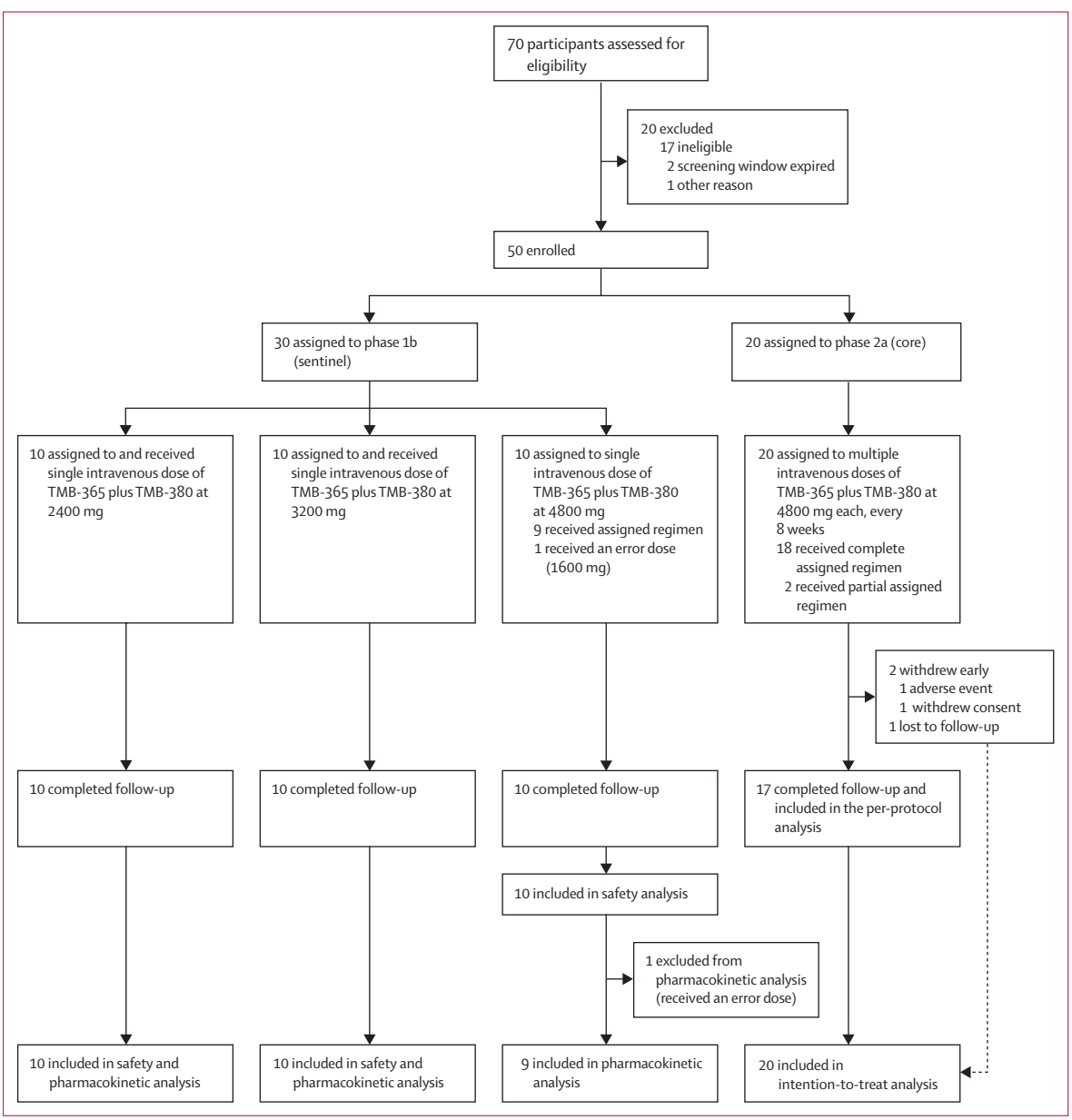


Figure 1: **Trial profile**

In phase 2a, before dosing and between the screening visit and the baseline visit, one participant had a gastrointestinal bleed and a resultant precipitous decline in haemoglobin (from 13·7 g/dL to 8·9 g/dL). This participant received one 4800 mg infusion of each antibody at baseline and was followed up for safety for 4 weeks, but further dosing and participation were contraindicated due to the presence of an acute, unidentified medical condition that preceded the initial dosing. This participant was not included in the efficacy analysis or any analysis and was replaced, per protocol, with an additional participant to reach the enrolment goal of 20 participants in phase 2a (figure 1). In phase 2a, two participants discontinued prematurely: one due to an adverse event (rash) and one due to withdrawal of consent for an atypical rash attributed to the study drug.One participant was lost to follow-up. All remaining participants completed the study.

	Sentinel groups (single dose)			Core group (repeat dose): 4800 mg every 8 weeks (n=20)
	2400 mg (n=10)	3200 mg (n=10)	4800 mg (n=10)	
Sex				
Male	10 (100%)	9 (90%)	9 (90%)	20 (100%)
Female	0	1 (10%)	1 (10%)	0
Age, years	44·5 (7·9, 36–58)	43·1 (12·1, 28–58)	45·6 (10·9, 29–60)	48·8 (12·4, 24–67)
Weight, kg	79·1 (13·6, 59·7–104·5)	92·7 (26·6, 55·7–147·7)	82·9 (20·1, 60·2–129·5)	83·6 (14·7, 58·3–111·4)
Ethnicity				
Hispanic or Latino	3 (30%)	5 (50%)	1 (10%)	5 (25%)
Neither Hispanic nor Latino	7 (70%)	5 (50%)	8 (80%)	14 (70%)
Not reported	0	0	1 (10%)	1 (5%)
Unknown	0	0	0	0
Race*				
American Indian or Alaska Native	0	0	0	0
Asian	1 (10%)	0	1 (10%)	1 (5%)
Black or African American	1 (10%)	3 (30%)	2 (20%)	5 (25%)
Native Hawaiian or other Pacific Islander	0	0	0	0
White	9 (90%)	6 (60%)	7 (70%)	15 (75%)
Not reported	0	1 (10%)	1 (10%)	0
Unknown	0	0	0	0
Childbearing potential				
Yes	0	1 (10%)	0	0
No	0	0	1 (10%)	1 (5%)
NA	10 (100%)	9 (90%)	9 (90%)	19 (95%)
Baseline ART				
INSTI + 2 NRTIs	6 (60%)	8 (80%)	6 (60%)	11 (55%)
INSTI + NRTI	1 (10%)	0	0	3 (15%)
INSTI + NNRTI	0	0	1 (10%)	2 (10%)
NNRTI + 2 NRTIs	1 (10%)	0	1 (10%)	3 (15%)
Protease inhibitor + 2 NRTIs + pharmacokinetic booster	2 (20%)	1 (10%)	2 (20%)	1 (5%)
2 NRTIs + INSTI + pharmacokinetic booster	0	1 (10%)	0	0
CD4 count, cells per mm^3	804·9 (217·7, 509–1158)	701·9 (303·7, 371–1149)	715·9 (143·4, 407–890)	652·7 (245·7, 283–1306)

Data are n (%) or mean (SD, range). ART=antiretroviral therapy. NA=not applicable. INSTI=integrase strand transfer inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. *One or more race could be recorded for a single participant.

Table 1: **Baseline characteristics**

No serious treatment-emergent adverse events, deaths, grade 3 (severe) or 4 (life-threatening) treatment-emergent adverse events, opportunistic infections, significant intercurrent infections, immune-mediated events, or acute infusion reactions were reported in any participant (table 2). 32 grade 1 (mild) and grade 2 (moderate) treatment-emergent adverse events were noted in phase 1b, with five attributed to the study drug, including delayed onset of hypersensitivity reaction (n=2), peripheral coldness (n=1), sneezing (n=1), and fatigue (n=1); appendix pp 3–4. In phase 2a, there were 48 mild-to-moderate treatment-emergent adverse events. 16 were attributed to antibody infusions, including fatigue (n=4), headache (n=3), rash (n=2), flushing (n=2), dermatitis (n=1), pain (n=1), urticaria (n=1), fever (n=1), and chills (n=1; appendix pp 3–4). Two phase 2a participants did not complete the study due to developing a rash (appendix p 2).

The mean CD4 cell count remained stable without signs of depletion in phase 1b and phase 2a throughout the study (appendix p 6), and no clinically important trends were evident over time for any of the laboratory variables, including other lymphocyte subsets.

Elimination of TMB-365 was slower at concentrations above approximately 10 µg/mL, followed by a more rapid terminal elimination below this threshold (figure 2). Mean concentrations at week 8 were 0·5 µg/mL, 1·9 µg/mL, and 15·1 µg/mL for the 2400 mg, 3200 mg, and 4800 mg dose groups, respectively. In the 4800 mg group, seven (78%) of nine participants met the trough target and eight (89%) of nine maintained 80% or greater receptor occupancy at week 8 (appendix p 7), supporting the selection of 4800 mg every 8 weeks as the regimen for the core phase. In the core phase, mean trough concentration was 29 µg/mL, with 16 (84%) of 19 participants, 17 (94%) of 18 participants, and 17 (100%) of 17 participants meeting the trough target at weeks 8, 16, and 24, respectively (figure 2). Mean receptor occupancy remained above 80% at these timepoints (appendix p 7).

A slow, capacity-limited elimination of TMB-365 was followed by markedly more rapid elimination as the serum concentration declined. The half-life when the CD4 receptor is saturated and the terminal half-life when the CD4 receptor is unsaturated were estimated to represent the slow elimination rate under saturating conditions and the rapid elimination rate below saturation, respectively. During the saturated elimination phase, the effective half-life was approximately 10 days. As TMB-365 concentrations declined to values associated with uncoating of CD4 cells, the elimination rate increased, with a half-life of approximately 3–5 days (table 3).

For TMB-380, mean concentrations at week 8 were 60 µg/mL, 63 µg/mL, and 86 µg/mL for the 2400 mg, 3200 mg, and 4800 mg dose group, respectively (figure 2). In the 4800 mg dose group, seven (78%) of nine participants met the trough target at week 8, supporting the selection of 4800 mg every 8 weeks as the regimen for the core phase. In the core phase, mean trough concentration was 93 µg/mL and 80% of participants met the trough target (figure 2). The elimination half-life of TMB-380 was 30–35 days (table 3). Low-titre anti-TMB-365 antibodies were observed in one core phase participant who had an unrelated grade 1 treatment-emergent adverse event with no effect on pharmacokinetics or HIV-1 RNA. No anti-TMB-380 antibodies were observed.

Among 20 participants in the ITT population, 17 completed week 24 with data, two discontinued early due to treatment-emergent adverse events, and one missed the week 24 visit. Among the available 17 datapoints at week 24, 16 participants had plasma HIV-1 RNA less than 50 copies per mL and one participant had plasma HIV-1 RNA of 59 copies per mL. Thus, 16 (94%, 95% CI 71–100) of 17 participants in the per-protocol population and 16 (80%, 56–94) of 20 participants in the ITT population remained suppressed. Notably, no participant had confirmed virological failure (two consecutive HIV-1 RNA measurements of >50 copies per mL at least 2 weeks apart).

Transient HIV-1 RNA elevations (200–300 copies per mL) were observed in three individuals, all with subsequent re-suppression; therefore, resistance testing was not performed, as per protocol (figure 3). In these participants, TMB-365 concentrations were less than 1 µg/mL and CD4 receptor occupancy less than 80%, suggesting that transiently elevated HIV-1 RNA might be associated with less-than-ideal TMB-365 concentrations. Similarly, TMB-380 concentrations in these participants were at the lower end of the observed exposure range, but remained at levels expected to provide adequate antiviral coverage. These three individuals had bodyweights more than 90 kg, indicating a potential association between higher bodyweight, lower TMB-365 exposure, and transient HIV-1 RNA elevations (figure 3).

Exploratory exposure–response analyses by use of trough data showed a strong association between TMB-365 concentration and receptor occupancy, and a trend towards a lower probability of detectable HIV-1 RNA with increasing TMB-365 concentration (appendix pp 8–9). In contrast, the relationship between receptor occupancy and virological outcome was less clearly defined, and no receptor occupancy threshold could be identified. In covariate analyses, inclusion of bodyweight on clearance improved model fit (change in objective function value –14·7), whereas baseline CD4 cell count did not (change in objective function value <3), supporting bodyweight as a covariate of TMB-365 exposure.

Participants reported greater treatment satisfaction, measured with the HIV Treatment Satisfaction Questionnaire status, on some of the items (appendix p 10), including convenience, flexibility, fits in with lifestyle, and recommend to others, at weeks 8 and 24, when receiving TMB-365 plus TMB-380 treatment. Responses to the other items were similar across baseline and weeks 8, 24, and 28.

	Sentinel groups (single dose)			Core group (repeat dose), 4800 mg every 8 weeks (n=20)
	2400 mg (n=10)	3200 mg (n=10)	4800 mg (n=10)	
Treatment-emergent adverse event	9 (90%)	9 (90%)	5 (50%)	14 (70%)
Serious treatment-emergent adverse event	0	0	0	0
Treatment-emergent adverse events leading to study drug discontinuation	0	0	0	2 (10%)
Treatment-emergent adverse events related to study drug	2 (20%)	3 (30%)	0	8 (40%)
Severe (grade 3) or worse treatment-emergent adverse events	0	0	0	0

Data are n (%).

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

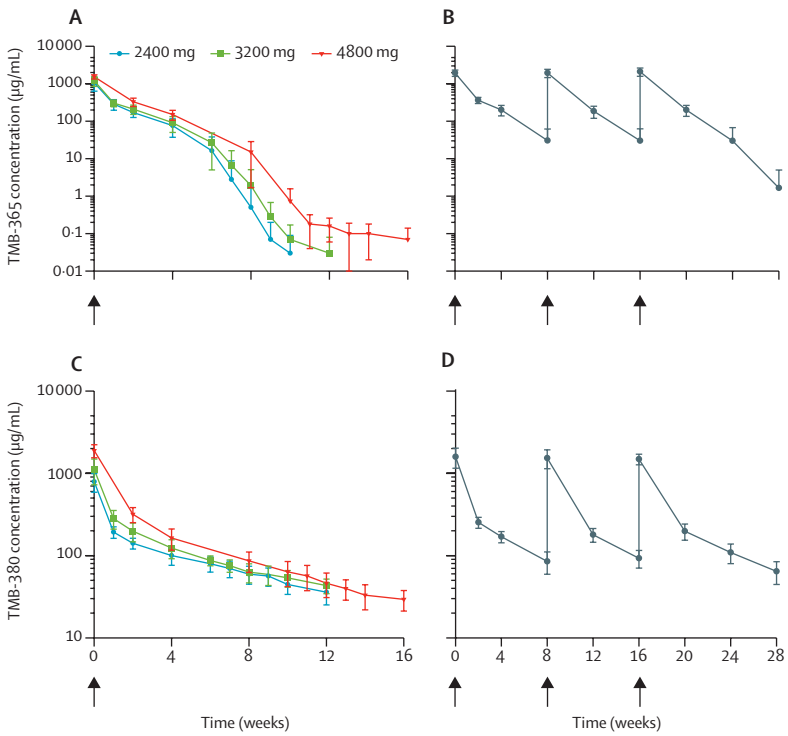


Figure 2: **Serum concentrations of TMB-365 and TMB-380**
Mean serum concentrations, with error bars indicating the SD, following a single administration of TMB-365 (A) or TMB-380 (C) in the sentinel group and following repeat administrations of TMB-365 (B) or TMB-380 (D) at weeks 0, 8, and 16 in the core group. Arrows indicate dosing timepoints.

Discussion

Long-acting agents for chronic HIV-1 infection are a promising strategy to improve treatment outcomes and

	T_{max} (days)	C_{max} (μg/mL)	AUC (days × μg/mL)	Clearance (mL/day)	$T_{1/2\beta}$ or $T_{1/2}$ (days)	$T_{1/2s}$ (days)
TMB-365						
2400 mg (n=10)	0·007	1067 (432)	7534 (2633)	358 (128)	3·4 (1·3)	10 (3·0)
3200 mg (n=10)	0·007	1192 (344)	8963 (2409)	381 (101)	3·4 (0·8)	10 (2·4)
4800 mg (n=9)	0·007	1536 (194)	15 822 (2957)	313 (58)	5·2 (0·8)	10 (1·7)
TMB-380						
2400 mg (n=10)	0·007	792 (202)	9006 (1505)	227 (44)	34·6 (5·1)	NA
3200 mg (n=10)	0·007	1110 (383)	12 083 (2774)	238 (55)	31·7 (3·8)	NA
4800 mg (n=9)	0·007	1890 (340)	21 802 (4144)	214 (39)	30·1 (1·7)	NA

Data are median or mean (SD). Pharmacokinetics were calculated for all participants who received a single dose of TMB-365 and TMB-380 in the sentinel groups. T_{max}=time to maximum serum concentration. C_{max}=maximum serum concentration. AUC=area under the concentration versus time curve. $T_{1/2\beta}$=terminal half-life when CD4 receptor is unsaturated (TMB-365). $T_{1/2}$=half-life (TMB-380). $T_{1/2s}$=half-life when CD4 receptor is saturated (TMB-365). NA=not available.

Table 3: **Pharmacokinetic parameters of TMB-365 and TMB-380**

the lives of people living with HIV. The combination of TMB-365, a CD4-directed monoclonal antibody, and TMB-380, a broadly neutralising monoclonal antibody, with complementary mechanisms of action and engineered for enhanced breadth, potency, and pharmacokinetics, is a promising all-antibody regimen for maintenance therapy.

We have shown that co-administration of TMB-365 and TMB-380 in a single intravenous infusion over 60 min in an outpatient clinical setting was safe. Treatment-emergent adverse events were all mild to moderate and no acute infusion reactions were observed at any dose. Premature discontinuation occurred after a single exposure due to rash; however, this is not unique to TMB-365 and TMB-380 and is a known treatment-emergent adverse event associated with monoclonal antibody therapy.[24]

TMB-380 was originally developed by the Vaccine Research Center and has been evaluated in approximately 30 clinical studies, with clearance of 226 mL/day (compared with 189 mL/day in VRC607) and observed half-life of 33 days, which was shorter than in VRC607 (56·5 days).[18] Differences in study design, sampling, and assay methods might affect terminal pharmacokinetic estimates. A half-life of approximately 33–38 days has also been reported in individuals without HIV infection, suggesting cross-study and population variability. Co-administration with TMB-365 could influence FcRn-mediated recycling because both antibodies incorporate site-directed mutations in the FcRn-binding domain to extend serum half-life. However, the contribution of co-administration with TMB-365 to the shorter half-life of TMB-380 was not evaluated in this study and remains speculative. Additional factors, including assay differences (Meso Scale Discovery electrochemiluminescence *vs* enzyme-linked immunosorbent assay), anti-drug antibodies, baseline IgG, albumin, and inflammatory status, could also contribute to differences.

Encouragingly, 94% of participants in the per-protocol analysis remained virologically suppressed on the combination, and no participants met the stringent protocol-defined criteria for virological failure despite the absence of prescreening for either antibody susceptibility, supporting further evaluation of the combination as a standalone maintenance therapy.

This was a small, open-label, phase 2a study conducted without prescreening, in which suppression was maintained in most participants, but the study does not suggest that susceptibility screening is unnecessary. Additionally, further investigation is needed to more precisely confirm the observed virological failure rate, as the 95% CI around the 0% rate in this small 24-week study might include a moderate percentage. The small sample size limits assessment of the effects of sex on treatment-emergent adverse events and efficacy. Although antibodies are considered to have a better safety profile, infusion reactions were observed and remain of interest for future studies. The potential for developing resistance to TMB-365 plus TMB-380 over a longer period of treatment is unknown. A long-acting regimen could benefit people living with HIV with multiple comorbidities, in whom drug–drug interactions preclude the use of select small molecules. However, antibody manufacturing costs, cold-chain requirements, and demand for intravenous infusion could limit the application of TMB-365 plus TMB-380 in resource-constrained settings.

We observed unsustained increases in HIV-1 RNA (200–300 copies per mL) in three of six individuals weighing more than 90 kg, isolated, associated with low TMB-365 concentrations, whereas participants weighing less than 90 kg did not show such increases. Despite the small number of participants, this could suggest a role for bodyweight-based dose escalation of TMB-365 in subsequent clinical trials. We tested the efficacy of this two-drug combination as maintenance therapy, consistent with successful two-agent regimens such as dolutegravir plus lamivudine and cabotegravir plus rilpivirine.[25,26]

In the phase 2 trial conducted by the AIDS Clinical Trials Group (ACTG A5357), VRC07-523LS was given at 40 mg/kg intravenously every 8 weeks, combined with monthly cabotegravir given intramuscularly as a 600 mg

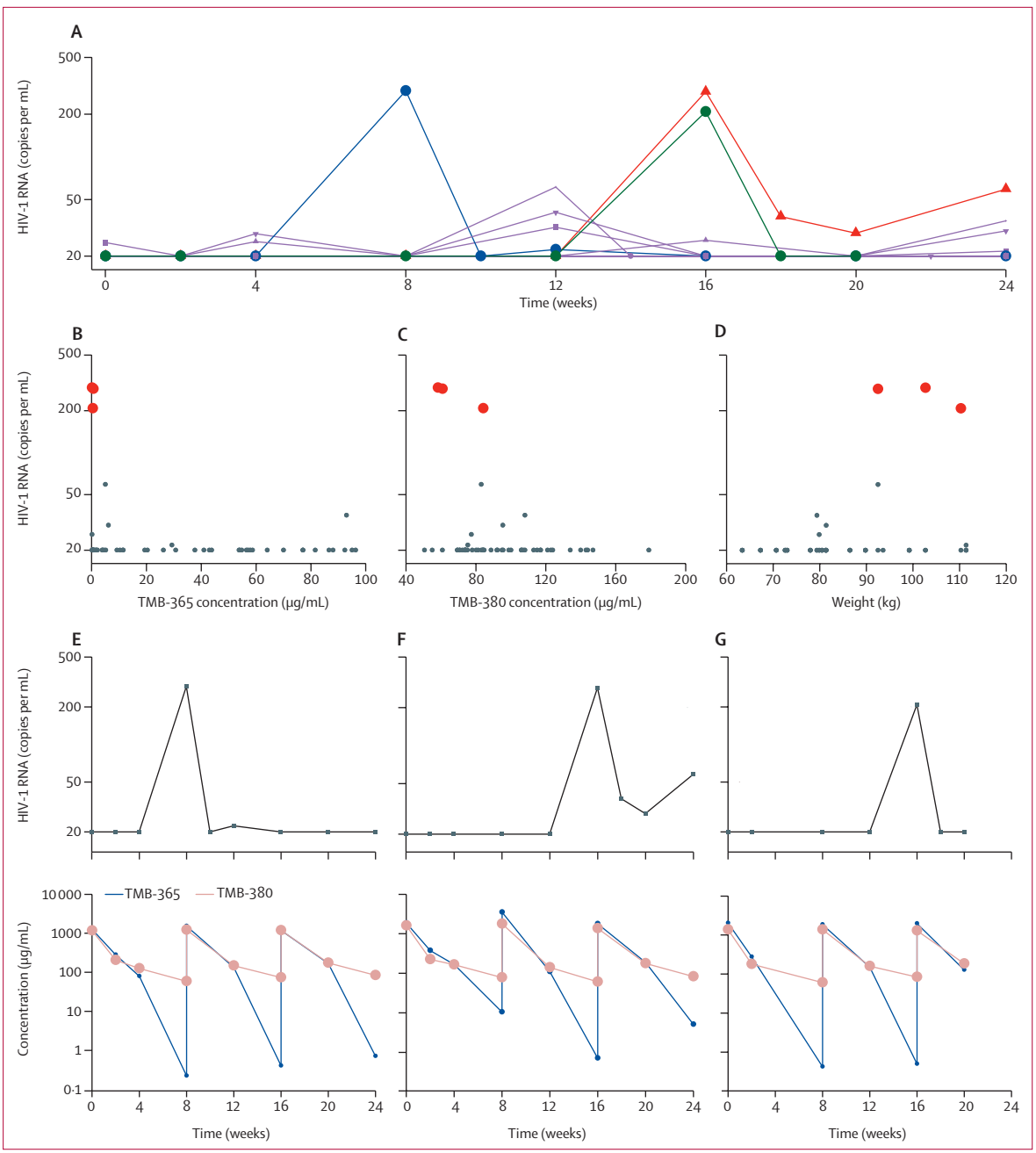


Figure 3: **HIV-1 RNA dynamics, exposure–response relationships, and individual longitudinal profiles**
(A) Participant-level HIV-1 RNA values over time. Undetectable HIV-1 RNA is plotted at 20 copies per mL. Each line represents an individual participant. Participants with transient HIV-1 RNA more than 200 copies per mL are coloured green, blue, and red; all other participants are shown in purple. Relationship between HIV-1 RNA and TMB-365 concentration (B), HIV-1 RNA and TMB-380 concentration (C), and HIV-1 RNA and bodyweight (D). Each point represents an individual observation at weeks 8, 16, and 24. Red points indicate observations with HIV-1 RNA more than 200 copies per mL; grey points indicate all other observations. (E–G) Participant-level longitudinal profiles for the three participants with HIV-1 RNA more than 200 copies per mL. HIV-1 RNA and serum TMB-365 and TMB-380 concentrations are shown over time. All available longitudinal viral load and pharmacokinetic data are shown.

load and 400 mg monthly as maintenance therapy, for 48 weeks.[20] Baseline susceptibility to VRC07-523LS (IC_{50} 0·25 µg/mL and maximum percent inhibition >98% on the Monogram PhenoSense mAb Assay with screening peripheral blood mononuclear cells) was an inclusion criterion and was the main reason for screen failure (25%). 12 (17%) participants met the primary safety endpoint; 11 (15%) had grade 3 or worse adverse events (eg, chills, myalgia, and fatigue), and one discontinued therapy due to a grade 1

infusion-related reaction. Virological failure (confirmed plasma HIV-1 RNA >200 copies per mL) was observed in five participants, with the cumulative probability of virological failure being 7% (95% CI 3–16) by week 44. In a separate study of lenacapavir plus teropavimab and zinlirvimab every 6 months, the screen failure rate due to absence of broadly neutralising monoclonal antibody susceptibility was 56%, with 15 screening participants having no results and 54 failing to meet criteria for susceptibility to both antibodies.[27] Despite prescreening, virological failure was documented in three participants: one at week 16 in the primary cohort (n=20), in which a Q67H amino acid substitution in capsid was identified, resulting in a 4·7-fold reduction in susceptibility to lenacapavir; and two with very low-level viraemia at week 26 in the pilot cohort (n=10) with no resistance data available due to HIV-1 RNA of 72 copies per mL plasma and 55 copies per mL plasma.[27–29]

In conclusion, single intravenous doses of TMB-365 plus TMB-380 were safe, and pharmacokinetics results supported dosing 4800 mg of each antibody intravenously every 8 weeks over 24 weeks. Phase 1b/2a data suggest the combination might be effective as maintenance therapy and support further evaluation in people living with HIV virologically suppressed on oral ART to explore the need for pretreatment screening for antibody susceptibility or maximum percent inhibition.

Contributors

MM contributed to medical monitoring. JPL, ED, MGS, GR, GC, MR, and MB were the principal investigators for the study and contributed to investigation and sample collection. MM, K-LK, and YL contributed to study design, data interpretation, and manuscript preparation. K-LK contributed to data analysis. YL contributed to project supervision. MM, K-LK, and YL accessed and verified the data. 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

MM served as a paid medical consultant to TaiMed Biologics and received reimbursement for meeting attendance. JPL, ED, MGS, GR, GC, MR, and MB, or their institutions, received research grants from TaiMed Biologics during this study. ED reports grants or contracts from Merck and GSK for investigator-initiated studies, and institutional funding from GSK, Gilead, and Merck for study conduction. MGS reports institutional research support from Gilead, Merck, and ViiV, and payment or honoraria for speakers bureaus from Gilead, ViiV, and Merck. GC reports grants or contracts from Gilead, ViiV, and Merck for HIV drug research. MR reports consulting fees from Merck, Abbot, Gilead, Shionogi, ViiV, and AiCuris, and payment or honoraria from Merck, Gilead, ViiV, and AbbVie. K-LK and YL were employees of TaiMed Biologics during the conduct of the study and held employee stock options.

Data sharing

Data generated in this study are available as de-identified data at ClinicalTrials.gov (NCT05275998). The study protocol and statistical analysis plan form are available at ClinicalTrials.gov. The study protocol is also available in the appendix. Any additional data can be made available upon request to the corresponding author.

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