Switch to fixed-dose ainuovirine, lamivudine, and tenofovir DF *versus* elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in virologically suppressed people living with HIV-1: the 48-week results of the SPRINT trial, a multi-centre, randomised, double-blind, active-controlled, phase 3, non-inferiority trial

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Summary

Background We compared the efficacy and safety profiles of ainuovirine (ANV), a new-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), with boosted elvitegravir (EVG), both coformulated with two nucleoside reverse transcriptase inhibitors (NRTIs), in people living with HIV-1 (PLWH) who had achieved virological suppression on previous NNRTI-based antiretroviral (ARV) regimen.

Methods This study was a multi-centre, randomised, double-blind, active-controlled, non-inferiority trial recruiting PLWH from 10 clinical centres across China. Main inclusion criteria included age of 18–65 years (inclusive), and stably staying on an ARV regimen combining an NNRTI with a two-drug NRTI backbone for at least 12 months. Eligible participants must have maintained plasma HIV-1 ribonucleic acid (RNA) titre below 50 copies per mL confirmed on two successive tests at an interval of at least one month prior to randomisation. Participants were randomly assigned to receive ANV 150 mg plus lamivudine (3TC) 300 mg, and tenofovir disoproxil fumarate (TDF) 300 mg (ANV/3TC/TDF), or cobicistat (Cobi) 150 mg boosted EVG plus emtricitabine (FTC) 200 mg, and tenofovir alafenamide (TAF) 10 mg. The primary efficacy endpoint was the proportion of participants with HIV-1 RNA titre at 50 copies per mL or above at week 48 using the US Food and Drug Administration snapshot algorithm, with a non-inferiority margin of 4 percentage points at a two-side 95% confidence level. This trial is active, but not recruiting, and is registered with Chinese Clinical Trial Registry (ChiCTR), number ChiCTR2100051605.

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Findings Between October 2021 and February 2022, 923 patients were screened for eligibility, among whom 762 participants were randomized and had received at least one dose of ANV/3TC/TDF (n = 381) or EVG/Cobi/FTC/TAF (n = 381). At week 48, 7 (1.8%) participants on ANV/3TC/TDF and 6 (1.6%) participants on EVG/Cobi/FTC/TAF had plasma HIV-1 RNA titre at 50 copies per mL or above, including missing virological data within the time window (the Cochran-Mantel-Haenszel method, estimated treatment difference [ETD], 0.3%, 95% CI −1.6 to 2.1), establishing the non-inferiority of ANV/3TC/TDF to EVG/Cobi/FTC/TAF. The proportions of participants experiencing at least one treatment-emergent adverse events (AEs) were comparable between the two arms (97.6% *versus* 97.6%). A small proportion of participants discontinued study drug due to AEs (0.3% *versus* 0.3%). Serious AEs occurred in 11 (2.9%) participants on ANV/3TC/TDF and 9 (2.4%) participants on EVG/Cobi/FTC/TAF, respectively, none of which was considered related to study drug at the jurisdiction of the investigator. At week 48, participants on ANV/3TC/TDF showed a significantly less weight gain from baseline compared to those on EVG/Cobi/FTC/TAF (least square mean, 1.16 *versus* 2.05 kg, ETD −0.90 kg, 95% CI, −1.43 to −0.37). The changes in serum lipids from baseline also favoured ANV/3TC/TDF over EVG/Cobi/FTC/TAF.

Interpretation In virologically suppressed PLWH on previous NNRTI-based ARV regimen, switch to ANV/3TC/TDF resulted in less weight gain, and improved lipid metabolism while maintaining virological suppression non-inferior to that to EVG/Cobi/FTC/TAF.

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Keywords: Ainuovirine; Switch therapy; Non-inferiority; Weight gain; Dyslipidaemia

Introduction

Integrase strand transferase inhibitor (INSTI)-based antiretroviral (ARV) regimens are highly recommended as the first-line treatment for HIV/AIDS by the World Health Organization, the International Antiviral Society–USA Panel, and the European AIDS Clinical Society.[1–3] A single-tablet regimen (STR) is also preferred over individual tablets with reducing pill burden, and increasing treatment compliance.[4] Therefore, switch to the first-line INSTI-based STR may be warranted in virologically suppressed people living with HIV (PLWH) to optimize treatment benefits, and improve quality of life. However, an unmet medical need arises from use of INSTI-based regimen; INSTI has been found to be associated with significant weight gain and dyslipidaemia compared to non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen.[5–8]

Ainuovirine (ANV) is a new-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with potent antiviral activity *in vitro*,[9] and favourable clinical pharmacology profile in humans (unpublished data). In treatment-naïve PLWH, ANV demonstrated a virological suppression proportion non-inferior to efavirenz (EFV) at week 48 (87.0% *versus* 91.7%), both combined with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), but superior to EFV in less frequent neuropsychiatric toxicities, dyslipidaemia, liver enzyme abnormalities, and rashes.[10] In the 48-week extension period, switching from EFV to ANV also resulted in a high virological suppression proportion at week 96 (95.1%).[10] The genotypic resistance profile of ANV was similar to that of EFV as shown in treatment-naïve PLWH. ANV 150 mg was further coformulated with 3TC 300 mg and TDF 300 mg into STR (ANV/3TC/TDF) with bioequivalence to individual tablets but without meaningful drug–drug interaction.[11,12] These characteristics justify ANV/3TC/TDF to be a desirable candidate for switching therapy in virologically suppressed PLWH.

We conducted a multi-centre, randomised, active-controlled phase 3 trial, namely, the **S**witching **P**LWH to **R**eceive **I**nnovative **N**NRTI-based **T**herapy (SPRINT) trial. This study aimed to evaluate the clinical efficacy, safety, tolerability, and resistance profile of switching to ANV/3TC/TDF STR compared to that to cobicistat-boosted elvitegravir coformulated with emtricitabine and tenofovir alafenamide (EVG/Cobi/FTC/TAF, 150 mg/150 mg/200 mg/10 mg), in virologically suppressed Chinese adult PLWH. Remaining on previous ARV regimens or delayed switch were normally used as control in previous registrational phase 3 trials of switch therapy. In contrast, switch to INSTI-based STR was used as comparator in the present study as the pill burden with remaining on previous EFV-based non-STR might confound the comparisons of efficacy and safety between the two arms. To the best of our knowledge, this trial is the first study to directly compare the efficacy and safety outcomes between NNRTI- and INSTI-based ARV regimens as switch therapy in a randomised,

Research in context

Evidence before this study

People living with HIV (PLWH) are at a high risk of cardiovascular diseases due to underlying HIV infection, traditional risk factors, and possibly antiretroviral treatment (ART). Virological suppression is known to be beneficial for cardiovascular outcome of PLWH. However, virologically suppressed PLWH are still at a higher risk of major adverse cardiovascular event compared to the seronegative counterpart. In consideration of overweight/obesity and dyslipidaemia also prevailing among PLWH, cardiometabolic health has become the primary treatment goal for PLWH. Moreover, integrase strand transferase inhibitor (INSTI) based regimen is one of the most recommended regimens by WHO, IAS, and EACS, and the most frequently prescribed regimen in developed countries. A major safety concern arises from use of INSTI-based regimen that PLWH on INSTI are more likely to gain weight, and develop dyslipidaemia compared to those on non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen. Therefore, a new ART regimen is warranted, as an alternative to current INSTI-based regimen, in virologically suppressed PLWH.

Ainuovirine is a new-generation NNRTI exhibiting potent antiviral activity alone, or in synergism with lamivudine and tenofovir against a variety of HIV strains. Ainuovirine also showed no clinically significant drug–drug interaction with lamivudine and tenofovir, and further coformulated into a single-tablet regimen as shown by pharmacokinetic bioequivalence. A previous randomised, controlled phase 3 study reported that ainuovirine was non-inferior to efavirenz, both combined with the backbone of lamivudine and tenofovir, in week 48 virological suppression for treatment-naïve PLWH. However, PLWH on ainuovirine-based regimen experienced less frequent neuropsychiatric side effects, liver toxicities, dyslipidaemia, and rashes compared to those on efavirenz-based regimen. Furthermore, we are more than interested in whether a new NNRTI, such as ainuovirine, is non-inferior to INSTI, both combined with the nucleoside reverse transcriptase inhibitor (NRTI) backbone, in virological suppression, but beneficial in weight gain control and lipid metabolism improvement for virologically suppressed PLWH.

Literature searches were conducted since preparation of study protocol for the SPRINT (**S**witching **P**LWH to **R**eceive **I**nnovative **N**NRTI-based **T**herapy) trial. We searched PubMed for randomised controlled clinical trials of switching therapy for virologically suppressed PLWH, with title or abstract search terms of "doravirine" OR "rilpivirine" OR "efavirenz" OR "bictegravir" OR "elvitegravir" OR "dolutegravir", AND "switching" OR "switch", AND "phase 3". Searches were limited to articles published in English, and non-controlled studies, e.g., single-arm studies, were excluded, but open-label studies were included if participants were randomly assigned to an intervention or comparator. This search was repeated on demand until the time of preparation of this manuscript. The last search was done on 20th December, 2023. Articles reporting 48-week treatment outcomes were used for final review.

Our searches yielded 14 articles of 15 phase 3 switching therapy studies in virologically suppressed PLWH. These included 5 articles of NNRTI-based regimen as intervention, and 9 articles of INSTI-based regimen as intervention ("immediate switch") (Supplementary Appendix IV). In all studies, the comparators included remaining on baseline regimen for 48 weeks ("no switch"), or remaining on baseline regimen for 24 weeks and then switching to the interventions for subsequent 24 weeks ("delayed switch"). Baseline regimens included NNRTIs (efavirenz, and rilpivirine), boosted or unboosted INSTIs (boosted elvitegravir, and dolutegravir), and boosted protease inhibitors (PIs), in combination with a two- or one-drug NRTI backbone. No two "immediate switch" therapy arms were compared in parallel.

Only one study involved comparison of efficacy and safety outcomes of an NNRTI-based regimen against those of a boosted INSTI-based regimen in some subset participants (DRIVE-SHIFT study, boosted elvitegravir, "delayed switch"). Six articles (seven studies) reported comparisons of a boosted or unboosted INSTI-based regimen against an NNRTI-based regimen in all or subset participants: GS-US-292-0109 study (boosted elvitegravir plus tenofovir alafenamide-based *versus* boosted elvitegravir, NNRTI, or boosted atazanavir plus tenofovir disoproxil fumarate-based), STRATEGY-NNRTI study (boosted elvitegravir *versus* NNRTI), STRIIVING study (dolutegravir *versus* boosted/unboosted INSTI or PI, or NNRTI), TANGO study, SALSA study, and SWORD-1/SWORD-2 studies (dolutegravir-based two-drug regimen *versus* INSTI, or NNRTI, or PI plus the two-drug NRTI backbone in the last four studies). The intervention therapy was non-inferior to the comparator therapy in virological efficacy at week 48 or 24 as per US Food and Drug Administration snapshot algorithm in all studies, except for one study using the time to loss of virologic response (TLOVR) algorithm (AI266073 study, efavirenz *versus* boosted/unboosted PI or NNRTI). All studies showed a favourable tolerability profile, except for AI266073 and STRIIVING studies, both with more than 10% of participants prematurely withdrawing from the study and approximately 5% due to adverse events for the intervention arm.

Added value of this study

To the best of our knowledge, the SPRINT trial is the first randomised controlled study to compare the efficacy and safety outcomes of ainuovirine, an NNRTI, against boosted elvitegravir, an INSTI, both combined with the NRTI backbone, in a head-to-head manner, for virologically suppressed PLWH. We used a "double-switch" rather than "no switch" or "delayed switch" design. This design mimicked the procedure of decision-making for treatment option of choice in real-world clinical practice. This study helps to determine whether to switch to ainuovirine- or boosted elvitegravir-

based regimen for virologically suppressed PLWH as evidenced by virological efficacy and cardiometabolic safety outcomes. Both treatment regimens were given in single tablet, avoiding confounding bias from pill burden and treatment adherence. This study showed an excellent medication compliance even in the pandemic of COVID-19. Ainuovirine-based regimen was non-inferior to boosted elvitegravir-based regimen in virological suppression failure at week 48, in accordance with the most recent definition of estimand using the "composite variable" strategy. This primary efficacy endpoint was also robustly justified by multiple sensitive analyses, including the most stringent tipping-point analysis. Two safety outcomes of interest, namely, weight gain and dyslipidaemia, were prespecified in the development processes of protocol and statistical analysis plan to ensure the validity and generalisability of the safety benefits of ainuovirine-based regimen. Tenofovir DF-containing, ainuovirine-based regimen was associated with less weight gain and improved lipid metabolism compared to tenofovir alafenamide-containing, boosted elvitegravir-based regimen. Moreover, an improved distribution of dyslipidaemia strata was associated with tenofovir DF-containing, ainuovirine-based regimen in comparison to a worsening panel with tenofovir alafenamide-containing, boosted elvitegravir-based regimen as per the primary prevention goal for atherosclerotic cardiovascular disease.

Implications of all the available evidence

As highly-active ART (HAART) prolongs PLWH's life expectancy, and PLWH are becoming older, this population become more frequently afflicted with cardiometabolic comorbidities. Consideration of a switch therapy of choice may include cardiometabolic safety issues beyond the era of HAART. Our previous phase 3 study in treatment-naïve PLWH showed remarkable safety benefits following switch to ainuovirine- from efavirenz-based regimen, including improved lipid metabolism, in a non-controlled manner. Our current findings further demonstrated non-inferior virological efficacy and additional cardiometabolic benefit of tenofovir DF-containing, ainuovirine-based regimen compared to tenofovir alafenamide-containing, boosted elvitegravir-based regimen in virologically suppressed PLWH. All these results help clinicians' decision to provide tenofovir DF-containing, ainuovirine-based regimen as a suitable care for PLWH with complicating cardiometabolic conditions, regardless of whether PLWH have been on ART or not, including efavirenz- and tenofovir alafenamide-containing, boosted elvitegravir-based regimen.

double-blind design. We reported the first 48-week results of the SPRINT trial here.

Methods

Study design and participants

The SPRTINT trial is a multi-centre, randomised, double-blind, double-dummy, active-controlled, parallel-group, non-inferiority phase 3 study done at 10 clinical sites of China (Supplementary Appendix I). The main inclusion criteria were as follows: age of 18–65 years (inclusive), documented serological positivity to HIV-1, and stably staying on ARV regimen combining an NNRTI with a two-drug nucleoside reverse transcriptase inhibitor (NRTI) backbone for at least 12 months. Eligible participants must have maintained virological suppression (plasma HIV-1 ribonucleic acid [RNA] titre below 50 copies per mL) confirmed on two successive tests at an interval of at least one month prior to randomization, without any restriction on CD4+ cell count. Participants would be excluded if being at the acute infection phase, with complicating acquired immunodeficient syndrome (AIDS) defining conditions, on medication with immunosuppressive agents, presenting with grade 3 or 4 adverse events (AEs) using *the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) Table*, co-infected with hepatitis B virus, hepatitis C virus, or active syphilis, or with complicating clinical significant liver (alanine transferase >5 × upper limit of normal), or renal impairment (estimated glomerular filtration rate <50 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) (Supplementary Appendix II). Previous ARV switch was allowed, but participants must agree not to switch their ARV regimens after screening until the end of this study. The study protocol was approved by the institutional review board or independent ethics committee at each participating site (Supplementary Appendix V). All participants gave written informed consent before receiving any study procedure. The study was conducted in accordance with *the Declaration of Helsinki*, *the International Council for Harmonisation Good Clinical Practice* (ICH GCP), and the applicable regulatory guidances.

Randomisation and masking

Participants were randomly assigned at 1:1 ratio to switch either to ANV/3TC/TDF or to EVG/Cobi/FTC/TAF, both in STR, using an interactive web response system (DaS for IWRS, BioVoice & BioGuider, Shanghai, China). A computer-generated randomisation allocation sequence was created by a contracted third party with a dynamic blocked randomisation. Randomisation was stratified by site, and duration of previous NNRTI-based regimen treatment (1–2 years, 2–3 years, and ≥3 years). All investigators, participants, and study staff were blind to treatment assignment. ANV/3TC/TDF tablets were taken on the empty stomach, and EVG/Cobi/FTC/TAF tablets were taken with a meal, both once daily. Participants received placebo tablets,

which matched the alternative study drugs ("dummies") under the corresponding conditions, and masked treatment assignment.

Study procedures

Participants were required to visit the clinical sites at screening, baseline, and post-baseline weeks 4, 12, 24, 36, and 48, during which participants were instructed to self-administer masked treatment. After week 48, participants entered into an optional extension treatment period, during which participants continued, or switched to open-label ANV/3TC/TDF STR ("partial crossover") taken on the empty stomach with visits every 24 weeks until week 96. Laboratory tests included haematology, urinalysis, urine pregnancy test (for women of childbearing potential), serum biochemistry, including serum lipids, coagulation function, centralised plasma HIV-1 ribonucleic acid (RNA) measurement using an Abbott RealTime HIV-1 assay (lower limit of quantification [LLoQ] = 40 copies per mL), and CD4+ cell count using flow cytometry at each participating site. Other medical examinations included 12-lead electrocardiography, chest X-ray scan, and abdominal ultrasonography. Self-reported and solicited adverse events, and concomitant medications were recorded, and assessed at each study visit. Medical coding was performed using *the Medical Dictionary for Regulatory Activities* (MedDRA, version 25.0) and *the WHO Drug Dictionary* (WHO Drug, version 2023), respectively.

For participants with plasma HIV-1 RNA titre equalling to or above 50 copies per mL at a given visit, HIV-1 RNA was remeasured at the participating site within 1 to 4 weeks after the given visit. Whether the participant was withdrawn from the study was determined by the investigator if the remeasured HIV-1 RNA titre was equalling to or above 50 but no more than 400 copies per mL (excluding poor adherence); the participant was withdrawn if the remeasured HIV-1 RNA titre above 400 copies per mL. For participants with confirmed HIV-1 RNA titre above 400 copies per mL, blood samples were retained, and sent to the central laboratory for genotypical resistance testing of substitutions associated with resistance to NNRTIs, NRTIs, protease inhibitors (PIs), and INSTIs. Genotypical resistance testing was also done at the time of treatment discontinuation and/or premature withdrawal if applicable.

Outcomes

The primary efficacy endpoint was the proportion of participants with plasma HIV-1 RNA titre equalling to or above 50 copies per mL at week 48 as defined by the US Food and Drug Administration snapshot algorithm.[13] The key secondary efficacy endpoint was the proportion of participants with plasma HIV-1 RNA titre below 50 copies per mL at week 48 with the snapshot algorithm. Other supportive secondary efficacy (virological) endpoints included the proportions of patients with HIV-1 RNA titre equalling to or above 50, and below 50 copies per mL at all other study visits, and below 40, above 400 or 200 (clinically significant viraemia), and above 50 but no more than 400 or 200 (low-level viremia) copies per mL at all study visits. Immunological efficacy endpoints included changes from baseline (CFBs) in CD4+ cell count at all study visits, and the proportion of participants with CD4+ cell count CFB equalling to or above 100 cells per μL or 30%. Safety assessments included routine treatment-emergent adverse events (TEAEs), body weight, vital signs, physical examination, laboratory tests, 12-lead electrocardiograph, chest X-ray, and abdominal ultrasound examinations. Severity of adverse events were evaluated using *the DAIDS Table*, or *the National Cancer Institute Common Terminology Criteria for Adverse Events* (CTCAE) version 5.0, where applicable.

Statistical analyses

A proportion of 3 percentage point was assumed for participants with plasma HIV-1 RNA titre equalling to or above 50 copies per mL at week 48 for both treatment arms. A sample size of 762 randomly assigned participants (381 participants for each arm) would achieve a power of at least 80 percentage point (beta = 0.2) to detect non-inferiority with a margin at 4 percentage point for the primary efficacy endpoint. A one-sided alfa of 0.025 was set, and a drop-out rate of 10 percentage point was considered.

Efficacy endpoints were analysed in the full analysis population (all randomly assigned participants exposed to at least one dose of study drug according to the exposed intention-to-treat [ITT-EXP] principle) and the per protocol population (all randomly assigned participants with good treatment compliance [≥90%] and without in-trial exposure to prohibited comedications or pregnancy [for women of childbearing potential]). Safety endpoints were analysed in the safety analysis population (all randomly assigned participants exposed to at least one dose of study drug, and with at least one post-treatment safety evaluation). Observation period included the in-trial period (the time from randomisation to last visit, regardless of treatment discontinuation or rescue intervention). All statistical analysis results were presented in a two-sided 95 percentage point confidence interval (95% CI) with the Newcombe-Wilson score method, and/or the corresponding *P*-value (with significance defined as <0.05) with the chi-square or Fisher exact probability method.[14] Multiple comparisons were not controlled for analyses of secondary efficacy endpoints (both key and other supportive) and safety endpoints as no definitive treatment effects were inferred. All reported results are for the full analysis population unless stated otherwise.

A single primary estimand (*de jure*) with the composite variable strategy was used to precisely describe

the treatment effect reflecting the primary objective of this study. This study was to confirm whether switch to ANV/3TC/TDF was non-inferior to that to EVG/Cobi/FTC/TAF in the proportion of participants with plasma HIV-1 RNA titre equalling to or above 50 copies per mL at week 48 in virologically suppressed PLWH previously on NNRTI-based regimen. Intercurrent events and missing virological data within time window were predefined as HIV-1 RNA titre equalling to or above 50 copies per mL. These events included treatment discontinuation due to lack of efficacy, and/or any reasons other than lack of efficacy and use of non-protocol-defining treatment, for example, rescue medication, as per the snapshot algorithm. The between-group estimated treatment difference (ETD) was analysed for the primary efficacy endpoint using the Cochran-Mantel-Haensel (CMH) method adjusted for duration of previous NNRTI-based regimen treatment. The non-inferiority was established if the upper bound of the 95% CI was below 4%; the hierarchical superiority was further established if the upper bound of the 95% CI was below zero. The key secondary efficacy endpoint was similarly analysed except for the adjusted CMH analysis. Subgroup analyses were similar performed for baseline covariates, including sex (male *versus* female), age (<50 *versus* ≥50 years), ethnicity (Han Chinese *versus* others), body mass index (<18.5 *versus* 18.5–23.9 *versus* ≥24 kg/m^2), previous duration of treatment with NNRTI-based regimen (≥1–<2 *versus* ≥2–<3 *versus* ≥3 years), class of previous NRTI backbone (TDF plus 3TC or FTC *versus* others), class of previous NNRTI (EFV *versus* others), and baseline CD4+ cell count (<200 *versus* 200–499 *versus* ≥500 cells per μL).

Weight gain and dyslipidaemia were two safety outcomes of special interest. ETDs of absolute and percentage CFBs (least square mean, LSMean) in body weight and serum lipids were compared as prespecified, including low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG).

This study is active but not recruiting, and registered with Chinese Clinical Trial Registry (ChiCTR), number ChiCTR2100051605.

Role of the funding source

Aidea Pharmaceutical funded the study, designed study protocol, monitored study conduct, analysed the data, and interpreted the results along with the leading principal investigator FJZ.

Results

Between November 5, 2021 and March 21, 2022, 923 participants were screened, 762 participants were randomised, and received at least one dose of study drug, and 160 participants failed screening mainly due to meeting the exclusion criteria (n = 90), not meeting the inclusion criteria (n = 39), or being unwilling to continue participation in the study (n = 19). Of these 762 randomised participants, 381 participants were randomly assigned to switch to ANV/3TC/TDF, and the remaining 381 participants were switched to EVG/Cobi/FTC/TAF; 3 participants and 2 participants (n = 5, 0.7%) withdrew prematurely from the study, respectively (Fig. 1). Good treatment compliance (drug accountability 90%–110%) was achieved in all participants (Supplementary Table S1). Baseline demographics and clinical characteristics were balanced between the two treatment arms (Table 1).

At week 48, the non-inferiority of switch to ANV/3TC/TDF was established compared to that to EVG/Cobi/FTC/TAF. The proportions of participants with plasma HIV-1 RNA titre equalling or above 50 copies per mL were 1.8% and 1.6%, respectively, as per the primary estimand; the ETD [95% CI] was 0.3% [–1.6, 2.1] adjusted for duration of previous NNRTI use with the upper bound of the 95% CI below the prespecified 4% margin (Table 2, and Supplementary Figure S1). Per protocol analysis also showed a similar result (0.5% [–0.7, 1.8]) (Supplementary Table S2). This non-inferiority was further confirmed in the prespecified multivariate logistic regression analysis with site, and duration of previous NNRTI use as covariates (0.3% [–1.6, 2.1]) (Supplementary Table S2), and tipping-point analysis with all the 3 virological data missings counted as equalling to or above 50 copies per mL for ANV/3TC/TDF arm, but as below 50 copies per mL for EVG/Cobi/FTC/TAF arm (1.1% [95% CI upper bound, 2.7], Supplementary Figure S2). Subgroup analyses showed no significant differences in the primary efficacy endpoint between the two treatment arms, regardless of participants' prespecified baseline demographics, and clinical characteristics (Supplementary Figure S3).

A high proportion of viral suppression was maintained in the two treatment arms throughout 48 weeks of treatment. Virological suppression was maintained in 98.2% and 98.4% of participants, respectively, at week 48 (Supplementary Figure S4). Low-level and clinically significant viraemia was occasionally observed in both treatment arms (at 1% or below, Supplementary Figures S5 and S6). Mean CFBs in CD4+ cell count were similar between the two treatment arms at week 48: 0.2 and 5.1 cells per μL (mixed-effect model for repeated measurement [MMRM], –4.9 cells per μL [–25.4, 15.7]; analysis of covariance [ANCOVA], –3.5 cells per μL [–24.1, 17.1]), respectively. Both treatment arms experienced a small magnitude of CD4+ cell count decrease within the first four weeks, but returned to the baseline at week 12, with a higher immunological response proportion in the ANV/3TC/TDF arm compared to that in the EVG/Cobi/FTC/TAF arm (22.4% *versus* 15.5%), and maintained afterwards until week 48 (data not shown).

None of participants met the criteria for resistance genotypic testing (confirmed HIV-1 RNA titre above 400

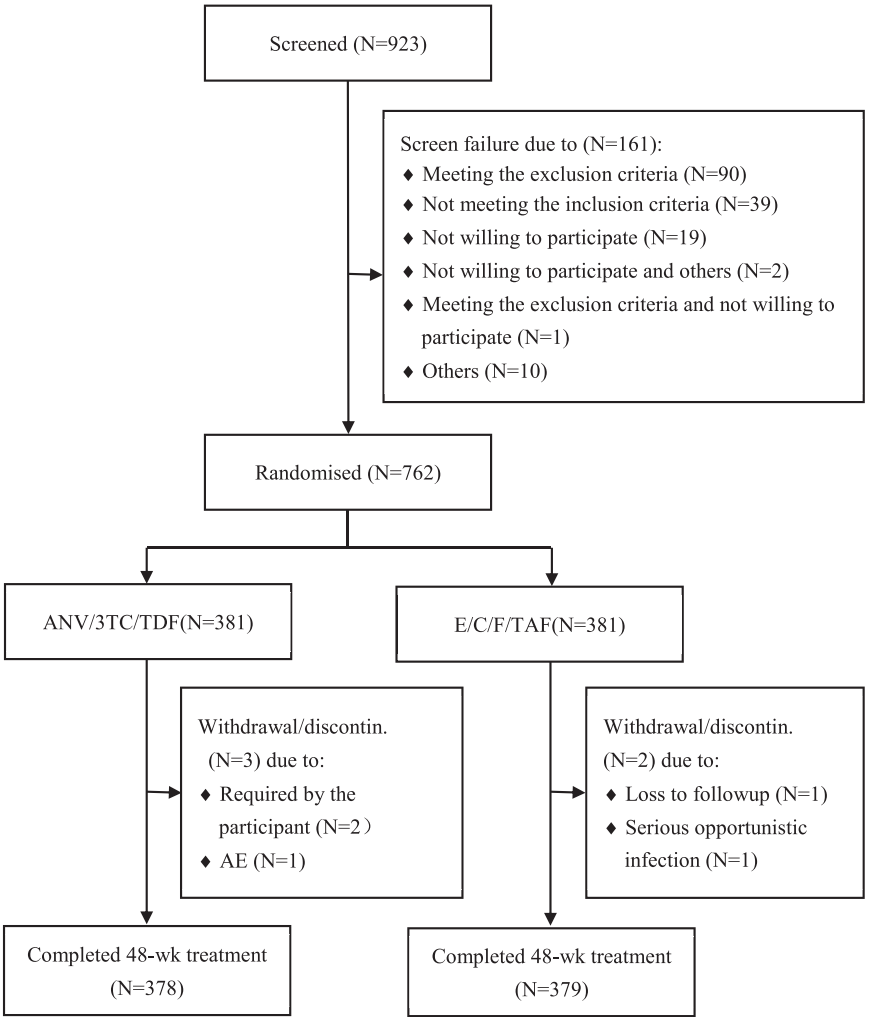


Fig. 1: **Participant disposition flow chart**. AE, adverse event; ANV/3TC/TDF, ainuovirine/lamivudine/tenofovir disoproxil fumarate; discontin., discontinuation; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

copies per mL) until week 48; resistance genotypic testing was ordered for 1 participant on ANV/3TC/TDF regimen due to poor treatment compliance at the discretion of the investigator, showing genotypic susceptibility to NNRTIs, NRTIs, and PIs. All the five participants discontinued treatment and/or withdrew prematurely from the study with HIV-1 RNA titre below 50 copies per mL.

Both treatment regimens were well tolerated, with the majority of adverse events reported as mild or moderate in severity (Table 3, and Supplementary Table S3). Treatment discontinuation due to adverse events was occasional by week 48: 0 participant in ANV/3TC/TDF arm *versus* 1 participant in EVG/Cobi/FTC/TAF arm. One participant withdrew prematurely from the study due to adverse event in each treatment arm. Types of adverse events were similar between the two treatment arms, except for adverse drug reaction (74.0% *versus* 86.9%), and grade 3–5 treatment-emergent adverse events (TEAE, 10.8% *versus* 24.9%). Most common TEAEs (preferred term ≥5% in either arm) were weight gain, weight loss, and clinical laboratory abnormalities; SARS-CoV-2 test positivity and (suspected) COVID-19 were also most commonly reported in the two treatment arms due to the global pandemic of the viral disease. Isolated serious adverse events occurred in 11 participants and 9 participants, respectively (Supplementary Table S4). None of these events were assessed to be related to study drug by the investigators. None of participants developed major adverse cardiovascular event, or died until the time of preparation of the manuscript.

A fewer proportion of participants experienced grade 2 (≥10% to <20%), or grade 3 (≥20%) weight gain AE

	ANV/3TC/TDF regimen (n = 381)	EVG/Cobi/FTC/TAF regimen (n = 381)
Age, year	34.2 (8.6)	34.4 (8.5)
<50 years	359 (94.2)	355 (93.2)
≥50 years	22 (5.8)	26 (6.8)
Sex		
Men	370 (97.1)	370 (97.1)
Women	11 (2.9)	11 (2.9)
Ethnicity		
Han Chinese	366 (96.1)	360 (94.5)
Others[a]	15 (3.9)	21 (5.5)
BMI, kg per m^2	22.8 (3.2)	23.2 (3.2)
<18.5	28 (7.4)	25 (6.6)
≥18.5 and ≤23.9	227 (59.7)	211 (55.4)
≥24	125 (32.9)	145 (38.1)
HIV infection duration, month	64.7 (36.0)	64.6 (33.8)
Previous ART course, month	58.2 (30.4)	58.5 (29.0)
NNRTI use course, month[b]		
≥12 and <24	45 (11.8)	47 (12.3)
≥24 and <36	58 (15.2)	54 (14.2)
≥36	278 (73.0)	280 (73.5)
NNRTI class		
EFV	375 (98.7)	374 (98.2)
Others	5 (1.3)	7 (1.8)
NRTI backbone class		
TDF+3TC or FTC	363 (95.5)	367 (96.3)
Others	17 (4.5)	14 (3.7)
Modification of NNRTI[c]	37 (9.7)	35 (9.2)
Modification of a first NRTI[d]	35 (9.2)	35 (9.2)
Modification of a second NRTI[e]	36 (9.5)	35 (9.2)
HIV-1 RNA titre, copies per mL		
<50	373 (97.9)	376 (98.7)
<40	372 (97.6)	373 (97.9)
≥50	8 (2.1)	5 (1.3)
≥50 and ≤200	6 (1.6)	4 (1.0)
≥50 and ≤400	7 (1.8)	5 (1.3)
>200	2 (0.5)	1 (0.3)
>400	1 (0.3)	0 (0)
CD4+ cell count, per μL	617.3 ± 232.0	626.4 ± 207.8
<200	1 (0.3)	1 (0.3)
≥200 and <500	121 (31.8)	118 (31.0)
≥500	259 (68.0)	262 (68.8)
Serological positivity		
HIV-1	381 (100.0)	381 (100.0)
HBsAg	0 (0)	0 (0)
Anti-HCV	2 (0.5)	0 (0)
Anti-Tp (RPR)	62 (16.3)	64 (16.8)

Data are presented in mean (standard deviation) or n (%). All study drugs were given in fixed-dose combination, and as single-tablet regimen with matching placebo. 3TC, lamivudine; ANV, ainuovirine; ART, antiretroviral treatment; BMI, body mass index; Cobi, Cobicistat; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RNA, ribonucleic acid; RPR, rapid plasma regain; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; Tp, *Treponema pallidum*. [a]Others include Hui, Man, Zhuang, and other Chinese ethnic minority people groups. [b]Stratification factor for randomisation. [c]Includes efavirenz, nevirapine, rilpivirine, or doravirine. [d]Includes tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine, or abacavir. [e]Includes lamivudine, emtricitabine, or azvudine.

Table 1: **Baseline demographic and clinical characteristics.**

(by MedDRA code) with ANV/3TC/TDF regimen than that with EVG/Cobi/FTC/TAF regimen (grade 2, 6.3% *versus* 13.9%; grade 3, 0.3% *versus* 1.6%) (Fig. 2A). The two arms showed a similar result of weight loss in severity (Fig. 2B). More specifically, the two treatment arms showed no significant change in body weight within the first 24 weeks, but a small magnitude weight gain from week 24 until week 48 (Supplementary Figure S7), with significant less weight gain with ANV/3TC/TDF regimen compared to that with EVG/Cobi/FTC/TAF regimen (ANCOVA, absolute CFB, –0.90 kg [–1.43, –0.37]; percentage CFB, –1.44% [–2.24, –0.65]) (Fig. 2C) (Supplementary Table S5).

A fewer proportion of participants experienced grade 2 or grade 3 dyslipidaemia AE (by MedDRA code) with ANV/3TC/TDF regimen than that with EVG/Cobi/FTC/TAF regimen (Fig. 3A). Serum lipids showed constant decreases with ANV/3TC/TDF regimen but marked increases with EVG/Cobi/FTC/TAF regimen, except for HDL-C, especially within the first four weeks (Supplementary Figure S8). At week 48, the ETDs of LSMean CFB with MMRM analysis were –0.39 mmol per L [–0.47, –0.32] for LDL-C, –0.69 mmol per L [–0.77, –0.60] for non-HDL-C, –0.84 mmol per L [–0.92, –0.75] for TC, –0.15 mmol per L [–0.18, –0.12] for HDL-C, and –0.98 mmol per L [–1.18, –0.78] for TG, respectively (Fig. 3B, and Supplementary Table S6). Moreover, analyses of atherosclerotic cardiovascular disease (ASCVD) risk-associated dyslipidaemia stratification (as per the primary prevention target for Chinese low-risk population) showed that the two treatment arms were comparable at the baseline (Supplementary Table S7, Fig. 4, and Supplementary Figure S9). The incidences of ASCVD risk-associated dyslipidaemia decreased in the ANV/3TC/TDF arm, but increased in the EVG/Cobi/FTC/TAF arm at week48, except for decreased HDL-C, the frequency of which was numerically higher in the ANV/3TC/TDF arm.

Changes from baseline in fasting serum glucose were similar between the two treatment arms at 48 weeks (–0.27 ± 0.03 *versus* –0.23 ± 0.03 mmol per L). Changes in uric acid were less with ANV/3TC/TDF regimen compared to those with EVG/Cobi/FTC/TAF at 48 weeks (7.72 ± 3.13 *versus* 49.78 ± 3.12 μmol per L). Liver, renal, and other system/organ dysfunction-associated TEAEs showed a similar profile between the two arms (Supplementary Table S8). Changes in liver function biochemistry measurements were also comparable between the two arms. Estimated glomerular filtration rate increased in both arms, accompanied by minimal changes in serum phosphate (Supplementary Table S9, and Supplementary Figure S10).

No participant on ANV/3TC/TDF regimen had a QTcF above 450 ms, while less than 1% of participants on EVG/Cobi/FTC/TAF regimen had at week 48. A small, similar proportion of participants had QTcF CFB more than 30 ms in both arms at week 48 (Supplementary Table S10).

	ANV/3TC/TDF regimen (n = 381)	EVG/Cobi/FTC/TAF regimen (n = 381)	ETD (95% CI)
HIV-1 RNA ≥50 copies per mL	7 (1.8)	6 (1.6)	0.3 (−1.6, 2.1)
Observed HIV-1 RNA ≥50 copies per mL	4 (1.0)	3 (0.8)	0.3 (−1.1, 1.6)
On treatment	4 (1.0)	3 (0.8)	NA
Discontinued due to lack of efficacy[a]	0 (0)	0 (0)	NA
Discontinued due to reasons other than lack of efficacy	0 (0)	0 (0)	NA
No virological data available	3 (0.8)	3 (0.8)	NA
On treatment	0 (0)	2 (0.5)	NA
Discontinued due to AE, death or any other reasons[b]	3 (0.8)	1 (0.3)	NA
HIV-1 RNA <50 copies per mL	374 (98.2)	375 (98.4)	−0.3 (−2.1, 1.6)
HIV-1 RNA <40 copies per mL	369 (96.9)	370 (97.1)	−0.3 (−2.7, 2.2)
HIV-1 RNA ≥50 and ≤400 copies per mL	4 (1.0)	3 (0.8)	0.3 (−1.1, 1.6)
HIV-1 RNA ≥50 and ≤200 copies per mL	3 (0.8)	3 (0.8)	0.0 (−1.2, 1.3)
HIV-1 RNA >400 copies per mL	3 (0.8)	3 (0.8)	0.0 (−1.3, 1.2)
HIV-1 RNA >200 copies per mL	4 (1.0)	3 (0.8)	0.2 (−1.1, 1.6)

Data are presented in n (%). All study drugs were given in fixed-dose combination, and as single-tablet regimen with matching placebo. The US Food and Drug Administration snapshot algorithm was used for definition of study visit time windows. The 95% confidence interval for estimated treatment difference was calculated using the Cochran-Mantel-Haensel method adjusted for baseline non-nucleoside reverse transcriptase inhibitor use course (≥1 and <2 *versus* ≥2 and <3 *versus* ≥3 years). 3TC, lamivudine; AE, adverse event; ANV, ainuovirine; CI, confidence interval; Cobi, cobicistat; ETD, estimated treatment difference; EVG, elvitegravir; FTC, emtricitabine; HIV, human immunodeficiency virus; N/A, not applicable; RNA, ribonucleic acid; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. [a]Lack of efficacy includes HIV-1 RNA ≥50 and ≤400 copies per mL on initial testing, and/or on repeated testing, HIV-1 RNA ≥400 copies per mL on initial testing, and/or on repeated testing, or occurrence of serious opportunistic infection. [b]Other reasons include discretion of investigator, virological failure, serious opportunistic infection, pregnancy, participant's noncompliance, protocol violation, or loss to followup.

Table 2: **Virological outcomes at 48 weeks window (days 295–378).**

Discussion

Cardiometabolic multimorbidity has become the major health concern for PLWH who have maintained virological suppression even with immunocompetency. Switch to INSTI-based from EFV-based regimen, especially in STR, can be beneficial for virologically suppressed PLWH, including in low-income and middle-income countries.[15,16] Weight gain is a well-known side effect associated with use of INSTI, especially with that of dolutegravir (DTG). On-treatment weight gain has a potentially negative effect on health benefit of INSTI-based regimen due to cardiometabolic multimorbidity associated with increased BMI.[17] Some early findings have also demonstrated that INSTIs initiation was associated with an early onset, excess incidence of cardiovascular disease in the first 2 years of exposure.[18] The benefit of switch to INSTI-based ARV regimen should be balanced against the potential cardiovascular risks especially in high-risk PLWH. Therefore, an alternative non-INSTI-based regimen is desirable if with comparable virological efficacy and improved cardiometabolic safety. Our study population showed an excellent treatment adherence (withdrawal 0.7%) even in the years of COVID-19 pandemic and was well supportive of validation of the efficacy and safety outcomes.

High viral suppression was maintained throughout 48-week treatment in both arms, without any participant with HIV-1 RNA titre constantly equalling to or above 50 copies per mL. No participant discontinued treatment, or withdrew prematurely due to lack of efficacy. Non-inferiority was established for ANV/3TC/TDF regimen to EVG/Cobi/FTC/TAF regimen. This non-inferiority was further validated by multiple sensitivity analyses, including the most stringent tipping-point analysis. No predefined baseline factor was identified to confound the efficacy conclusion as an overall virological response was achieved up to more than 98% in both arms. No participant had confirmed HIV-1 RNA titre above 400 copies per mL, which disabled genotypic resistance testing. CD4+ cell on-treatment response was small as the study population had been on stable ARV regimen for a mean duration of approximately 5 years, and virologically suppressed; however, a small decrease in CD4+ cell count occurred in both arms within the first four weeks of treatment. All the aforementioned findings supported switch from EFV- to ANV-based regimen in virologically suppressed PLWH as high virological suppression was maintained and non-inferior to INSTI-based regimen. As far as we are aware, the present study was the first to demonstrate the virological efficacy non-inferiority of an NNRTI-based regimen to an INSTI-based regimen in virologically suppressed PLWH.

The TEAEs profile was comparable between the two treatment arms through 48-week treatment, with occasional treatment discontinuation or premature withdrawal due to TEAEs. As the study population had been on EFV-based regimen for at least 12 months, the most common reported TEAEs were weight change, including both gain and loss, and dyslipidaemia, while

	ANV/3TC/TDF regimen (n = 381)	EVG/Cobi/FTC/TAF regimen (n = 381)	*P*-value
Any TEAE	372 (97.6)	372 (97.6)	>0.999
ADR	282 (74.0)	331 (86.9)	<0.001
Grade 3–5 TEAE	41 (10.8)	95 (24.9)	<0.001
SAE	11 (2.9)	9 (2.4)	0.650
Treatment discontinuation due to TEAE[a]	0 (0)	1 (0.3)	>0.999
Premature withdrawal due to TEAE[b]	1 (0.3)	1 (0.3)	>0.999
Most common TEAE by PT ≥5%			N/A
Weight gain	89 (23.4)	129 (33.9)	
Weight loss	53 (13.9)	55 (14.4)	
Increased serum LDL-C	23 (6.0)	81 (21.3)	
Increased serum cholesterol	19 (5.0)	121 (31.8)	
Increased serum triglyceride	45 (11.8)	130 (34.1)	
Decreased serum HDL-C	36 (9.4)	21 (5.5)	
Increased serum uric acid	44 (11.5)	101 (26.5)	
Increased serum glucose	16 (4.2)	22 (5.8)	
Fatty liver degeneration	12 (3.1)	37 (9.7)	
Increased serum ALT	15 (3.9)	23 (6.0)	
Increased serum AST	18 (4.7)	23 (6.0)	
Increased serum GGT	26 (6.8)	9 (2.4)	
Increased serum CPK	27 (7.1)	26 (6.8)	
Increased serum globulin	13 (3.4)	20 (5.2)	
Decreased plasma fibrinogen	24 (6.3)	13 (3.4)	
Urine WBC positivity	27 (7.1)	31 (8.1)	
Detected urine protein	27 (7.1)	26 (6.8)	
SARS-CoV-2 test positivity	83 (21.8)	71 (18.6)	
COVID-19	77 (20.2)	71 (18.6)	
Suspected COVID-19	50 (13.1)	53 (13.9)	
Upper respiratory tract infection	66 (17.3)	74 (19.4)	
Diarrhoea	12 (3.1)	32 (8.4)	
Nausea	8 (2.1)	22 (5.8)	
Sinus bradycardia	31 (8.1)	14 (3.7)	
Dizziness	11 (2.9)	27 (7.1)	

Data are presented in n (%). All study drugs were given in fixed-dose combination, and as single-tablet regimen with matching placebo. Treatment-emergent adverse event was defined as any adverse event that occurred, and/or worsened following medication with the first dose of study drug. Adverse drug reaction was defined as treatment-emergent adverse event, definitely, probably, or likely related to study drug. Severity of adverse event was rated by the investigator using *the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events* v2.1., or *the Common Terminology Criteria for Adverse Events* (CTCAE) v5.0 if applicable. 3TC, lamivudine; ADR, adverse drug reaction; ALT, alanine transferase; ANV, ainuovirine; ASCVD, atherosclerotic cardiovascular disease; AST, asparate transferase; Cobi, cobicistat; CPK, creatinine phosphokinase; EVG, elvitegravir; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable; PT, preferred term; SAE, serious adverse event; SARS, severe acute respiratory syndrome; TAF, tenofovir alafenamide; TC, total cholesterol; TDF, tenofovir disoproxil fumarate; TEAE, treatment-emergent adverse event; TG, triglyceride. [a]One participant in the boosted elvitegravir group discontinued study treatment and prematurely withdrew from the trial due to infectious pneumonitis. [b]One participant in the ainuovirine group prematurely withdrew from the trial due to pulmonary tuberculosis with complicating tuberculous pleuritis.

***Table 3*: Summary of treatment-emergent adverse events.**

CNS-associated symptoms were occasionally reported at both baseline and post-treatment visits. This probably reflected tolerance for the well characterized side effects of EFV. Our previous study showed that switch EFV- to ANV-based regimen was beneficial in lipid metabolism in a non-controlled extension study period.[10] In the present study, switch to ANV/3TC/TDF regimen was associated with significantly less frequent, and less severe weight gain, and dyslipidaemia compared to that to EVG/Cobi/FTC/TAF, accompanied by downgraded *versus* upgraded ASCVD-risk associated dyslipidaemia stratum at week 48. This produced new knowledge regarding cardiometabolic safety of TDF-containing, new-generation NNRTI- compared to TAF-containing, boosted INSTI-based regimen in a double-blind, randomised, controlled fashion although some previous non-randomized, non-controlled studies also presented similar results.[19–21]

In NAMSAL ANRS 12313 trial, more weight gain was observed with DTG-based regimen compared to with low-dose EFV-based regimen: median weight gain, 5.0 *versus* 3.0 kg, and incidence of obesity, 12.3% *versus* 5.4%.[22] In ADVANCE study, weight gain (both lean and fat mass) was greatest with TAF-containing, DTG-based regimen compared to TDF-containing, DTG-, and EFV-based regimens: weight gain, 6 *versus* 3 *versus* 1 kg, and newly emerging obesity, 14% *versus* 7% *versus* 6%.[23] Phase 3 trials of EVG/Cobi/FTC/TAF regimen did not report the results of body weight change in either treatment-naïve or virologically suppressed participants.[24–26] Bictegravir (BIC)/FTC/TAF, the latest approved INSTI-based STR, was seldomly reported for body weight outcome either. A network meta-analysis reported DTG with the highest rank order of probability for weight gain, but EVG with the lowest.[27] Another network meta-analysis reported that BIC-based regimen had a weight gain effect similar to DTG-based regimen through 96 weeks of treatment.[28] Our on-treatment body weight change analyses showed a small increase in both arms within the first 12–24 weeks, probably due to the long-last inhibitory post effect of EFV on weight gain[29,30]; body weight continued to increase in both arms to a similar extent until week 48 with a greater gain seen with TAF-containing, boosted EVG-based regimen (+1.16 *versus* +2.05 kg). A pooled analysis of randomised controlled studies of switch therapy demonstrated that the greatest risk of weight gain was associated with switch-off EFV to rilpivirine or to EVG/Cobi, and also with switch-off TDF to TAF.[31] However, Palella et al. noted that in the first 8 months post-switch weight gain was primarily (87%) associated with switch to INSTI; after the first 8 months it was mainly (73%) with use of TAF.[32] Therefore, it can be concluded that weight gain in both arms resulted from diminished long-lasting inhibitory post-effect of EFV but was observed with a greater extent in the comparator arm due to both further switch to EVG/Cobi, a boosted INSTI, and switch-off TDF.

Considering the relatively lower baseline body weight in Chinese and other Asian populations, even a small amount of absolute weight gain would convert to a higher percentage gain: +1.77% *versus* +3.22% in the present study. It has been reported that even 1%–5% weight gain was associated with significant increases in

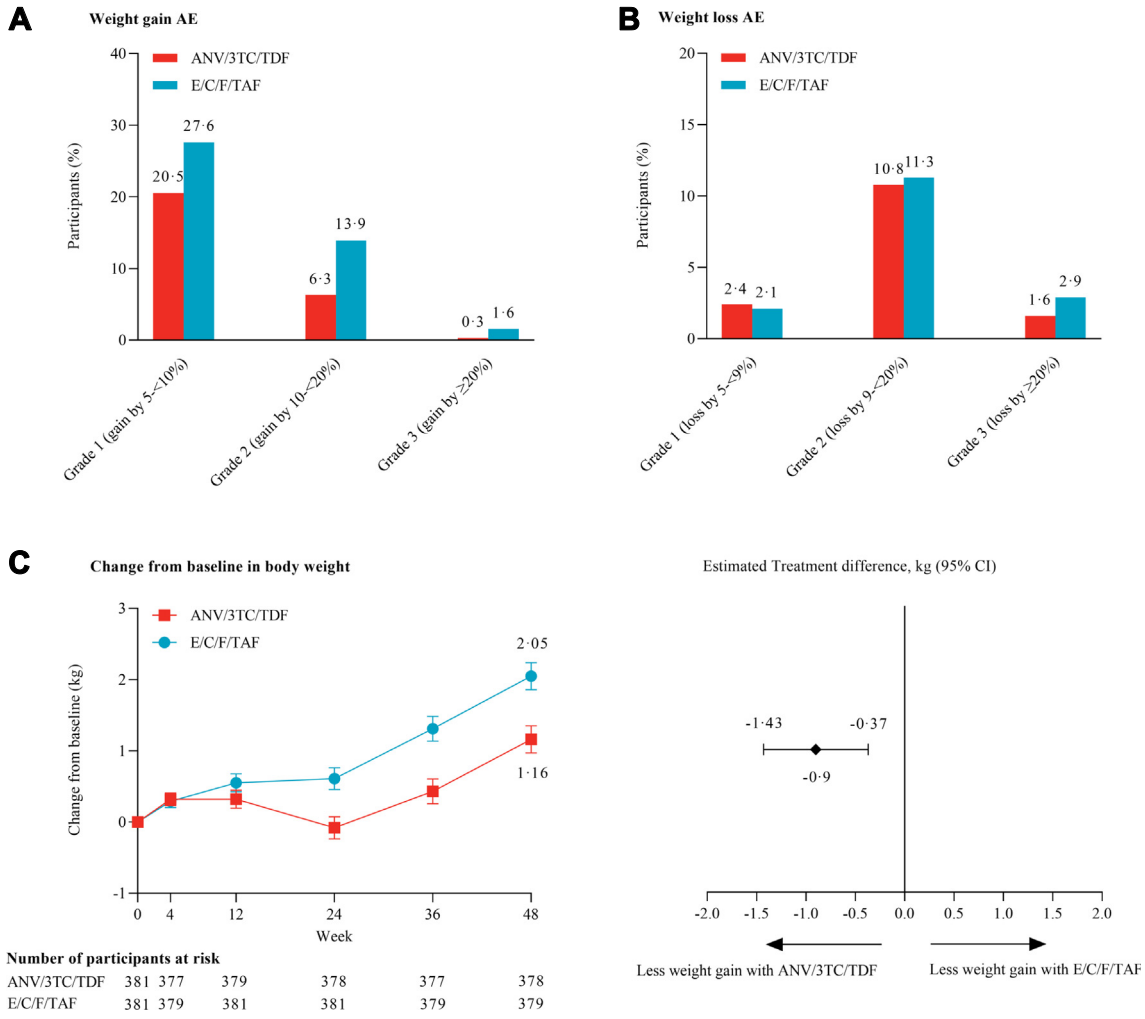
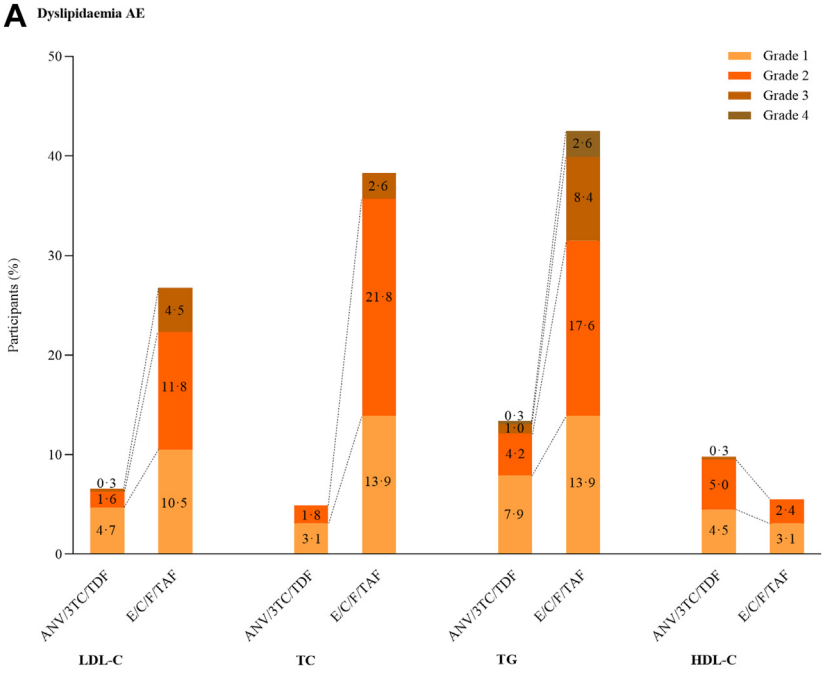
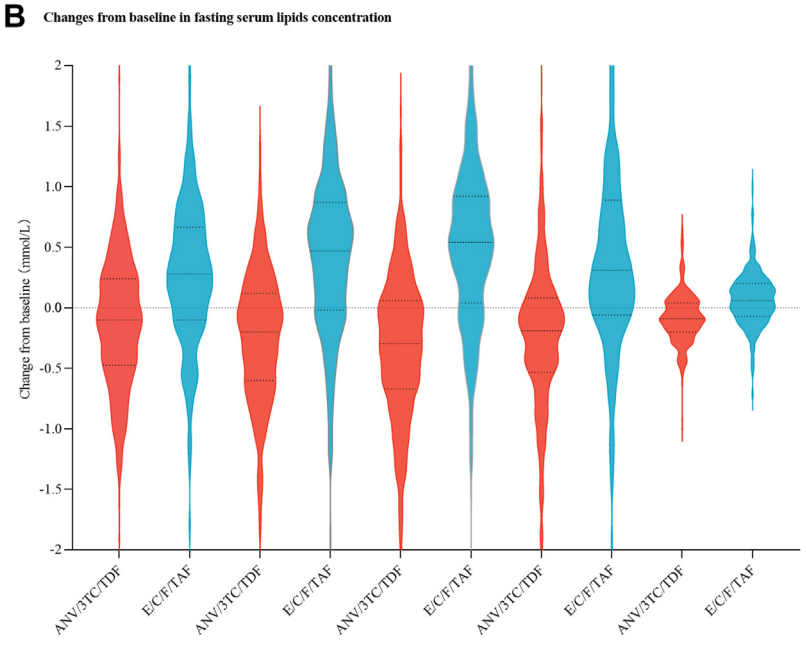


Fig. 2: **Proportions of PLWH experiencing (A) weight gain, and (B) weight loss AEs (MedDRA) by severity over 48-week treatment, and (C) changes from baseline in body weight over 48-week treatment**. Severity of weight gain AE as determined by the investigator in reference to *the Common Terminology Criteria for Adverse Events* (CTCAE) v5.0 as follows: grade 1, ≥5% to <10% gain in body weight from baseline; grade 2, ≥10% to <20% gain in body weight from baseline; and grade 3, ≥20% gain in body weight from baseline. Severity of weight loss AE as determined by the investigator in reference to *the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events* v2.1 as follows: grade 1, ≥5% to <9% loss in body weight from baseline; grade 2, ≥9% to <20% loss in body weight from baseline; and grade 3, ≥20% loss in body weight from baseline. AE, adverse event; ANV/3TC/TDF, ainuovirine/lamivudine/tenofovir disoproxil fumarate; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; MedDRA, *Medical Dictionary for Regulatory Activities*; PLWH, people living with HIV. ANV/3TC/TDF *versus* E/C/F/TAF at week 48 by analysis of covariance.

the risk of metabolic syndrome among Asian PLWH: high blood pressure (hazard ratio [HR] (95% CI), 1.8 [1.2, 3.0]), and increased fasting TG (1.8 [1.3, 3.0]).[33]

Switch to E/C/F/TDF from EFV-based regimen resulted in a small magnitude decrease in LDL-C compared to continuation of baseline regimen (–0.10 *versus* 0.10 mmol/L, $P = 0.001$).[34] Further switch to E/C/TAF from EFV-based regimen led to increase in LDL-C by 0.23 mmol/L in virologically suppressed PLWH at week 48.[25] In the clinical trials comparing EVG/Cobi/FTC/TAF regimen and EVG/Cobi/FTC/TDF regimen, median CFBs at week 48 were 14 *versus* 5 mg per dL for LDL-C, 29 *versus* 14 mg per dL for TC, 19 *versus* 8 mg per dL for TG, and 7 *versus* 4 mg per dL for HDL-C, respectively (all *P*-values <0.001, except for $P = 0.027$ with TG), for treatment-naïve patients; fasting elevated LDL-C and hypercholesterolaemia of grade 3 or 4 occurred in 5% *versus* 2% and 2% *versus* 1%, respectively.[24] Switch to EVG/Cobi/FTC/TAF regimen was also associated with a more remarkable median fasting lipid increase compared to stay on previous TDF-based regimen at week 48: 9 *versus* 2 mg per dL for LDL-C,





	LDL-C		non-HDL-C		TC		TG		HDL-C	
No.	365	373	365	373	378	379	378	379	365	373
Median	-0·10	0·28	-0·20	0·48	-0·30	0·54	-0·19	0·33	-0·09	0·06
Q1	-0·47	-0·10	-0·60	-0·02	-0·67	0·04	-0·53	-0·05	-0·20	-0·07
Q3	0·24	0·66	0·12	0·87	0·06	0·92	0·08	0·91	0·04	0·19
Mean	-0·13	0·27	-0·25	0·44	-0·33	0·51	-0·36	0·60	-0·08	0·07
ETD	-0.39		-0.69		-0.84		-0.98		-0.15	
95%CI	(-0·47, -0·32)		(-0·77,-0·60)		(-0·92, -0·75)		(-1.18, -0·78)		(-0·18, -0·12)	

***Fig. 3*: Proportions of PLWH experiencing (A) dyslipidaemia AE (MedDRA) by severity, and (B) changes from baseline in fasting serum lipids concentration over 48-week treatment**. Serum lipids concentration as determined by local pathology laboratories. Severity of

20 *versus* 2 mg per dL for TC, 11 *versus* 2 mg per dL for TG, and 2 *versus* 1 mg per dL for HDL-C, respectively (all *P*-values <0.001 except for $P = 0.003$ with HDL-C).[25] These findings suggested that boosted EVG could not fully offset the adverse effects of coformulated TAF on serum lipids although it was favoured over EFV.

Subgroup analyses included Asian participants (N = 184) from the aforementioned three trials, and another single-arm, open-label study involving virologically suppressed participants with mild to moderate renal impairment.[35] Both naïve and suppressed Asian participants on EVG/Cobi/FTC/TAF regimen experienced a small but statistically significant in all fasting lipid parameters compared to those on control regimen. Another pooled analysis of suppressed Asian participants switch to BIC/FTC/TAF from DTG-, boosted EVG-, or boosted PI-based regimens showed a similar, unchanged fasting lipid profile to comparator regimens at week 48, except for a significant decrease in fasting TG with BIC/FTC/TAF regimen.[36]

Dyslipidaemia is prevalent in PLWH, especially among young and middle-aged men compared to counterpart women.[37] Multiple cholesterol-lowering medications have been trialed in PLWH to evidence their benefits for PLWH at a high risk of ASCVD, and improve cardiovascular outcomes in PLWH.[38–40] However, it is clinically more reasonable to prescribe an ARV regimen with less adverse effects on lipid metabolism. Our analyses of dyslipidaemia showed a favourable effect in AE frequency, AE severity, absolute change, and ASCVD risk stratum with ANV/3TC/TDF regimen compared to the comparator regimen. This lipid metabolism benefit associated with use of TDF-containing, NNRTI-based regimen was also seen in previous non-controlled Chinese suppressed PLWH studies.[19–21] Of note, HDL-C decreased with ANV-based regimen, but increased with TAF-containing boosted EVG-based regimen. The clinical significance of this finding remains unknown as ASCVD risk is primarily driven by LDL-C, and non-HDL-C.

Long-term use of TDF may be associated with an increased risk of renal tubulopathy and osteopathy. However, renal function improved, and serum phosphate showed minimal differences between the two treatment arms, with comparable renal-, and bone-associated TEAEs reported in our study. Our study population was at a relatively younger age, and had less frequent pre-existing commodities, with moderately, or severely renal impaired participants excluded. Routine renal and bone safety monitoring using sensitive biomarkers is also required for patients on ANV/3TC/TDF regimen.

There are some limitations in the present study. First, only a small portion of participants were women (<5%), and no older participants (above 65 years), or those with moderate to severe liver, or renal impairment, or with complicating coinfection with hepatitis virus were enrolled due to protocol restrictions. However, the aforementioned characteristics are known to have minimal effect on the virological efficacy of INSTI-based regimen.[41] Of note, our participant population was also assessed to be at a higher risk of cardiovascular disease as the majority of participants were men, one third to fourth of whom were overweighted, obese, or with fatty liver disease.[42] Second, a boosted rather than unboosted INSTI-based regimen was used as comparator in communication with the regulatory agency. EVG/Cobi/FTC/TDF regimen (FDA 2012) was the first approved INSTI-based STR worldwide, and EVG/Cobi/FTC/TAF regimen was the first STR approved in China (2018). These two fixed dose combinations required no pre-baseline delicate human leukocyte antigen genotyping with use of DTG/3TC/abacavir, the first approved unboosted INSTI-based STR (FDA 2014, and 2017 in China). EVG was thought to have a low genetic resistance barrier; however, a high suppression was achieved with EVG/Cobi/FTC/TAF regimen in both the previously reported phase 3 trial (97%),[25] and the present study (98.4%) for virologically suppressed participants. Coformulated Cobi might confound interpretations of our findings on lipid profiles. Cobicistat is thought to affect lipid profiles to a lesser extent than ritonavir, the classical booster when combined with PI.[43] EVG was associated with increased serum lipids in treatment-naïve PLWH when combined with FTC/TDF although to a lesser extent compared to EFV, and similarly to atazanavir/ritonavir.[44,45] Last, inclusion of TAF rather than TDF in the comparator NRTI backbone might also disfavour weight control, and serum lipids in the comparator arm. However, the most common INSTI-based STRs, such as BIC/FTC/TAF, contain TAF rather than TDF in current practice.

dyslipidaemia AE as determined by the investigator in reference to *the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events* v2.1. In each histogram for dyslipidaemia (upper panel), the numbers in the grids indicate proportions of participants experiencing dyslipidaemia AE by severity. In each violin plot for serum lipids (lower panel), the median was indicated by a horizontal line, and the interquartile range (Q1–Q3) by the top and bottom of a box; whiskers indicate the 5th and 95th percentiles, and the tapering points reflect the shape of the distribution. AE, adverse event; ANV/3TC/TDF, ainuovirine/lamivudine/tenofovir disoproxil fumarate; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; ETD, estimated treatment difference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MedDRA, *Medical Dictionary for Regulatory Activities*; non-HDL-C, non-low-density lipoprotein cholesterol; PLWH, people living with HIV; TC, total cholesterol; TG, triglyceride. ANV/3TC/TDF *versus* E/C/F/TAF at week 48 by mixed model for repeated measures analysis.

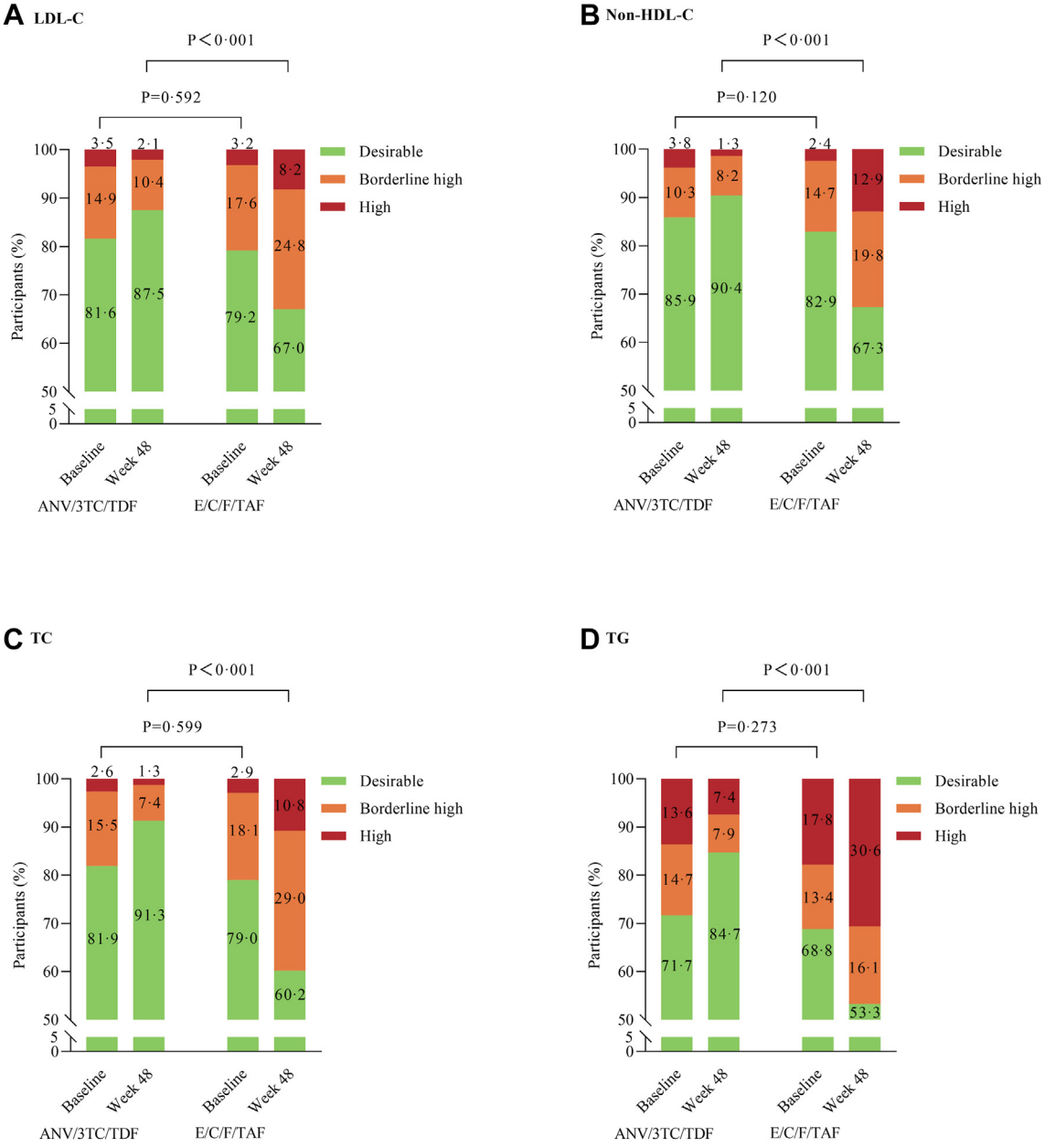


Fig. 4: **Atherosclerotic cardiovascular disease risk-associated dyslipidaemia stratification at baseline and week 48**. The atherosclerotic cardiovascular disease risk-associated dyslipidaemia was stratified in accordance with *the Chinese Guidelines for Lipid Management* (2023) published by the Joint Committee on the Chinese Guidelines for Lipid Management as per the primary prevention target for Chinese low-risk population as follows: (A) high LDL-C, ≥4.1 mmol per L; (B) high non-HDL-C, ≥4.9 mmol per L; (C) high TC, ≥6.2 mmol per L; and (D) high TG, ≥2.3 mmol per L. ANV/3TC/TDF, ainuovirine/lamivudine/tenofovir disoproxil fumarate; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride. Non-HDL-C (mmol per L) = total cholesterol – high-density lipoprotein cholesterol.

In conclusion, switch to ANV-based STR was non-inferior to that to boosted EVG-based regimen in virological efficacy at week 48 for virologically suppressed PLWH. Both regimens showed a favourable tolerability profile; however, switch to TDF-containing, ANV-based regimen was favoured over that to TAF-containing, boosted EVG-based regimen due to less frequent, and less marked weight gain, and dyslipidaemia. The present study together with our previous study demonstrated that fixed-dose ANV/3TC/TDF was an

efficacious, well tolerated regimen for both treatment-naïve and virologically suppressed PLWH with potential cardiometabolic benefits.

Contributors

All authors were involved in development of the manuscript, interpretation of data, have reviewed, and approved the final version, and have met the criteria for authorship as established by the ICMJE. FJZ, HW, and WPC enrolled participants, collected, and analysed the data, independently interpreted the results, and reviewed, edited, and approved the manuscript. PM, QXZ, HXW, HZL, HW, ZC, SHH, YKC, and MW enrolled participants, collected, and reviewed the data, and approved the manuscript. HQ designed the statistical analysis plan, analysed the data, and drafted the manuscript. WW analysed the data, wrote the study report, and helped to draft the manuscript. HLF conceived the study design, oversaw the study conduct, reviewed the data, and revised the manuscript. All authors contributed to edits of the final manuscript. FJZ, HW, WPC and HLF made the decision to submit the manuscript for publication.

Data sharing statement

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author/s.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101143.

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