Efficacy and safety of ainuovirine versus efavirenz combination therapies with lamivudine/tenofovir disoproxil fumarate for medication of treatment-naïve HIV-1-positive adults: week 48 results of a randomized controlled phase 3 clinical trial followed by an open-label setting until week 96

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Summary

Background Ainuovirine (ANV) is a new non-nucleoside reverse transcriptase inhibitor (NNRTI), which was initially synthesized in Korea and later further developed in both Korea and China.

Methods A randomized, double-blind, double-dummy, positive parallel group, non-inferiority, phase 3 trial was conducted in 7 sites across China. Eligible HIV-1-positive antiretroviral therapy (ART)-naïve adults aged 18–65 years were randomly assigned in a 1:1 ratio to receive tenofovir disoproxil fumarate and lamivudine (TDF+3TC) in combination with either ANV (ANV group) or efavirenz (EFV group) for up to 48 weeks. Subsequently, participants in both groups received one of the two drug combinations according to their choice until week 96 in an observational study under an open-label setting. The primary endpoint was the proportion of participants achieving HIV RNA <50 copies/mL at week 48, with non-inferiority pre-specified at a margin of 10%. The secondary efficacy endpoints were logarithmic changes in HIV RNA, percentage of participants with HIV RNA levels ≤400 copies/mL and changes in the CD4 T-cell count after 48 and 96 weeks of treatment, as well as the percentage of participants with HIV RNA levels <50 copies/mL at 96 weeks of treatment. Safety endpoints were the incidence of adverse events and laboratory abnormalities evaluated according to the Division of AIDS criteria. This study was registered with the Chinese Clinical Trial Registry (Registration number: ChiCTR1800019041).

Findings Between November 27, 2018 and March 11, 2021, a total of 826 participants were screened, and 630 were finally enrolled and randomly assigned (1:1) to either ANV (n = 315) or EFV (n = 315) groups. The mean age was 30.6 ± 9.4 years and most participants were male (94.6%). At week 48, 274 (87.0%) of 315 participants in the ANV group and 288 (91.7%) of 314 in the EFV group achieved HIV-1 RNA <50 copies/mL and non-inferiority was established (difference: −4.7%, 95% CI: −9.6 to 0.1). In the period, 293 participants continued to take the ANV regimen and 287 switched from the EFV to the ANV regimen. During the open-label period, 92.5% (271/293) of participants in the continued ANV group and 95.1% (273/287) in the ANV to EFV transfer group remained

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virologically suppressed (HIV-1 RNA <50 copies/mL) at week 96 (*p* = 0.189). The incidence of NNRTI treatment-related adverse events (TEAEs) at week 48 was 67.6% in 315 participants in the ANV group, which was significantly lower than in 91.4% of 314 participants in the EFV group (*p* < 0.001). The most common TEAEs (weeks 0–48) were dizziness (10.5%) and dyslipidemia (22.2%) in the ANV group vs. 51.0% and 34.4% in the EFV group, respectively, followed by transaminase elevation (9.2% vs. 29.0%), γ-glutamyl transferase elevation (8.3% vs. 19.1%), and rash (7.9% vs. 18.8%) (all *p* < 0.001). After switching from EFV to ANV, TEAEs in the former EFV participants were significantly reduced in the following observational period of 48–96 weeks.

Interpretation The week 48 results indicated that the efficacy of ANV was non-inferior to EFV when combined with two NRTIs. The per-protocol risk difference at week 48 for the primary endpoint also supported non-inferiority. TEAEs in ANV treated participants were less frequent with regard to liver toxicity, dyslipidemia, neuropsychiatric symptoms and rash compared to the EFV group during the first 48 weeks of therapy. The effects were maintained during the 48–96 weeks of therapy.

Introduction

According to the World Health Organization (WHO) guidelines for HIV therapy, initial antiretroviral therapy (ART) regimens should consist of a nucleoside reverse transcriptase inhibitor (NRTI) backbone combined with dolutegravir (DTG) or alternatively with efavirenz (EFV).[1] A previous study with an NRTI combination with DTG was shown to be no inferior to EFV.[2] A recent report noted an EFV viral suppression rate comparable to that of the Integrase Strand Transfer Inhibitor (INSTI) group over a 7-year follow-up period.[3] According to the most recent Chinese guidelines, tenofovir disoproxil fumarate (TDF)+lamivudine (3TC) or emtricitabine (FTC) + EFV or rilpivirine (RPV) should be the choice for first-line HIV/AIDS treatment.[4] In order to find new generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) that are as effective as EFV but with fewer side effects,[5] much research is ongoing. As a result, several new NNRTIs, which when combined with an NRTI backbone have been approved for clinical use in China without the requirement to conduct additional clinical trials in Chinese patients. Marketing was approved by the National Medical Products Administration (NMPA) for doravirine (DOR)[6] in 2020 in combination with other ART, and RPV[7] in 2022 as DTG/RPV tablet, and these NNRTIs have been widely adopted in the clinic.

Ainuovirine (ANV) is a novel NNRTI approved in China in 2021. Preclinical and phase 1 clinical studies have shown that ANV had low drug–drug interaction (DDI) potential, favorable pharmacokinetic/pharmacodynamic (PK/PD) characteristics, good tolerability and no serious side effects, as well as antiviral activity against several HIV strains in addition to synergistic activity with 3TC and TDF.[8,9] The present phase 3 trial was conducted to compare the efficacy and safety of ANV vs. EFV with 3TC/TDF as co-medications in treatment-naïve HIV-1-positive adults.

Methods
Study design and participants
A randomized, double-blind, double-dummy, positive parallel group, non-inferiority, phase 3 trial was conducted to evaluate the efficacy and safety of ANV + 2 NRTIs for treatment-naïve HIV-1 positive adults. The trial was conducted in 7 clinical centers (Appendix p3) across 6 cities in China, namely Beijing, Chongqing, Guangzhou, Zhengzhou, Nanjing and Changsha. Eligible participants had an HIV-1 infection but no previous exposure to antiretroviral drugs or therapeutic vaccines. The inclusion criteria were ages 18–65 years and ≥1000 plasma HIV-1 RNA copies/mL. Exclusion criteria were participants who were pregnant, breastfeeding, had severe hepatic impairment, renal failure, severe immunological diseases, psychiatric illness or active tuberculosis co-infection. More detailed information is provided in Appendix p4.

The research protocol was approved by the Independent Ethics Committee for each study center. The trials were conducted in conformance with Good Clinical Practice (GCP) Guidelines and applicable statutes and regulations regarding the protection of human participants in biomedical research. This study was registered with the Chinese Clinical Trial Registry (Registration number: ChiCTR1800019041). All participants provided written informed consent before the study procedures were performed. The data cutoff for this report (week 96) was March 11, 2021.

Research in context

Evidence before this study

The new generation non-nucleoside reverse transcriptase inhibitor (NNRTI) known as ainuovirine (ANV) was initially synthesized in Korea and later developed in both Korea and China under the R&D codenames of KM-023 and ACC007, respectively. A preclinical study revealed that ANV exhibited potent antiviral activity against various HIV strains *in vitro*, as well as a synergistic effect with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF). According to unpublished pre-clinical studies, ANV was mostly metabolized by CYP2C19 rather than other common CYP enzymes such as CYP3A4, suggesting a low potential of drug–drug interactions (DDIs). ANV was further evaluated in the MDS Pharma Lead Profiling Screen comprising of 68 ion channels and the CEREP safety profile screen comprised of 115 mammalian receptors and 42 enzymes, and it was found that it did not significantly bind to any target at a concentration of 10 mM. The data also indicated that the off-target impact of ANV on the central nervous system (CNS) may be comparatively less compared to efavirenz (EFV). Previous phase 1 clinical studies conducted in both Korea and China revealed that ANV had dose-dependent and time-dependent nonlinear pharmacokinetic characteristics, favorable tolerability and induced no serious side effects. Completed ANV trials thus far include a first-in-human (FIH) trial, a trial for single or multiple dose administration and drug pharmacokinetics, a trial for the pharmacokinetics of food influence, and a phase 2a PK/PD study. In a first in human trial (phase 1) with a single ascending dose, ANV tolerability and pharmacokinetic was assessed for 30 healthy Chinese subjects in 75, 150 and 300 mg groups, with 10 subjects in each dose group. Then, a multiple ascending dose study was performed in 3 dose groups (75 mg/8 patients, 150 mg/10 patients, 300 mg/10 patients) for 10 days to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of ANV in primary HIV-infected patients. After 10 days of continuous administration, the dose was increased from 75 mg to 300 mg which was well tolerated by all of the participants. Of note, there was no accumulation of the study drug in the 75 mg, 150 mg and 300 mg groups. Pharmacodynamic results showed a significant decrease in the HIV viral load in participants at doses of 75 mg, 150 mg and 300 mg, with decreases of 1.73 $\log_{10}$, 1.72 $\log_{10}$ and 1.66 $\log_{10}$, respectively. Based on these clinical trials, the preliminary results found that ANV tablets had good safety and efficacy, and a recommended dose was established. Therefore, the Chinese Center for Drug Evaluation allowed directly the conduction of a phase 3 clinical trial of ANV without requiring a phase 2b dose finding study.

Added value of this study

To the best of our knowledge, this study is the first to investigate the efficacy and safety of ANV compared to EFV in a multicenter, randomized, double blind, double dummy, positive parallel control phase 3 clinical trial for the initial treatment for HIV-1-positive adults. The results demonstrated that the antiretroviral efficacy of ANV+3TC+TDF was non-inferior to that of EFV+3TC+TDF at week 48, and that the regimen of ANV+3TC+TDF elicited fewer side effects with regard to liver, lipid and central nervous system toxicities. Moreover, 271 (92.5%) of 293 participants and 273 (95.1%) of 287 participants in the ANV continued treatment group, and from the EFV to ANV transfer group, had <50 HIV-1 RNA copies/mL at week 96 ($p = 0.189$). The study revealed that ANV treatment was effective with a low incidence of adverse events (AEs) for the initial antiviral treatment period and during a switch regimen of HIV-1-positive participants for 96-weeks.

Implications of all the available evidence

The safety and efficacy profiles of ANV observed in this study in China are in good agreement and supplements data from previous studies of NNRTI based treatment regimens. The results showed that ANV (150 mg) combined with two NRTIs, administered once daily orally, provided a valuable treatment option for therapy of treatment-naïve participants and a switch option in virally-suppressed individuals.

Randomization and masking

Eligible participants were randomly assigned (1:1) to receive the ANV-based regimen (ANV group) or the EFV-based regimen (EFV group) as a positive parallel group. Randomization was stratified by the sites. The randomization list was created and validated by the interactive web response system (IWRS) vendor (Beijing BioVoice Technology Co., Ltd). The randomization had a block size of 6 generated with SAS (ver. 9.4). During the initial 48 weeks of the randomized clinical trial (RCT) phase, all the investigators and participants were blinded to treatment group assignments. At the end of 48 weeks treatment, the database was locked and eligible participants were given the option to continue on their actual treatments or switch to either ANV+3TC+TDF or EFV+3TC+TDF in an open-label extension phase from week 48 to week 96.

Procedures

Participants received once daily oral therapy comprised of either ANV (75 mg/tablet × 2 tablets) + 300 mg 3TC (1 tablet) + 300 mg TDF (1 tablet) (ANV group) or 600 mg EFV (1 tablet) + 1 tablet mimetic matching placebo for ANV + 300 mg 3TC (1 tablet) + 300 mg TDF

(1 tablet) (EFV group) at night before bedtime for 96 weeks. The group of participants who continued on ANV+3TC+TDF after 48 weeks was defined as the continued group, while the EFV group participants who switched to ANV+3TC+TDF during week 48–96 was defined as the transfer group.

Trial visits were scheduled at baseline and at weeks 4, 12, 24, 36 and 48 in the RCT period, and the parameters of week 48 were defined as baseline$_{48}$ for the open-label observation period. Laboratory tests included hematological analysis, urinalysis, serum chemistry tests, fasting lipids, renal function (serum creatinine and glomerular filtration rate). Plasma HIV-1 RNA quantification was performed on all follow-up visits from baseline to week 96 by the Central Laboratory of the Beijing Ditan Hospital, Capital Medical University using an Abbott RealTime HIV-1 assay (lower limit of quantification [LLoQ] was 40 copies/mL). CD4 T-cell counts were determined on each study visit day using flow cytometry.

Blood samples were retained at baseline for all participants in the study. After 24 weeks following the initiation of antiviral treatment, participants with HIV RNA >400 copies/mL were regarded as protocol-defined virologic failures (PDVF). The results of the central laboratory review were used as the criteria for determining and judging PDVF of the participants. The principal investigator decided whether a particular participant was withdrawn from the study or decided the subsequent treatment regimen for the PDVF cases. The study drug adherence was computed as the number of tablets taken divided by the number of tablets prescribed, where the number of tablets taken was the number of tablets dispensed minus the number of tablets returned. This phase 3 clinical trial was set up to perform medication recall and counts at the 4th, 12th, 24th, 36th, 48th, 72nd and 96th week of follow-up visits. The medication was counted at each visit point and then the participant was given the next phase medication, allowing the calculation of the actual dosage of medication used to determine compliance. Participants with HIV RNA >400 copies/mL due to poor medication adherence, DDI, malabsorption syndrome and other influencing factors were excluded. In this study, the medication adherence of participants was required to be ≥90% and ≤110%. The blood samples of participants with virologic failure at baseline and at week 24 and 48 visits were all sent to a central laboratory for genotypic resistance testing. Phenotypic viral resistance was assessed on the difference between the IC$_{50}$ values for participants in both groups and the wild-type virus at baseline and week 48, respectively.

Safety was assessed by vital signs, physical examinations, laboratory tests, a 12-lead electrocardiogram, ultrasonography, chest X-ray, concomitant drugs at each visit and the adverse events (AEs) reported by participants and study investigators, which were coded by the Medical Dictionary for Regulatory Activities (Med DRA, version 22.0).

Outcomes

The primary objective of the study was to assess whether the efficacy of ANV+3TC+TDF was non-inferior to that of EFV+3TC+TDF. The key efficacy endpoint was the proportion of participants with plasma HIV RNA levels <50 copies/mL, defined by the Food and Drug Administration (FDA) snapshot algorithm at week 48 in the Full Analysis Set (FAS), with non-inferiority pre-specified at a margin of 10%. The secondary efficacy endpoints were the logarithmic change of HIV RNA at weeks 48 and 96 of treatment, percentage of participants with HIV RNA levels ≤400 copies/mL at weeks 48 and 96 of treatment, percentage of participants with HIV RNA levels <50 copies/mL at week 96 of treatment and changes in the CD4 T-cell count at weeks 48 and 96 of treatment. Safety analysis included all randomized participants who received at least one dose of the study drug. Safety outcomes were recorded as the incidence of AEs, which occurred during 48 weeks and 96 weeks in both study periods, including the vital signs and the change of laboratory values graded from baseline. The analysis especially focused on NNRTI mechanism-based AEs, including the incidence of rash and neuropsychiatric events, the severity of drug-induced hepatitis and changes in fasting serum lipids from baseline to week 96. AEs and laboratory abnormalities that emerged during treatment were graded according to the Division of AIDS (DAIDS) criteria.[10]

Statistical analyses

According to the current HIV/AIDS treatment regimens in China, the percentage of post-treatment HIV RNA levels <50 copies/mL was estimated to be 80% in the EFV group and with one sided α = 0.025 and a non-inferiority margin of 10% (based on published US FDA regulatory guidance[8]), 252 participants per group would provide about 80% power to show non-inferiority for the proportion of participants with HIV RNA levels <50 copies/mL at week 48.[11] Allowing for a 20% dropout, the target sample size was set at 630. If the lower boundary of the two-sided 95% confidence intervals (CI) for the treatment difference (ANV group minus EFV group) was >−10%, non-inferiority would be established.

The primary efficacy analysis was the proportion of participants with plasma HIV-RNA <50 copies/mL using the FDA Snapshot algorithm at week 48 in the FAS, which included all randomized participants who received at least one dose of the study drugs in each treatment group according to intention to treat (ITT) principles. The between group risk difference for the primary endpoint and its 95% CI were computed using the Newcombe method. The proportion and 95% CIs of HIV-RNA <50 copies/mL by time and by subgroup (baseline HIV-RNA stratum: ≥100,000 vs. <100,000

copies/mL) were compared by Fisher's exact test and plotted for the FAS. To assess the impact of important protocol deviations, statistical analyses were repeated using the per-protocol population set (PPS) and compared for consistency with the results from the primary FAS population analysis.

The secondary endpoints analysis included the proportion of participants with HIV RNA <50 copies/mL at week 96 and the proportion of participants with HIV RNA ≤200 or 400 copies/mL during the whole study period of 96 weeks, evaluated using the same method as for the primary endpoint (*vide supra*). Changes in CD4 T-cell counts at week 48 and in HIV RNA $\log_{10}$ at week 48 were analyzed using covariance analysis (ANCOVA) to compare the difference between groups, with the group and center as the fixed effect and the baseline value as the covariate.

Safety analyses were carried out for the safety set (SS) population, who received at least one treatment and had complete post-dose safety data. All AE summaries were restricted to treatment-emergent adverse events (TEAEs), which were defined as AEs that occurred after dosing as well as existing AEs that worsened during the study. The incidence of AEs, drug-related AEs, most common TEAEs (that occurred at a rate >5% in any of the two treatment groups) were compared between two treatment groups using a chi-squared test or Fisher's exact probability method. The mean change in the ratio of total cholesterol (TC) and triglyceride (TG) between the two treatment groups was also calculated. According to the Snapshot Approach recommended by FDA, all participants with missing data were considered to be treatment failures. For participants with missing data of CD4 T-cells, the last observation after randomization was carried forward to substitute. The interim analyses were assessed at week 24 for safety analysis, when the last participant had completed 24 weeks of treatment. All data analyses were conducted using SAS ver. 9.4 statistical software (SAS Institute Inc., Cary, NC, USA).

Role of the funding source

Results

Between November 27, 2018 and March 11, 2021, a total of 826 participants were screened for inclusion, of whom 196 were excluded leaving 630 eligible participants who were randomly assigned at a 1:1 ratio to ANV and EFV groups. All participants had received at least 1 dose of a study drug, with the exception of 1 participant in the EFV group who was withdrawn during the 48-week period. In total, 37 (5.9%) of 630 participants (18 in the ANV group and 19 in the EFV group) had discontinued the study treatment by week 48, and 14 (2.4%) of 580 participants (10 in the continued group and 4 in the transfer group) were withdrawn between weeks 48 and 96. The most common reasons for withdrawal were AEs, serious protocol violations, failed to follow-up and noncompliance with the trial treatment (Fig. 1).

The demographic and prognostic characteristics were generally well-balanced between both treatment groups at baseline (Table 1).

The mean age of the participants was 30.6 ± 9.4 years (range 18~61), with most being males (595, 94.6%) of Han (512, 81.4%) ethnicity. The mean CD4 T-cell count was 380.4 ± 183.6 cells/μL (range 72~1313) and the mean plasma HIV-1 RNA level was 4.48 ± 0.651 $\log_{10}$ copies/mL (range 2.5~6.3). The adherence was in the postulated range of ≥90% and ≤110% (Appendix p5).

For the primary endpoint, at week 48, 274 (87.0%) of 315 participants in the ANV group and 288 (91.7%) of 314 participants in the EFV group achieved a HIV-1 RNA of <50 copies/mL and non-inferiority was established (–4.7%, 95% CI: –9.6 to 0.1) between the ANV+3TC+TDF vs. EFV+3TC+TDF regimens (Fig. 2). Data using the PPS are shown in Appendix p6 and led to a difference at week 48 of –5.0% (95% CI: –8.9% to –1.5%) and non-inferiority was also observed for ANV+3TC+TDF compared to EFV+3TC+TDF regimens. The number and types of NNRTI resistance related mutations are shown in Appendix p7.

For the secondary outcomes in FAS, the proportion of participants with plasma HIV-1 RNA <50 copies/mL at week 48 was significantly different for participants with baseline HIV-1 RNA <100,000 copies/mL and baseline HIV-1 RNA >100,000 copies/mL in both treatment groups. Among participants with a baseline CD4 T-cell count of >200 cells/μL, the proportion of participants with plasma HIV-1 RNA <50 copies/mL at week 48 was significantly higher in the EFV group than in the ANV group ($p = 0.003$). It is noteworthy that both subgroups developed the same virologic suppression until week 96 in the open-label observation period (Fig. 3).

In addition, the proportion of participants with plasma HIV-1 RNA <50 copies/mL was not significantly different between the ANV group and EFV switched to ANV group at week 96 ($p = 0.189$ for FAS analysis, $p = 0.831$ for PPS analysis) (Fig. 2 and Appendix p6). The proportion of participants with plasma HIV-1 RNA <200 copies/mL and HIV-1 RNA <400 copies/mL was not significantly different between the ANV and EFV groups at week 48 and week 96 ($p_{48} = 0.079$, $p_{96} = 0.059$ for HIV-1 RNA <200 copies/mL and $p_{48} = 0.136$, $p_{96} = 0.076$ for HIV-1 RNA <400 copies/mL) (Fig. 4). The mean change of CD4 T-cell counts from baseline to week 96 was higher in the ANV group than that in
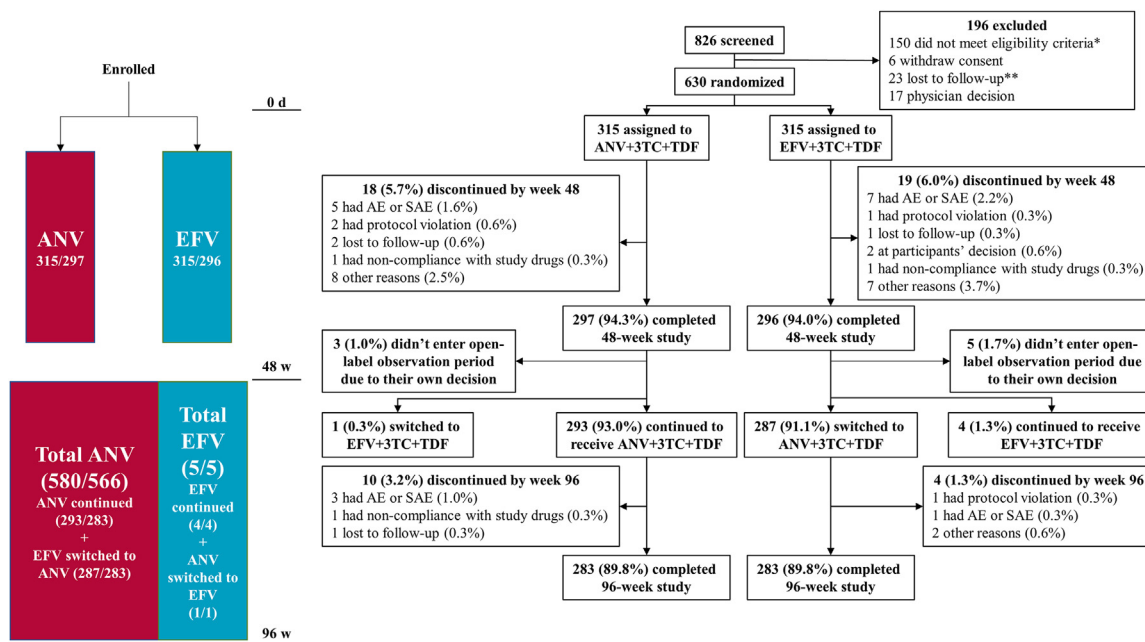
Fig. 1: Flowchart through week 48 and weeks 48–96. ANV+3TC+TDF = ainuovirine (ANV) at 150 mg, lamivudine (3TC) at 300 mg and tenofovir disoproxil fumarate (TDF) at 300 mg; EFV+3TC+TDF = efavirenz (EFV) at 600 mg, 3TC at 300 mg and TDF at 300 mg. *Of 196 excluded participants, 150 did not meet the eligibility criteria since they did not receive the test drugs on time, changed to other drugs or had poor medication adherence; **some were lost in follow-ups due to COVID-19. ANV, Ainuovirine; EFV, Efavirenz.

	ANV group (N = 315)	EFV group (N = 314)
Age (years), mean ± SD	31.1 ± 9.9	30.1 ± 8.8
Gender, n (%)		
Female	18 (5.7)	16 (5.1)
Male	297 (94.3)	298 (94.9)
Ethnicity, n (%)		
Han	254 (80.6)	258 (82.2)
Others	61 (19.4)	56 (17.8)
Mean CD4 T-cell count (cells/μL), mean ± SD	383 ± 183	378 ± 185
CD4 T-cell counts (cells/μL), n (%)		
<200	47 (14.9)	39 (12.4)
200–350	116 (36.8)	125 (39.8)
351–499	80 (25.4)	81 (25.8)
≥500	72 (22.9)	69 (22.0)
HIV-1 RNA [$\log_{10}$ (copies/mL)], mean ± SD	4.5 ± 0.7	4.5 ± 0.7
Plasma HIV-1 RNA (copies/mL), n (%)		
<100,000	244 (77.5)	253 (80.6)
≥100,000	71 (22.5)	61 (19.4)
Baseline resistance mutations, n (%)		
NRTI	2 (0.6)	0 (0)
NNRTI	6 (1.9)	5 (1.6)
Others	1 (0.3)	0 (0)

ANV, Ainuovirine; EFV, Efavirenz; NRTI, Nucleoside reverse transcriptase inhibitor; NNRTI, Non-nucleoside reverse transcriptase inhibitor.

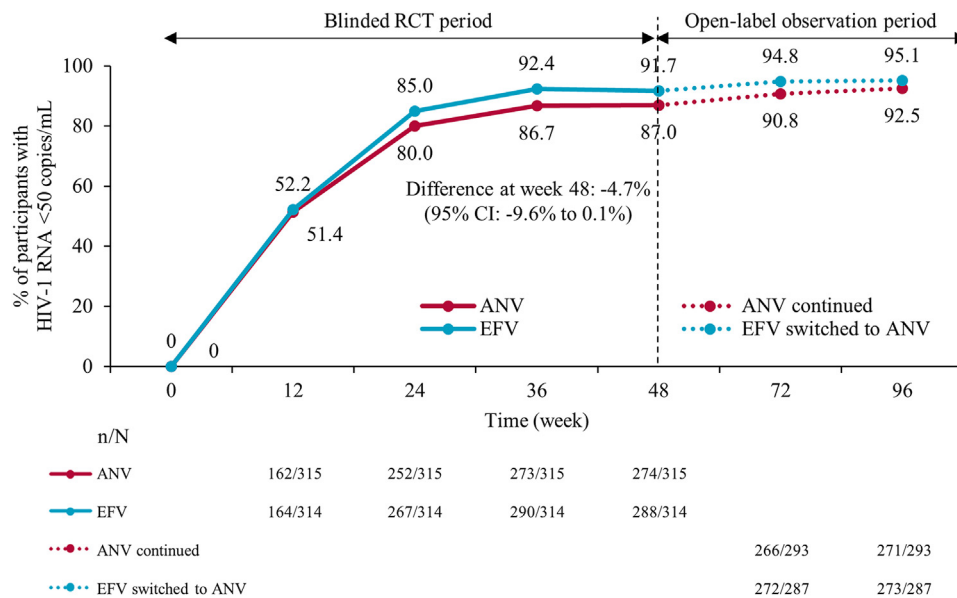*Table 1:* **Baseline demographics and clinical characteristics.**

Fig. 2: Proportion of participants with HIV-1 RNA of <50 copies/mL until week 96 (Food and Drug Administration snapshot approach). Bold lines show the period at 48 weeks in the primary analysis, while the dashed lines show the subsequent 48 weeks analysis; the numbers under the figure show the number of participants included in the analysis. There was 1 case without using medication in the EFV group leaving a total of 314 cases. The method used to compare between groups was Fisher's exact test. ANV, Ainuovirine; EFV, Efavirenz.

EFV group during the entire trial including at week 48 and week 96 ($p < 0.05$), respectively (Fig. 5A). There was no significant difference regarding the mean change of $\log_{10}$ HIV-1 RNA from baseline to week 96 between the two groups ($p_{96} = 0.561$) (Fig. 5B).

For the safety analysis, both treatment regimens were shown to be well tolerated and the recorded AEs were mostly mild to moderate in severity during the entire study period. The results of ultrasound, ECG and chest X-rays were all normal and were not indicative of any AEs or safety concerns. The incidence of NNRTI-related AEs in the EFV group was nearly 1.35 times higher than that in the ANV group from baseline to week 48 ($p < 0.001$). In the open-label observation period from week 48 to week 96, the incidence of NNRTI related AEs decreased in the ANV continued group (55.7%) and in the EFV switched to ANV group (64.1%), but the number of NNRTI-related TRAEs was still significantly higher in the former EFV in comparison to the continued ANV group ($p = 0.040$). Also, grade 3 to 4 AEs associated with NNRTIs were less frequent in the ANV group compared to the EFV group during weeks 0–48 (3.8% vs. 8.9%, $p = 0.009$) and similar results were obtained in the ANV continued vs. the EFV switched to ANV group (2.1% vs. 5.2%, $p = 0.044$). Six participants suffered drug-related SAEs during the entire study, mainly in the first 48 weeks (1 participant with drug-induced liver injury (DILI) in the ANV group vs. 5 participants in the EFV group including 1 DILI, 2 mental disorders such as depression and anxiety, 1 dizziness and 1 nausea event).

A participant with ANV-DILI was diagnosed with DAIDS classification grade 2 liver injury after 3 months of treatment. After an additional 4 months treatment, liver function test results of alanine aminotransferase (ALT) 647 U/L, aspartate aminotransferase (AST) 793 U/L and total bilirubin (TBiL) 91.4 μmol/L gave the investigator the option to discontinue ANV with maintained TDF+3TC therapy, which was also paused 1 month later due to ALT 37 U/L, AST 133 U/L, TBiL 312.1 μmol/L findings. He received magnesium isoglycyrrhizate 200 mg iv. gtt qd, bicyclol tablets 25 mg tid, dangfeiliganning tablets 0.9 g tid and ursodeoxycholic acid 0.25 g bid. After 6 weeks ART was restarted with TDF+3TC+ raltegravir (RAL) medication, while liver functions gradually returned to normal, with latest follow-up results of AST 30 U/L, ALT 35 U/L and TBiL 21 μmol/L.

AEs that led to withdrawal from the trial occurred in 6 (1.9%) participants who received ANV (3 active pulmonary tuberculosis cases, 1 case of peripheral neuropathy, 1 DILI and 1 sinus bradycardia) and in 8 (2.5%) participants (2 dizziness cases, 1 DILI, 2 mental disorders, 1 low platelet count, 1 acute lymphoblastic leukemia and 1 case of drug induced hypersensitivity) who received the EFV regimen within the first 48 weeks. Between weeks 48 and 96, 3 participants (1 active pulmonary tuberculosis, 1 cerebral hemorrhage, and 1 fever case) withdrew from the trial due to AEs in the ANV continued group, and 1 participant (with active
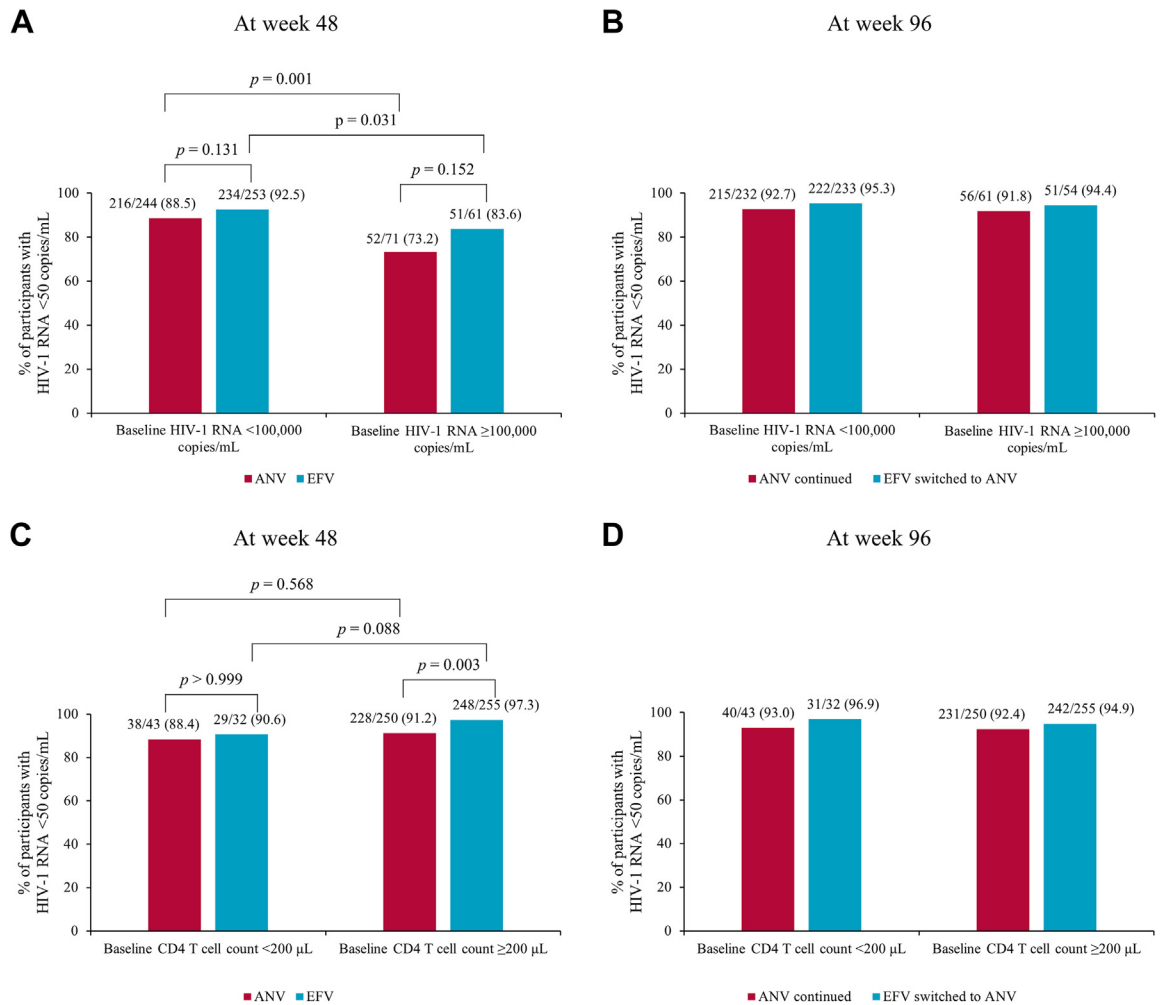
Fig. 3: Virologic outcomes of participants with different baseline HIV-1 RNA (≥100,000 copies/mL or <100,000 copies/mL) and different baseline CD4 T-cell count (≥200 cells/μL or <200 cells/μL) at week 48 and week 96. (A) Percentage of participants with HIV-RNA <50 copies/mL divided into baseline concentrations of <100,000 copies/mL and ≥100,000 copies/mL at 48 weeks and (B) at 96 weeks; (C) percentage of participants with HIV-RNA <50 copies/mL divided into baseline CD4 T-cell count of <200 cells/μL and ≥200 cells/μL at week 48 and (D) at 96 weeks. ANV, Ainuovirine; EFV, Efavirenz.

pulmonary tuberculosis) withdrew from the trial in the ANV transferred group. No deaths occurred during the 96-week trial.

It is noteworthy that the most common AEs, with incidences >5% for both ANV and EFV, were generally similar. They included upper respiratory infection, insomnia, hyperuricemia, creatine kinase-myocardial band (CK-MB) elevation, diarrhea and others. However, during the blinded-RCT period, significant differences between the ANV and EFV groups were found for dizziness, dyslipidemia, transaminase elevation, γ-glutamyl transferase elevation, abnormal dreams and rash, which occurred more frequently in the EFV group (all $p < 0.05$). The incidences of nervous system disorders were also significantly higher in EFV treated participants ($p < 0.001$). In the open-label observation period,

significant differences in the rate of occurrence of AEs only occurred for dizziness and dyslipidemia in the EFV switched to ANV participants in comparison to the continued ANV group ($p = 0.041$, $p = 0.017$) (Table 2).

For lipid profiles, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), TG and TC serum concentrations shifted to significantly lower levels in the ANV compared to the EFV group (all $p < 0.05$) during the first 48 weeks of treatment.

After switching from EFV to ANV, the downward changes in HDL-C, LDL-C, TG and TC were greater in the former EFV than in the ANV continued group (all $p < 0.05$), and therefore the final differences between the treatment groups were not significant at week 96 (all $p > 0.05$) (Fig. 6).
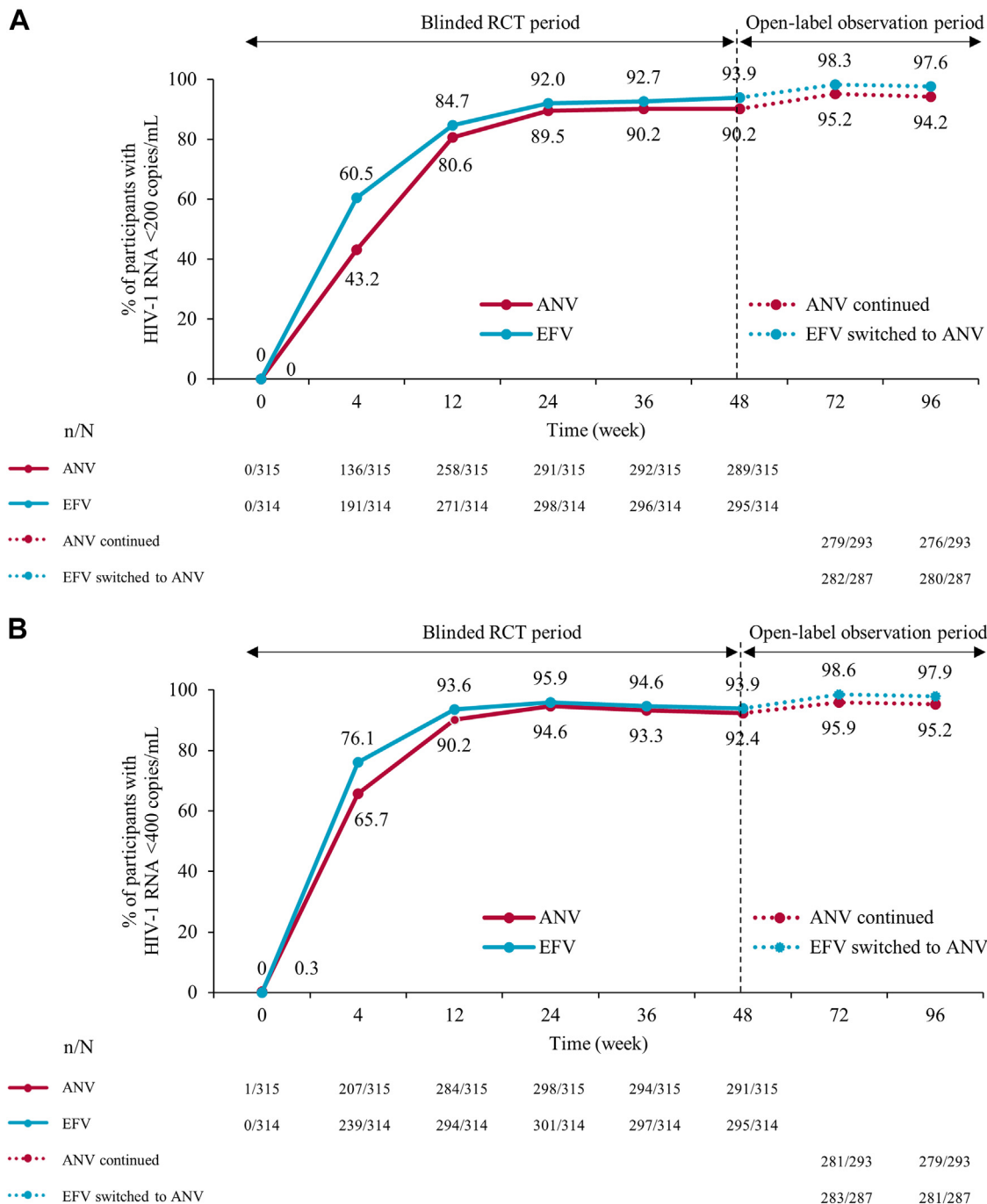
Fig. 4: Proportion of participants with HIV-1 RNA of <200 copies/mL and <400 copies/mL until week 96. (A) HIV-1 RNA <200 copies/mL, (B) HIV-1 RNA <400 copies/mL; the numbers under the figure show the number of participants included in the analysis. ANV, Ainuovirine; EFV, Efavirenz.

Discussion

In this phase 3, randomized, double-blind, multicenter, clinical trial, it was found that the HIV-1 RNA <50 copies/mL rate of ANV+3TC+TDF treatment was non-inferior to that of EFV+3TC+TDF at week 48 (87.0% vs. 91.7%). In addition, the virologic response rates of both groups were significantly lower in participants with baseline HIV-1 RNA levels of ≥100,000 copies/mL in

A

B
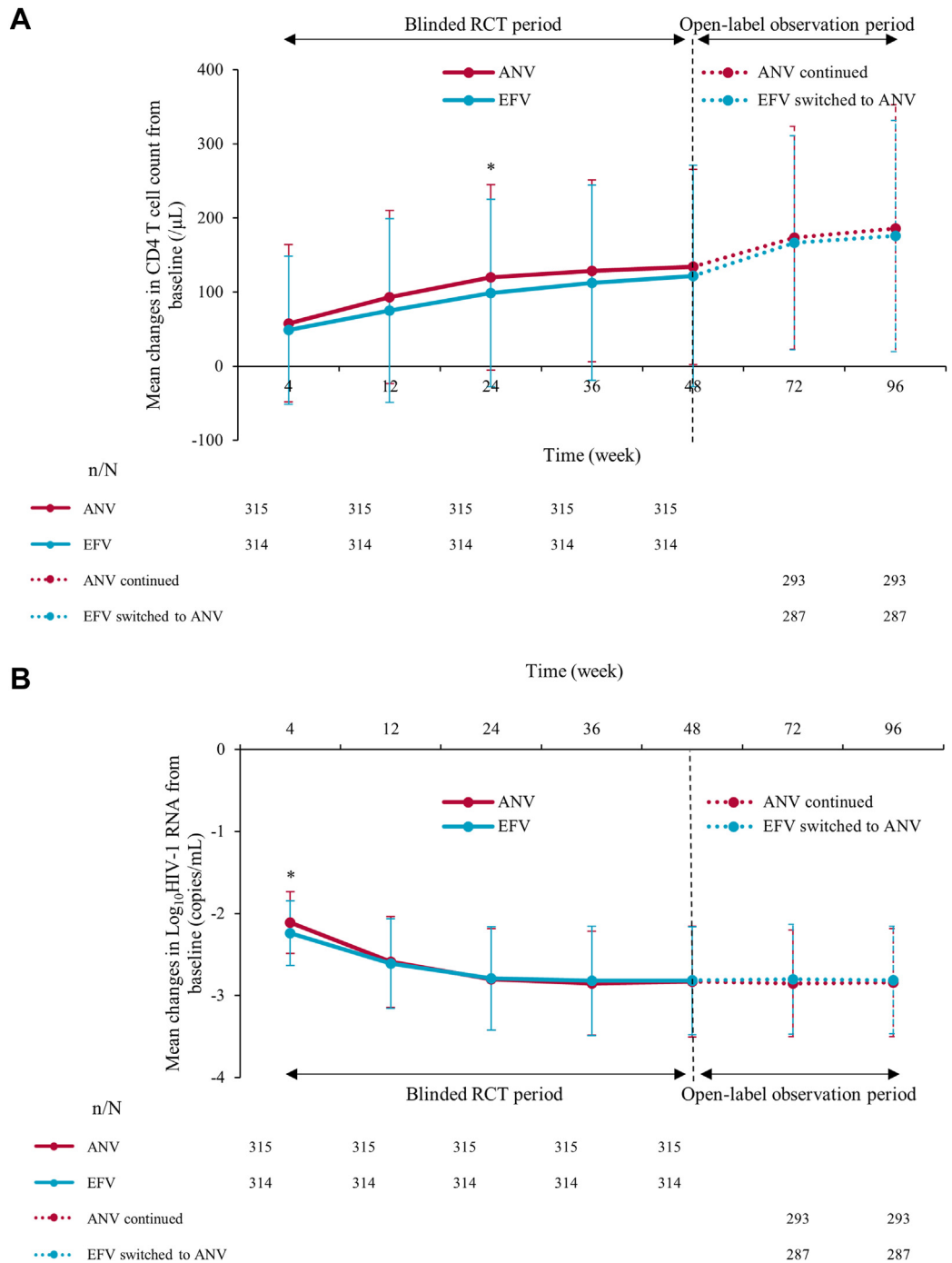
Fig. 5: **Mean change from baseline in the CD4 T-cell count (cells/µL) and log$_{10}$ HIV-1 RNA (copies/mL) at the different visiting times.** (A) CD4 T-cell count, (B) log$_{10}$ HIV-1 RNA. ANV, Ainuovirine; EFV, Efavirenz.

comparison to those with baseline HIV-1 RNA levels of <100,000 copies/mL at week 48. A delayed efficacy outcome with NNRTI treatments for high initial viral loads has also been described in the literature.[12] When comparing DTG + abacavir (ABC) + 3TC to

EFV+TDF+FTC treatments, the proportion of participants with HIV-1 RNA level <50 copies/mL was about 50% at week 12 in the EFV+TDF+FTC group,[13] which was similar to the treatment outcome in the present study, but had been 80% for the DTG+ABC+3TC group

	ANV	ANV continued	EFV	EFV switched to ANV	p-value$_{0\sim48w}$ (ANV vs. EFV)	p-value$_{48\sim96w}$ (ANV continued vs. EFV switched to ANV)
	0~48 weeks	48~96 weeks	0~48 weeks	48~96 weeks		
N	315	289	314	287		
Any TEAE, n (%)	283 (89.8)	233 (80.6)	300 (95.5)	241 (84.0)	0.006	0.292
NNRTIs related TEAE, n (%)	213 (67.6)	161 (55.7)	287 (91.4)	184 (64.1)	<0.001	0.040
NNRTIs related SAE, n (%)	1 (0.3)	0 (0)	5 (1.6)	0 (0)	0.123	–
NNRTIs related grade 3–4 TEAE, n (%)	12 (3.8)	6 (2.1)	28 (8.9)	15 (5.2)	0.009	0.044
NNRTIs related TEAE led to withdrawal from the trial, n (%)	1 (0.3)	0 (0)	0 (0)	0 (0)	>0.999	–
NNRTIs related TEAE led to drug suspension, n (%)	2 (0.6)	0 (0)	6 (1.9)	0 (0)	0.177	–
Most common TEAE (incidence >5%), n (%)						
Dizziness	33 (10.5)	4 (1.4)	160 (51.0)	12 (4.2)	<0.001	0.041
Abnormal dreams	31 (9.8)	10 (3.5)	51 (16.2)	17 (5.9)	0.017	0.168
Dyslipidemia	70 (22.2)	58 (20.1)	108 (34.4)	82 (28.6)	<0.001	0.017
Upper respiratory infection	72 (22.9)	12 (4.2)	66 (21.0)	20 (7.0)	0.578	0.140
Insomnia	56 (17.8)	16 (5.5)	67 (21.3)	24 (8.4)	0.260	0.182
Hyperuricemia	66 (21.0)	44 (15.2)	56 (17.8)	43 (15.0)	0.323	0.935
Transaminase elevation	29 (9.2)	39 (13.5)	91 (29.0)	50 (17.4)	<0.001	0.192
CK-MB elevation	49 (15.6)	45 (15.6)	46 (14.6)	34 (11.8)	0.751	0.194
γ-glutamyl transferase elevation	26 (8.3)	39 (13.5)	60 (19.1)	45 (15.7)	<0.001	0.458
Rash	25 (7.9)	6 (2.1)	59 (18.8)	7 (2.4)	<0.001	0.769
Hypophosphatemia	34 (10.8)	7 (2.4)	36 (11.5)	18 (6.3)	0.789	0.023
Weight loss	24 (7.6)	12 (4.2)	31 (9.9)	16 (5.6)	0.317	0.427
Diarrhea	24 (7.6)	4 (1.4)	22 (7.0)	1 (0.3)	0.768	0.373
Urinary tract infection	24 (7.6)	14 (4.8)	20 (6.4)	11 (3.8)	0.539	0.551
Hepatic steatosis	8 (2.5)	21 (7.3)	18 (5.7)	22 (7.7)	0.044	0.855
Blood glucose elevation	18 (5.7)	27 (9.3)	16 (5.1)	17 (5.9)	0.732	0.122
Events of clinical interest, n (%)						
Nervous system disorders	55 (17.5)	19 (6.6)	170 (54.1)	23 (8.0)	<0.001	0.506
Psychiatric disorders	53 (16.8)	14 (4.8)	72 (22.9)	22 (7.7)	0.055	0.162

A chi-squared test or Fisher's exact probability method was used to compare the differences between groups. p means a difference between the trial and control groups. ANV, Ainuovirine; EFV, Efavirenz; NNRTI, Non-nucleoside reverse transcriptase inhibitor; SAE, Serious adverse event; TEAE, Treatment-related adverse event.

Table 2: Occurrence of adverse events during the study.

at week 12. A later study proposed that for patients with high initial viral load, DTG-based therapy would have a higher likelihood of achieving viral suppression than non-DTG-containing therapies.[14]

The median change of HIV-1 RNA $\log_{10}$ from baseline to week 48 was −2.90 (95% CI: −2.91 to −2.75) in the ANV group and −2.80 (−2.89 to −2.74) in the EFV group, but the apparent difference did not reach statistical significance. The results for efficacy outcomes at week 48 were similar: 84.3% and 80.8% at week 48 in the previous DRIVE-AHEAD study that compared DOR+3TC+TDF with EFV+FTC+TDF regimens.[6] Other trials with various treatment strategies reported efficacies of 88%[15] as well as 84% and 80%[16] at week 48. A total of 17 (5.4%) of 315 participants in the ANV group and 13 (4.1%) of 314 participants in the EFV group met the criteria for PDVF in the first 48 weeks of the trial, findings consistent with the data reported in the DRIVE-AHEAD study at 48 weeks[6] in which 22 participants (6.0%) in the DOR+3TC+TDF

group and 14 (3.8%) in the EFV+FTC+TDF group met the criteria for confirmed PDVF. The ADVANCE trial reported that in 120 (13.7%) of 874 participants with successful sequencing in South Africa, NNRTI resistance-associated mutations were detected in the initial treatment group of HIV-1-positive participants in 2020, which has been attributed to an incidence of 10%–20% HIV-1 NNRTI mutations due to poor adherence to the EFV treatments used since 2004 in this region.[17] In the present trial, at baseline 9 (2.8%) of 315 participants in the ANV group and 5 (1.59%) of 314 participants in the EFV group (p = 0.765) had HIV-1 NNRTI mutations. At week 48, 7 (2.22%) of 315 participants in the ANV group and 2 (0.64%) of 314 participants in the EFV group (p = 0.177) had additionally detected drug resistance mutation sites for NNRTIs. The baseline resistance rate in this study was similar to that previously reported for HIV-1-transmitted drug resistance among ART-naïve youths in China.[18] However, no participant developed additional drug
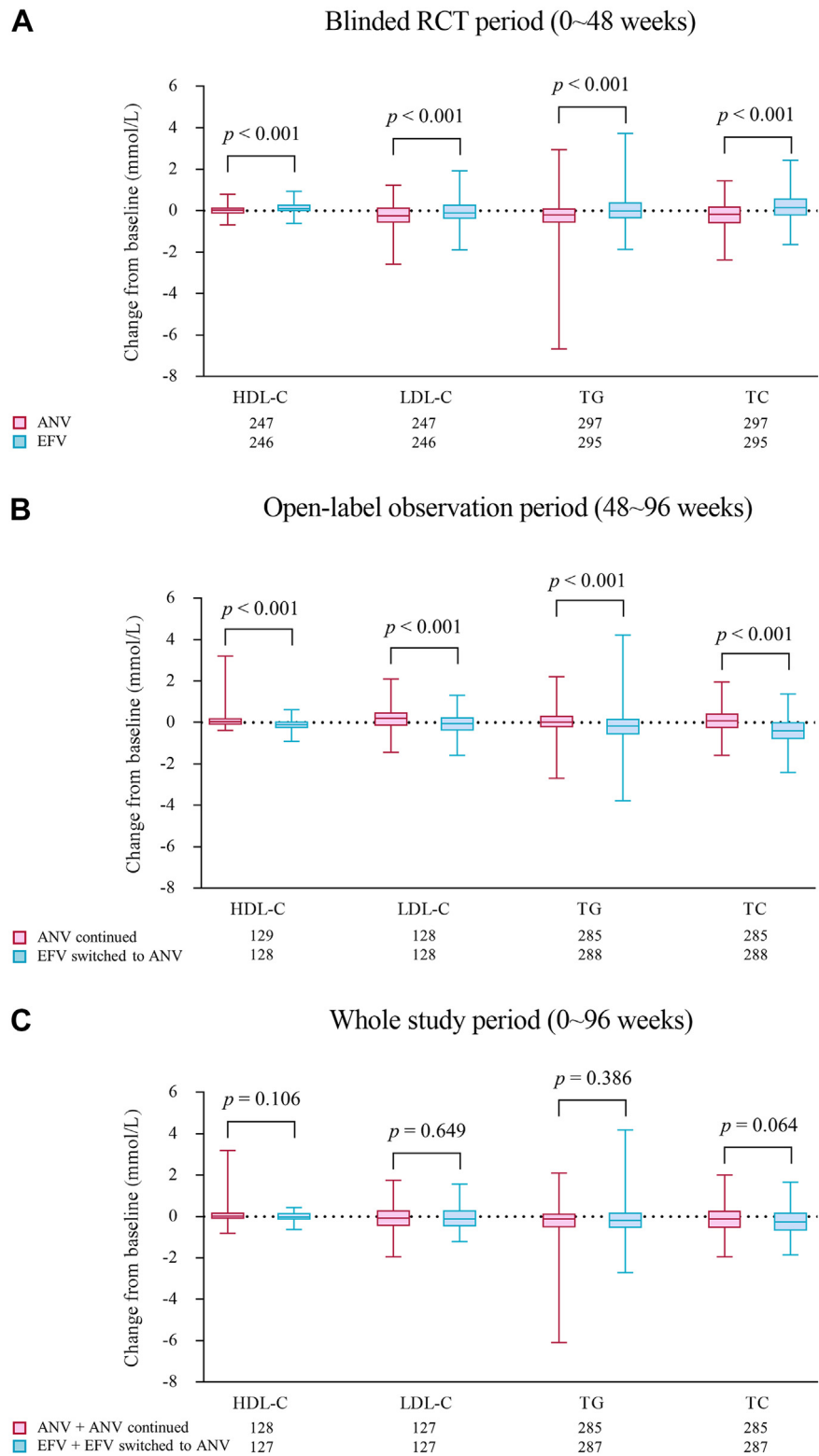
Fig. 6: **Median changes of lipid sub fractions in the ANV and EFV treatment groups.** HDL-C, LDL-C, TG and TC changes (A) from baseline to week 4, (B) in the open-label period (48-96 weeks) and (C) during the entire study period of 96 weeks. ANV, Ainuovirine; EFV, Efavirenz; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TG, Triglyceride; TC, Total cholesterol.

resistance from week 48 to week 96 of therapy. This finding indicated that the resistance incidence to ANV at 96 weeks was low and mostly occurred in the first 48 weeks, similar to EFV.

Consistent with previous studies, the common resistance-associated mutations for NNRTIs were K103N and V106M.[19] Similar to DOR,[20,21] ANV also demonstrated *in vitro* activity against the HIV-1 resistance mutations K103N and V106M.[9] However, even though 1 participant with the mutation of K103N at baseline had undetectable HIV RNA at week 96, further evidence will be required in future studies in order to prove that ANV is active against the HIV-1 resistance mutations in K103N *in vivo*.

At week 96, the HIV-1 RNA <50 copies/mL rate of the ANV+3TC+TDF continued treatment group was also non-inferior to that of the EFV+3TC+TDF switched to ANV+3TC+TDF group (92.5% vs. 95.1%). The mean changes in values of HIV-1 RNA $\log_{10}$ from baseline to week 96 were also similar for both treatment groups. Virtually identical results were found for the mean change in the CD4 T-cell count, but a higher elevation of CD4 T-cell counts from baseline to week 96 was found in the ANV-based treatment group, especially at week 24, indicating effective CD4 T-cell recovery.[22]

The ANV-based regimen had a good safety profile and was generally well tolerated by participants, with fewer incidences of AEs and drug-related AEs, including dizziness and rash which presented more significantly in EFV compared to ANV-treated participants. The most common AEs in the EFV-based therapy group have previously been reported to be dizziness, dyslipidemia, hepatotoxicity and rash.[23] In the present trial, the incidence of rash was 18.8% in the EFV vs. 7.9% in the ANV group at week 48, the latter value being similar to data reported in the DRIVE-FORWARD study 48-week results for DOR (7%).[11] Although rash and neuropsychiatric AEs in the ANV transfer group were still slightly higher than in the ANV continued group, there was no significant difference between the two groups during the 48–96 week period, indicating that by replacing EFV with ANV after ART had stabilized patients they would then benefit from reduced neuropsychiatric toxicity and rash.

Hyperlipidemia is a high-risk factor for diabetes, steatosis of the liver and cardiovascular disease.[24] Among lipids, LDL-C is considered to be highly correlated with atherosclerotic cardiovascular disease.[25–27] In the present study, ANV demonstrated a less atherogenic lipid profile in comparison to EFV at week 48. Participants who switched from EFV to ANV clearly showed a significant downward trend particularly in their TG and TC lipid levels through week 48 to week 96, which might be related to the enhanced lipid levels induced during the preceding EFV treatment.

Severe hepatotoxicity in HIV-infected patients treated with EFV has been reported. A meta-analysis that investigated 34 studies found an incidence of 2.31% (95% CI: 1.42–3.21%) for severe hepatotoxicity in patients treated with EFV.[28]

During the first 48 weeks of the present study, the incidence of hepatic dysfunction was higher in participants who received EFV therapy. According to a recent review, etravirine, RPV and DOR have been listed as NNRTIs with few hepatotoxic effects and were proposed as alternatives for HIV-1 treatments.[29] We suggest that ANV might also be a candidate for switching treatments after the occurrence of severe AEs during EFV treatment regimens.

There were several limitations to our study. First, only a small sample size of participants switched to the EFV+3TC+TDF regimen during week 48–week 96, and this arm was not further analyzed. Second, the small number of women in our study might compromise the generalizability of the trial to a mixed gender population. On the other hand, a recent epidemiological report showed that in a total of 23,307 newly HIV positive young students in China, with a gender ratio of 33.9:1 (Male 22,640: Female 667) from 2010−2019,[30] which was even higher than the 17.5:1 rate in the present study and a long term investigation report also noted that the incidence of HIV is higher in Chinese men than in women.[31] Other limitations of the present study were besides missing weight gain data (1) the lack of racial/ethnic diversity among the study participants; in this study all participants were Chinese of East Asian origin; (2) since only a single NRTI backbone 3TC/TDF was used, it is not clear how well ANV would work with other backbones; (3) the relatively small proportion of study participants with advanced HIV disease; 132 (21%) had a baseline viral load >100,000 copies/mL and only 86 (14%) had a CD4 T cells <200 cells/μL. Specifically, in participants with baseline viral load ≥100,000 copies/mL, the proportion of ANV-treated participants with a viral load <50 copies/mL at week 48 was only 73% (vs. 84% with EFV), probably reflecting a missing significance due to the low numbers in this subset, and was significantly lower than for ANV-treated participants with viral loads <100,000 (88.5%, $p = 0.001$). Furthermore, in the present study serious exclusion criteria were applied including participants with hepatitis C since the fluctuation of liver functions would have affected safety evaluations of liver functions. Also comorbidities in participants older than 65 years might have influenced safety assessments. However, in future post-marketing studies hepatitis C patients as well as HIV-infected individuals older than 65 years will be included.

In conclusion, the present trial demonstrated that the efficacy of ANV+3TC+TDF was non-inferior to that of the EFV+3TC+TDF regimen at week 48. The ANV continued regimen was well tolerated and produced comparable viral suppression and had a favorable safety profile with regard to liver toxicity, dyslipidemia,

neuropsychiatric symptoms and rash for the treatment-naïve HIV-infected participants for 96 weeks. ANV will likely become an NNRTI alternative for HIV-1 treatment after the occurrence of severe AEs during EFV treatment regimens.

Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100769.

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