Original Article

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Efficacy and effect on lipid profiles of Ainuovirine-based regimen versus Efavirenz-based regimen in treatment-naïve people with HIV-1 at week 24: A real-world, retrospective, multi-center cohort study

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SUMMARY This study aimed to compare the efficacy and effect on lipid profiles of Ainuovirine (ANV)- and efavirenz (EFV) -based regimens in treatment-naïve people living with HIV-1 (PLWH) at week 24. The proportion of PLWH achieving HIV-1 RNA < the limit of quantification in the ANV group was significantly higher than that in the EFV group (89.18% *vs.* 76.04%, $P = 0.002$). The mean change of $\log_{10}$ HIV-1 RNA from baseline was greater (-4.34 *vs.* -4.18, $P < 0.001$), the median change from baseline in CD4+ T cell count increased more (106.00 cells/μL *vs.* 92.00 cells/μL, $P = 0.007$) in the ANV group, while the CD4+/CD8+ ratio was similar (0.15 *vs.* 0.20, $P = 0.167$) between the two groups. The mean changes from baseline in total cholesterol (-0.02 for ANV *vs.* 0.25 mmol/L for EFV, $P < 0.001$), triglyceride (-0.14 for ANV *vs.* 0.11 mmol/L for EFV, $P = 0.024$), and low-density lipoprotein cholesterol (-0.07 for ANV *vs.* 0.15 mmol/L for EFV, $P < 0.001$) was significantly different between the two groups. The percentage of patients with improved lipid profiles was significantly higher in the ANV group (37.44 %) than in the EFV group (29.55%, $P = 0.0495$). The incidence of any adverse events in the ANV group was significantly lower than that in the EFV group at week 12 (6.2% *vs.* 30.7%, $P < 0.001$) and was comparable at week 24 (3.6% *vs.* 5.5%, $P = 0.28$). The ANV-based regimen was well tolerated and lipid-friendly in treatment-naïve PLWH.

Keywords Ainuovirine, efavirenz, HIV infection, lipid profile, safety, treatment-naïve

1. Introduction

Antiretroviral therapy (ART) significantly reduces acquired immunodeficiency syndrome-related mortality and extends life expectancy in people living with HIV-1 (PLWH) (*1-3*). However, we are still far away from achieving the fourth 90, which is 90% of HIV-1 virologically suppressed PLWH achieving good health-related quality of life (*4*).

Ainuovirine (ANV, also known as ACC007) is a novel non-nucleoside reverse transcriptase inhibitor developed in China (*5,6*). The 96-week data from Phase III study demonstrated that the efficacy of ANV was non-inferior to efavirenz (EFV) and the treatment-related adverse effects (AEs), such as liver toxicity, dyslipidemia, neuropsychiatric symptoms, were less frequent (*7*). In a previous real-world study, we have verified good efficacy and favorable lipid changes of ANV in treatment-experienced PLWH versus EFV (*8*). In this paper, we want to verify these results further in treatment-naïve PLWH from real-life clinical practice. Compared with virologically suppressed PLWH, high HIV duplicate in treatment-naïve PLWH is the predominant reason that cause several metabolic disorders such as blood lipid

abnormalities, weight gain and adipocyte metastasis due to chronic inflammation and chronic immune activation (*9-11*). Reportedly, dyslipidemia occurred in up to 51.7% ART-naïve PLWH (*12*), which was significantly higher than that in general population in China (40.4%) (*13*). Therefore, "metabolically friendly" antiviral drugs are preferred to avoid further exacerbation of metabolic abnormalities. (*14*). In addition to metabolic safety, other drug safety profile also raises concerns in ART-naïve patients, whom are usually prone to adverse events, such as central nervous system (CNS) toxicities and rash due to tolerance has not yet been established. It is reported that AEs in CNS increased from 74.5% to 95.6% after 3 months of treatment in PLWH newly received ART in the first year, which had a great impact on their health-related quality of life (*14*). These AEs usually reduced with the extension of drug treatment time (*15*). Drug toxicity and intolerance are important reasons for at least one drug discontinuance (*16*). Thus, initial ART regimen can be a powerful predictor of long-term compliance and effectiveness.

This study is a multicenter, real-world, retrospective cohort study, aiming to compare the efficacy and safety of ANV- and EFV-based regimens in treatment-naïve PLWH after 24 weeks of treatment, and to further verify the advantage of ANV in altering lipid profiles.

2. Materials and Methods

2.1. Study design and participants

The data of participants receiving ANV-based or EFV-based treatment regimens were collected through the HIV real-world research platform (i-Study) from six clinical centers in China (Table S1, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=199*). Written informed consent form were signed by all participants. Participants in the ANV group received once-daily oral therapy comprising either ANV (75 mg/tablet × 2 tablets) + 3TC (lamivudine, 300 mg/tablet × 1 tablet) + TDF (tenofovir, 300 mg/tablet ×1 tablet) (ANV group) or an ANV/3TC/TDF fixed-dose compound tablet. The regimens for the EFV group were EFV (600 mg/tablet ×1 tablet) + 3TC (300 mg/tablet × 1 tablet) + TDF (300 mg/tablet ×1 tablet) (EFV 600 mg group) or EFV (200 mg/tablet × 2 tablets) + 3TC (300 mg/tablet × 1 tablet) + TDF (300 mg/tablet ×1 tablet) (EFV 400 mg group).

2.2. Inclusion and exclusion criteria

The inclusion criteria were (1) age ≥ 18 years; (2) diagnosis of HIV-1-positive, never received ART, and judged suitable for ART by a physician; and (3) complete data on four items of lipid profile, including total cholesterol (TC), total triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

The exclusion criteria were as follows: (1) currently suffering from serious chronic, metabolic, cardiovascular, and neurological and psychiatric diseases; (2) pregnant or lactating females or females of childbearing age who were unable to use effective contraception or whose partners were unable to use effective contraception; (3) those who had participated in other clinical trials within 8 weeks prior to enrollment in this study; and (4) those who were judged by the investigator to be unsuitable for participation in the trial based on the results of laboratory tests or for other reasons.

2.3. Procedures/Measurements

Data from visit 0 at baseline, visit 1 at 12 ± 2 weeks, and visit 2 at 24 ± 2 weeks were collected from participants, including demographic data (age, sex, height, weight, body mass index (BMI), and blood pressure), HIV infection information (plasma HIV-1 RNA level, CD4+ T cell count and CD4+/CD8+ ratio), biochemical indexes (hematology, liver enzyme levels, total bilirubin, direct bilirubin, blood glucose, uric acid, serum creatinine, and serum urea nitrogen as well as lipid profiles, including TC, TG, HDL-C, and LDL-C) and disease information (World Health Organization (WHO) staging and complications). HIV-1 RNA level was quantified in the clinical laboratory at each center using a real-time polymerase chain reaction-based assay. Safety was assessed during the study through self-reports by the participants or evaluations conducted by the investigators. AEs recorded at weeks 12 and 24 were collected.

2.4. Study endpoints

The maximum duration of observation was 24 weeks. The primary endpoints included the efficacy of the HIV-1 RNA suppression rate calculated by the HIV-1 RNA below the LOQ (the definition or standard of LOQ in each center is shown in Table S2, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=199*) at week 24 and the lipid profile changes, including TC, TG, HDL-C, and LDL-C from the baseline at week 24.The secondary endpoints included changes in immune function (CD4+ T-cell count and CD4+/CD8+ ratio) at weeks 12 and 24 from baseline, TC/HDL-C and TG/HDL-C changes at weeks 12 and 24 from the baseline, and lipid profile changes, including TC, TG, HDL-C, and LDL-C at week 12 from the baseline. The safety endpoint was the incidence of AEs over 24 weeks.

2.5. Statistical analysis

All statistical analyses were performed using R 4.2.2 (Lucent Technologies, Mount Murray, NJ, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Baseline

information, including age, sex, weight, WHO stage, comorbidities, baseline HIV-1 RNA level, and CD4+ T cell count, was weighted according to the overlap weights calculated by the propensity score. Continuous variables were displayed as mean (standard deviation). Independent-samples *t*-test or paired *t*-test were used for intergroup and intragroup comparisons, respectively. Categorical variables were displayed as number of cases (percentage), and comparisons between the two groups were performed using χ^2 test. The lipid profile changes at week 12/24 from baseline were described as the mean (95% CI). Covariate adjustment was performed for balancing baseline covariates. According to the lipid profile changes at week 12/24 from baseline, the patients were further divided into unchanged, improved, and worsened groups, and the data were weighted for description. Improved of four items of lipid profile defined as improved in any of the four items and without any item become worsen. Comparisons between groups were performed using χ^2 test. Results were visualized using GraphPad Prism 9.5.1 (Boston, MA, USA).

3. Results

3.1. Baseline demographics of participants

We retrospectively identified 274 eligible patients treated with ANV+3TC+TDF or ANV/3TC/TDF and 541 patients treated with EFV+3TC+TDF. After propensity score weighting using overlapping weights, the baseline information of the participants was generally balanced between the two groups (Table 1). Majority of the patients in both groups (ANV group: 78.8%, EFV group: 82.8%) were male (P = 1.000), and the mean ages of the ANV and EFV groups were 41.66 ± 14.28 and 40.15 ± 14.54 years, respectively (P = 1.000). No significant difference was observed in the proportion of comorbidities between the two groups at baseline (P = 1.000). Moreover, there were no significant differences in baseline plasma HIV-1 RNA levels, mean CD4+ T cell counts, or the CD4+/CD8+ ratios between the two groups (P > 0.05).

The mean concentrations of TC, TG, HDL-C, and LDL-C at baseline were 4.06 ± 0.95, 1.80 ± 1.42, 0.98 ± 0.33, and 2.39 ± 0.78 mmol/L for the ANV group and 4.13 ± 1.08 (P = 0.138 *vs.* ANV), 1.79 ± 1.24 (P = 0.727), 1.08 ± 0.39 (P < 0.001), and 2.49 ± 0.93 mmol/L (P = 0.014) for the EFV group, respectively. The percentage of patients with normal HDL-C in the ANV group was significantly lower than that in the EFV group (41.2% *vs.* 53.4%, P = 0.001); however, the percentage of patients with normal LDL-C in the ANV group was markedly higher than that in the EFV group (90.2% *vs.* 83.6%, P = 0.013).

3.2. Efficacy

The percentage of PLWH achieving HIV-1 RNA level below the LOQ in the ANV group was obviously higher than that in the EFV group (89.18% for ANV *vs.* 76.04% for EFV, P = 0.002, Table 2) and the $\log_{10}$ (HIV-1 RNA) at week 24 from baseline had a more pronounced decrease in the ANV group than in the EFV group [−4.34(−4.46 to −4.21) for ANV *vs.* −4.18(−4.27 to −4.10) for EFV, P < 0.001] despite different EFV doses (EFV 400 mg: −4.19(−4.31∼−4.07) and EFV 600mg: −4.20(−4.33∼−4.08); P < 0.05) (Table 2).

As shown in Table 3, both ANV and EFV treatments significantly improved the CD4+ T cell count at weeks 12 and 24 from baseline (P < 0.001). The median increase of CD4+ T cell count at week 24 from baseline in the ANV group was 106.00 cells/μL (interquartile range [IQR], 30.00 to 208.00), which was greater than that in the EFV group (92.00 cells/μL, IQR, 19.00 to 173.00) (P = 0.007). The median increase in CD4+ T cell count at week 12 from baseline in the ANV group was 122.00 cells/μL (IQR, 67.00–189.00), which was also greater than that in the EFV group [87.00 cells/μL (IQR, 25.00 to 163.00)] (P = 0.038). Both ANV and EFV treatments could improve CD4+/CD8+ ratio at week 24 from baseline [0.15 (IQR, 0.06 to 0.28) in the ANV group; 0.20 (IQR, 0.08 to 0.37) in the EFV group] and week 12 from baseline [0.12 (IQR, 0.05 to 0.22) in ANV group; 0.13 (IQR, 0.04 to 0.25) in EFV group] (all P < 0.01). There were no statistical differences between the two groups (P = 0.167 at week 24, P = 0.546 at week 12).

3.3. Changes in lipid profiles

There were significant differences in the mean changes of TC, TG, and LDL-C levels at week 24 from baseline between patients treated with ANV and EFV (P < 0.05; Table 4 and Figure 1A). The mean (95% confidence interval [CI]) changes in TC were −0.02 mmol/L (−0.13 to 0.09) for ANV and 0.25 mmol/L (0.16 to 0.34) for EFV (P < 0.001). TG levels were decreased with ANV (−0.14 mmol/L; 95% CI, −0.37 to 0.09) and increased with EFV (0.11 mmol/L; 95% CI, −0.01 to 0.23; P < 0.001). The increases in HDL-C were 0.14 mmol/L (0.10 to 0.19) and 0.11 mmol/L (0.07 to 0.16) for ANV and EFV, respectively (P = 0.088). The LDL-C was decreased to −0.07 mmol/L (−0.15 to 0.02) with ANV and increased to 0.15 mmol/L (0.08 to 0.22) with EFV (P < 0.001). The ANV group revealed a more pronounced reduction in TC/HDL-C, TG/HDL-C, and log (TG/HDL-C), although the difference between the groups was not significant (P = 0.055, P = 0.141, and P = 0.069, respectively).

Patients were further stratified into baseline dyslipidemia, never taken lipid-lowing drugs, and baseline dyslipidemia & never taken lipid-lowering drugs subgroups for further analysis in order to exclude the confounding factor of lipid-lowering drugs (Table 4). In the baseline dyslipidemia subgroup, the mean

Table 1. The baseline demographics and clinical characteristics

Items	Unweighted				Propensity score overlap weighting			
	ANV group (n = 274)	EFV group (n = 541)	P	SMD	ANV group	EFV group	P	SMD
Age (mean (SD)), years	41.66 (14.28)	40.15 (14.54)	0.159	0.105	40.96 (14.01)	40.96 (14.86)	1.000	< 0.001
Sex, n (%)								
Male	216 (78.8)	448 (82.8)	0.199	0.101	140.7 (80.3)	140.7 (80.3)	1.000	< 0.001
Female	58 (21.2)	93 (17.2)			34.5 (19.7)	34.5 (19.7)		
CD4+ count (mean (SD)), cells/μL	313.12 (216.50)	285.70 (200.10)	0.073	0.132	304.88 (215.12)	304.88 (223.06)	1.000	< 0.001
CD4+/CD8+ (mean (SD))	0.34 (0.25)	0.32 (0.27)	0.521	0.051	0.33 (0.24)	0.35 (0.32)	0.336	0.082
HIV RNA (%), copies/mL								
< 100,000	206 (75.2)	364 (67.3)	0.016	0.220	127.6 (72.8)	127.6 (72.8)	1.000	< 0.001
100,000-500,000	45 (16.4)	137 (25.3)			33.6 (19.2)	33.6 (19.2)		
> 500,000	23 (8.4)	40 (7.4)			14.0 (8.0)	14.0 (8.0)		
WHO stage (%)								
I stage	148 (54.0)	246 (45.5)	0.056	0.208	90.0 (51.4)	90.0 (51.4)	1.000	< 0.001
II stage	44 (16.1)	89 (16.5)			28.7 (16.4)	28.7 (16.4)		
III stage	21 (7.7)	68 (12.6)			15.6 (8.9)	15.6 (8.9)		
IV stage	61 (22.3)	138 (25.5)			40.8 (23.3)	40.8 (23.3)		
Complications (hypertension, diabetes), n (%)								
Yes	38 (13.9)	46 (8.5)	0.024	0.171	19.9 (11.4)	19.9 (11.4)	1.000	< 0.001
No	236 (86.1)	495 (91.5)			155.3 (88.6)	155.3 (88.6)		
Weight (mean (SD)), kg	61.84 (11.91)	63.65 (11.00)	0.031	0.158	62.52 (12.09)	62.52 (10.65)	1.000	< 0.001
Height (mean (SD)), cm	166.97 (9.21)	168.57 (8.17)	0.012	0.184	167.43 (9.13)	167.93 (8.40)	0.455	0.057
BMI (mean (SD)), kg/m^2	22.10 (3.28)	22.34 (3.16)	0.316	0.074	22.23 (3.33)	22.11 (3.03)	0.632	0.037
< 18.5	33 (12.1)	55 (10.2)	0.621	0.100	19.8 (11.4)	19.7 (11.3)	0.711	0.088
18.5-24	162 (59.6)	334 (61.7)			102.1 (58.7)	109.7 (62.6)		
24-28	69 (25.4)	129 (23.8)			46.5 (26.7)	40.7 (23.2)		
≥ 28	8 (2.9)	23 (4.3)			5.4 (3.1)	5.1 (2.9)		
Systolic pressure (mean (SD)), mmHg	117.51 (12.82)	123.80 (11.19)	< 0.001	0.523	117.45 (12.61)	124.39 (11.85)	< 0.001	0.567
Diastolic pressure (mean (SD)), mmHg	77.59 (9.12)	74.53 (9.41)	0.001	0.330	77.52 (9.13)	74.81 (9.60)	0.005	0.290
Red blood cell count (mean (SD))	4.63 (0.75)	4.67 (0.67)	0.488	0.052	4.64 (0.75)	4.67 (0.66)	0.597	0.042
Hemoglobin (mean (SD)), g/L	139.58 (23.43)	141.57 (23.52)	0.255	0.085	139.78 (23.47)	141.37 (23.69)	0.375	0.067
Blood platelet count (mean (SD))	209.26 (72.20)	212.39 (70.70)	0.556	0.044	209.30 (71.74)	211.85 (69.13)	0.633	0.036
White blood cell count (mean (SD))	5.45 (1.92)	5.48 (2.07)	0.852	0.014	5.47 (1.95)	5.46 (2.04)	0.977	0.002
Alanine transaminase (mean (SD)), U/L	33.39 (38.23)	28.71 (24.99)	0.037	0.145	33.63 (38.92)	28.21 (23.90)	0.039	0.168
Aspertate aminotransferase (mean (SD)), U/L	32.67 (25.21)	29.59 (19.48)	0.056	0.137	32.68 (25.26)	29.56 (19.75)	0.080	0.138
Total bilirubin (mean (SD)), mmol/L	13.37 (9.38)	12.36 (7.46)	0.095	0.120	13.31 (9.40)	12.57 (7.38)	0.263	0.087
Direct bilirubin (mean (SD)), mmol/L	4.61 (5.71)	3.82 (2.71)	0.011	0.178	4.62 (5.78)	3.84 (2.81)	0.045	0.171
Blood glucose (mean (SD)), μmol/L	5.85 (1.87)	5.52 (1.83)	0.020	0.177	5.82 (1.81)	5.54 (1.90)	0.051	0.150
Uric acid (mean (SD)), μmol/L	365.13 (105.74)	364.06 (121.38)	0.903	0.009	367.05 (106.35)	358.08 (117.70)	0.282	0.080
Serum creatinine (mean (SD)), μmol/L	69.50 (14.60)	67.07 (13.94)	0.022	0.170	69.58 (14.66)	66.51 (14.22)	0.006	0.212
Serum urea nitrogen (mean (SD)), mmol/L	4.68 (1.51)	4.60 (3.41)	0.700	0.032	4.65 (1.51)	4.61 (3.28)	0.827	0.015

Table 1. The baseline demographics and clinical characteristics (continued)

Items	Unweighted				Propensity score overlap weighting			
	ANV group (n = 274)	EFV group (n = 541)	P	SMD	ANV group	EFV group	P	SMD
TC (mean (SD)), mmol/L	4.06 (0.95)	4.13 (1.08)	0.394	0.065	4.03 (0.95)	4.14 (1.05)	0.138	0.109
Normal	238 (86.9)	482 (89.1)	0.411	0.069	153.0 (87.3)	155.4 (88.7)	0.567	0.043
Abnormal	36 (13.1)	59 (10.9)			22.2 (12.7)	19.8 (11.3)		
TG (mean (SD)), mmol/L	1.80 (1.42)	1.79 (1.24)	0.912	0.008	1.82 (1.45)	1.78 (1.24)	0.727	0.027
Normal	181 (66.1)	334 (61.7)	0.258	0.090	114.9 (65.6)	109.2 (62.3)	0.372	0.068
Abnormal	93 (33.9)	207 (38.3)			60.3 (34.4)	66.0 (37.7)		
HDL-C (mean (SD)), mmol/L	0.98 (0.33)	1.08 (0.39)	< 0.001	0.274	0.97 (0.33)	1.08 (0.38)	< 0.001	0.321
Normal	117 (42.7)	284 (52.5)	0.010	0.197	72.2 (41.2)	93.5 (53.4)	0.001	0.246
Abnormal	157 (57.3)	257 (47.5)			103.0 (58.8)	81.7 (46.6)		
LDL-C (mean (SD)), mmol/L	2.39 (0.78)	2.49 (0.93)	0.105	0.124	2.38 (0.79)	2.54 (0.96)	0.014	0.184
Normal	247 (90.1)	460 (85.0)	0.054	0.156	158.0 (90.2)	146.5 (83.6)	0.013	0.197
Abnormal	27 (9.9)	81 (15.0)			17.1 (9.8)	28.7 (16.4)		
TC/HDL-C (mean (SD))	4.51 (1.51)	4.24 (1.80)	0.040	0.157	4.53 (1.52)	4.24 (1.78)	0.015	0.178
$\log_{10}$(TC/HDL-C) (mean (SD))	0.63 (0.14)	0.60 (0.16)	0.002	0.232	0.63 (0.14)	0.60 (0.16)	0.001	0.251
TG/HDL-C (mean (SD))	2.26 (2.64)	2.07 (2.36)	0.284	0.078	2.32 (2.74)	2.05 (2.36)	0.181	0.106
$\log_{10}$(TG/HDL-C) (mean (SD))	0.21 (0.32)	0.17 (0.34)	0.076	0.132	0.22 (0.32)	0.17 (0.33)	0.022	0.172

EFV 400 mg group and EFV 600 mg group were combined into EFV group for data analysis. Propensity scoring factors: age, sex, WHO stage, complications (hypertension, diabetes), CD4+ cell count, baseline HIV RNA level and weight. All results were weighted according to the overlap weighting calculated by propensity score. ANV, ainuovirine; BMI, body mass index; EFV, efavirenz; HDL-C, high-density lipoprotein; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein; SD, standard deviation; SMD, standardized mean difference; TC, total cholesterol; TG, triglyceride; WHO, world health organization. Comparisons between groups were performed by independent-samples t-test for continuous data or χ^2 test for categorical data. $P < 0.05$ regarded as statistical significance level.

Table 2. The outcome of log_{10} (HIV-1 RNA) at week 24

Comparisons	ANV group (n = 274)	EFV group (n = 541)	P
Below the LOQ, %	89.18	76.04	0.002
Above the LOQ, %	10.82	23.96	
[20, 200)	7.19	17.12	
[200, 400)	1.50	2.13	
≥ 400	2.13	4.71	
Log_{10} (HIV-1 RNA) at week 24 from baseline, mean (95% CI)	−4.34 (−4.46~−4.21)	−4.18 (−4.27~−4.10)	< 0.001
EFV 400 mg group		−4.19 (−4.31~−4.07)	< 0.001
EFV 600 mg group		−4.20 (−4.33~−4.08)	0.003

The sample size was unweighted, and the remaining results were obtained through weighted analysis on propensity score. Comparisons between groups were performed by covariance analysis. ANV, ainuovirine; CI, confidence interval; EFV, efavirenz; HIV, human immunodeficiency virus; LOQ, limit of quantification (definition or standard of LOQ in each center is shown in Table S2, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=199*).

Table 3. The median changes from baseline of immune functions at week 12 and week 24

Variations	ANV group (n = 274)	EFV group (n = 541)	t	P
The CD4+ cell count change at week 24 from baseline, cells/μL			2.71	0.007
Median (IQR), cells/μL	106.00 (30.00~208.00)***	92.00 (19.00~173.00)***		
The CD4+/CD8+ change at week 24 from baseline			−1.38	0.167
Median (IQR)	0.15 (0.06~0.28)***	0.20 (0.08~0.37)**		
The CD4+ cell count change at week 12 from baseline, cells/μL			2.08	0.038
Median (IQR), cells/μL	122.00 (67.00~189.00)***	87.00 (25.00~163.00)***		
The CD4+/CD8+ change at week 12 from baseline			−0.60	0.546
Median (IQR)	0.12 (0.05~0.22)***	0.13 (0.04~0.25)***		

The number of samples was unweighted, and the remaining results were obtained through weighted analysis on propensity score. Covariance analysis was used for inter-group comparisons, and paired t-test was used for intra-group comparisons (follow-up vs baseline). The $\chi 2$ test was used to compare the categorical variables between groups. **, ***indicated $P < 0.01$, $P < 0.001$ for intra-group comparisons. ANV, ainuovirine; CI, confidence interval; EFV, efavirenz; IQR, interquartile ranges.

changes of TC, TG, LDL-C, TC/HDL-C, TG/HDL-C, and log_{10} (TG/HDL-C) were more favorable with ANV than with EFV ($P < 0.05$). HDL-C at week 24 from baseline increased in the ANV (0.21 mmol/L; 95% CI, 0.16 to 0.26) and EFV groups (0.17 mmol/L; 95% CI, 0.10 to 0.23; $P = 0.335$). For participants who had never taken lipid-lowering drugs, the mean changes of TC and LDL-C from baseline were −0.01 (−0.14 to 0.13) and −0.12 (−0.22 to −0.02) in ANV group whereas TC and LDL-C were increased by 0.23 (0.15 to 0.31) and 0.18 (0.10 to 0.26), respectively, in the EFV group (all $P < 0.001$). No statistical differences were observed in the other variables, including TG, HDL-C, TC/HDL-C, TG/HDL-C, and log_{10} (TG/HDL-C) between the ANV and EFV groups ($P > 0.05$). However, the data showed a decreasing trend in the ANV group. For participants in baseline dyslipidemia & never taken lipid-lowering drugs subgroup, the mean changes in TC, TG, LDL-C, TC/HDL-C, TG/HDL-C, and log_{10} (TG/HDL-C) from baseline were more favorable with ANV than with EFV at week 24. HDL-C was increased in both ANV (0.24 mmol/L; 95% CI, 0.17 to 0.30) and EFV groups (0.14 mmol/L; 95% CI, 0.05 to 0.22; $P = 0.713$).

For sub-group analysis between ANV and EFV 400 mg groups, the mean changes of TC (−0.03 *vs.* 0.30 mmol/L, $P < 0.001$) and LDL-C (−0.04 *vs.* 0.09 mmol/L, $P = 0.018$) from baseline was significantly different. The mean changes of all variables from baseline, except TC/HDL-C, were significantly different between the ANV and EFV 600 mg groups ($P < 0.05$) (Table 4).

For the secondary endpoints of mean changes of lipid profiles between the groups at week 12 from baseline, TC, TG, and LDL-C were significantly lower in the ANV group than in the EFV group ($P < 0.05$), whereas no significant difference was observed in the mean change in HDL-C ($P > 0.05$, Figure 1B).

According to the lipid profile change at week 12/24 from baseline, the patients were further divided into unchanged, improved, and worsened subgroups. As shown in Figure 2, at week 24, the percentage of patients with improved TC was about two-fold higher in the ANV group (10.33%) than in the EFV group (5.75%), whereas the percentage of patients with worsened LDL-C levels in the ANV group (2.42 %) was only approximately a quarter of that in the EFV group (9.21%). Overall, the percentage of patients with improved 4 items of lipid profiles was significantly higher in the ANV group (37.44 %) than in the EFV group (29.55%), whereas the percentage of patients with worsened lipid profiles was significantly lower in the ANV group (23.53 %) than in the EFV group (35.18%) ($P = 0.0495$). No significant difference was observed between the two groups at week

Table 4. The mean changes from baseline of lipid profiles at week 24

Variables	ANV group (n =274), mean (95% CI)	EFV group (n =541), mean (95% CI)	Inter-group difference (95% CI)	P
ANV group *vs.* EFV group (EFV 400 mg + EFV 600 mg)				
TC, mmol/L	−0.02 (−0.13~0.09)	0.25 (0.16~0.34)	−0.33 (−0.44~−0.22)	< 0.001
TG, mmol/L	−0.14 (−0.37~0.09)	0.11 (−0.01~0.23)	−0.23 (−0.42~−0.03)	0.024
HDL-C, mmol/L	0.14 (0.10~0.19)	0.11 (0.07~0.16)	−0.05 (−0.10~0.01)	0.088
LDL-C, mmol/L	−0.07 (−0.15~0.02)	0.15 (0.08~0.22)	−0.29 (−0.38~−0.19)	< 0.001
TC/HDL-C	−0.67 (−0.86~−0.47)	−0.27 (−0.44~−0.11)	−0.18 (−0.36~0.00)	0.055
TG/HDL-C	−0.58 (−0.94~−0.21)	−0.15 (−0.38~0.07)	−0.21 (−0.48~0.07)	0.141
Log_{10}(TG/HDL-C)	−0.10 (−0.15~−0.06)	−0.03 (−0.06~−0.01)	−0.04 (−0.08~0.00)	0.069
Baseline dyslipidemia subgroup				
TC, mmol/L	−0.01 (−0.15~0.13)	0.25 (0.12~0.37)	−0.39 (−0.53~−0.25)	< 0.001
TG, mmol/L	−0.37 (−0.62~−0.12)	0.04 (−0.13~0.21)	−0.45 (−0.67~−0.22)	< 0.001
HDL-C, mmol/L	0.21 (0.16~0.26)	0.17 (0.10~0.23)	−0.04 (−0.11~0.04)	0.335
LDL-C, mmol/L	−0.07 (−0.17~0.03)	0.09 (0.01~0.18)	−0.28 (−0.39~−0.17)	< 0.001
TC/HDL-C	−0.99 (−1.22~−0.77)	−0.48 (−0.71~−0.25)	−0.35 (−0.58~−0.12)	0.003
TG/HDL-C	−0.98 (−1.44~−0.52)	−0.33 (−0.65~−0.00)	−0.48 (−0.84~−0.12)	0.010
Log_{10}(TG/HDL-C)	−0.18 (−0.23~−0.14)	−0.08 (−0.12~−0.04)	−0.08 (−0.13~−0.03)	0.001
Never taken lipid-lowering drugs subgroup				
TC, mmol/L	−0.01 (−0.14~0.13)	0.23 (0.15~0.31)	−0.28 (−0.40~−0.16)	< 0.001
TG, mmol/L	−0.12 (−0.44~0.19)	0.10 (−0.03~0.23)	−0.17 (−0.41~0.08)	0.184
HDL-C, mmol/L	0.16 (0.10~0.22)	0.08 (0.03~0.13)	−0.04 (−0.11~0.03)	0.246
LDL-C, mmol/L	−0.12 (−0.22~−0.02)	0.18 (0.10~0.26)	−0.31 (−0.42~−0.20)	< 0.001
TC/HDL-C	−0.72 (−0.96~−0.48)	−0.17 (−0.35~0.02)	−0.19 (−0.41~0.03)	0.086
TG/HDL-C	−0.53 (−0.96~−0.10)	−0.10 (−0.35~0.15)	−0.16 (−0.49~0.17)	0.344
Log_{10}(TG/HDL-C)	−0.12 (−0.17~−0.06)	−0.02 (−0.05~0.01)	−0.04 (−0.09~0.01)	0.084
Baseline dyslipidemia & never taken lipid-lowering drugs subgroup				
TC, mmol/L	−0.00 (−0.17~0.16)	0.22 (0.12~0.32)	−0.33 (−0.48~−0.18)	< 0.001
TG, mmol/L	−0.41 (−0.71~−0.11)	0.01 (−0.17~0.20)	−0.46 (−0.72~−0.20)	< 0.001
HDL-C, mmol/L	0.24 (0.17~0.30)	0.14 (0.05~0.22)	−0.02 (−0.12~0.08)	0.713
LDL-C, mmol/L	−0.13 (−0.25~0.00)	0.11 (0.02~0.21)	−0.30 (−0.43~−0.17)	< 0.001
TC/HDL-C	−1.09 (−1.35~−0.82)	−0.35 (−0.62~−0.08)	−0.43 (−0.72~−0.15)	0.003
TG/HDL-C	−0.96 (−1.45~−0.48)	−0.27 (−0.66~0.11)	−0.55 (−0.99~−0.10)	0.015
Log_{10}(TG/HDL-C)	−0.20 (−0.26~−0.15)	−0.07 (−0.12~−0.03)	−0.10 (−0.16~−0.04)	< 0.001
ANV group *vs.* EFV 400 mg group				
TC, mmol/L	0.03 (−0.08~0.14)	0.22 (0.10~0.34)	−0.25 (−0.38~−0.12)	< 0.001
TG, mmol/L	−0.10 (−0.34~0.14)	0.08 (−0.07~0.23)	−0.09 (−0.33~0.15)	0.464
HDL-C, mmol/L	0.16 (0.11~0.20)	0.15 (0.10~0.19)	−0.01 (−0.06~0.04)	0.672
LDL-C, mmol/L	−0.04 (−0.12~0.04)	0.09 (0.02~0.16)	−0.11 (−0.20~−0.02)	0.018
TC/HDL-C	−0.69 (−0.89~−0.50)	−0.45 (−0.65~−0.25)	−0.19 (−0.39~0.02)	0.074
TG/HDL-C	−0.57 (−0.95~−0.19)	−0.20 (−0.53~0.13)	−0.14 (−0.49~0.22)	0.448
Log_{10}(TG/HDL-C)	−0.11 (−0.15~−0.06)	−0.06 (−0.10~−0.02)	−0.03 (−0.08~0.02)	0.219
ANV group *vs.* EFV 600 mg group				
TC, mmol/L	−0.03 (−0.14~0.08)	0.30 (0.17~0.42)	−0.39 (−0.53~−0.25)	< 0.001
TG, mmol/L	−0.21 (−0.43~0.02)	0.16 (−0.01~0.34)	−0.39 (−0.62~−0.15)	0.001
HDL-C, mmol/L	0.14 (0.09~0.19)	0.08 (−0.00~0.17)	−0.09 (−0.18~−0.01)	0.037
LDL-C, mmol/L	−0.08 (−0.17~0.01)	0.21 (0.08~0.34)	−0.45 (−0.59~−0.31)	< 0.001
TC/HDL-C	−0.65 (−0.84~−0.46)	−0.07 (−0.33~0.19)	−0.18 (−0.42~0.07)	0.153
TG/HDL-C	−0.65 (−1.01~−0.28)	−0.08 (−0.38~0.22)	−0.33 (−0.65~−0.02)	0.038
Log_{10}(TG/HDL-C)	−0.11 (−0.15~−0.07)	−0.00 (−0.04~0.04)	−0.06 (−0.11~−0.01)	0.015

The sample size was unweighted, and the remaining results were obtained through weighted analysis on propensity score. Baseline dyslipidemia was defined as those with baseline total cholesterol ≥5.2 mmol/L or triglyceride ≥1.7 mmol/L or HDL-C < 1 mmol/L or LDL-C ≥3.4 mmol/L. Never used lipid-lowering drugs were those reported no for whether lipid-lowering drugs were used at baseline, week 12 and week 24. Comparisons between groups were performed by covariance analysis. ANV, ainuovirine; CI, confidence interval; EFV, efavirenz; HDL-C, high-density lipoprotein; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.

12 (P > 0.05, data not shown).

3.4. BMI changes

We compared the BMI changes of participants at week 12/ 24 from baseline in the ANV or EFV group, as well as between the ANV and EFV groups, and no significant difference was found in intra- or inter-group comparisons (P > 0.05, Table S3, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=199*).

3.5. Safety evaluation

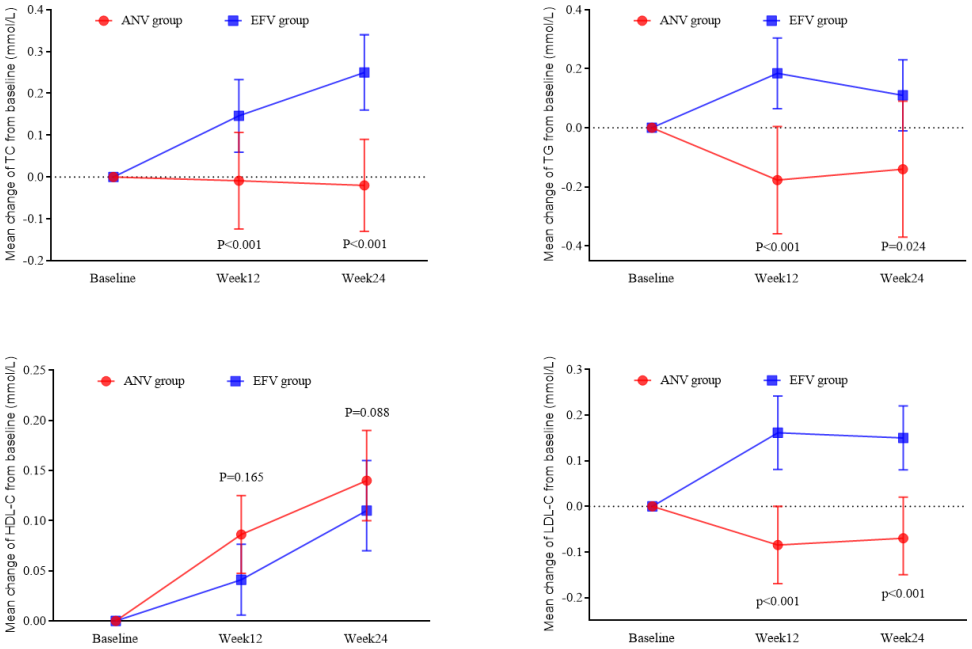

Figure 1. Mean changes in lipid profile at week 24 (A) and week 12 (B) from baseline. The results were obtained through weighted analysis on propensity score. Inter-group comparisons were completed by the analysis of covariance and intra-group comparisons were performed by paired *t* test. ANV, ainuovirine; EFV, efavirenz; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride. *indicates $P < 0.05$ for lipid parameters at week 24 from baseline.

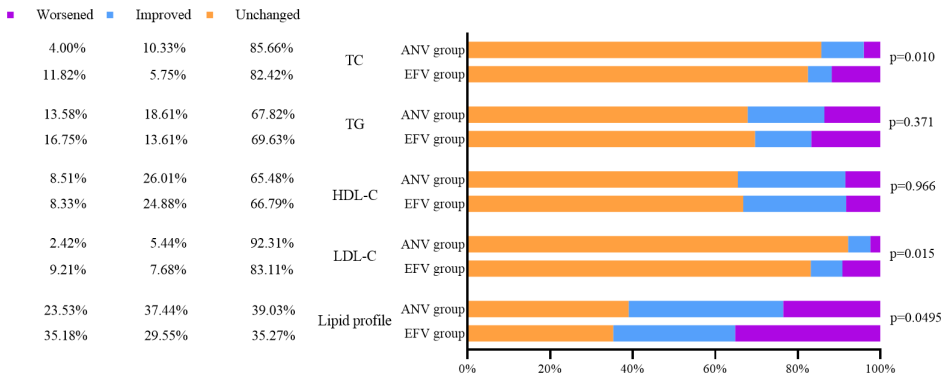

Figure 2. Percentage of patients with worsened, improved, and unchanged lipid profile at week 24. The results were obtained through weighted analysis on propensity score. TC ≥ 5.2 mmol/L, TG ≥ 1.7 mmol/L, HDL-C < 1.0 mmol/L and LDL-C ≥ 3.4 mmol/L were considered abnormal. In the analyses, worsen defined as the lipid level changed from normal at baseline to abnormal; improve defined as the lipid level changed from abnormal at baseline to normal; the lipid level remained normal or abnormal defined as unchanged. Improve of four items of lipid profile defined as improved in any of the four items and without any item become worsen. ANV, ainuovirine; EFV, efavirenz; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

At week 12, only 17 AEs (6.2%), including 11 mild AEs (4%) and 6 moderate AEs (2.2%), were reported in the ANV group. In contrast, there were 134 AEs (30.7%) in the EFV group, including 109 mild AEs (25%), 21 moderate AEs (4.8 %), and 4 severe AEs (0.9 %). The incidence of any AEs at week 12 in the ANV group was significantly lower than that in the EFV group ($P <$ 0.001). The most common AEs in the EFV group were related to the CNS (95, 21.8%), including 76 (17.4%) cases of dizziness, 2 (0.5%) of abnormal dreams, 15 (3.4%) of insomnia, and 2 (0.5%) of anxiety/depression. There were 12 cases of CNS-related AEs (4.4%) in the ANV group, including 7 (2.5%) cases of dizziness, 3 (1%) of abnormal dreams, and 2 (0.8%) of insomnia. The incidence of rashes was also significantly lower in the ANV group than in the EFV group (1.5% *vs.* 4.6%, $P = 0.03$). There were three (0.2%) cases of severe rashes in the EFV group, two of which remitted after treatment. At week 24, the incidence rate of AEs in the ANV group was reduced to 3.6%, which was lower than that in the EFV group (5.5%), but the difference was not statistically significant ($P = 0.28$) (Table 5).

4. Discussion

In this multicenter, real-world, retrospective cohort study, we found that 89.18% of the treatment-naïve PLWH in the ANV group and 76.04% of those in the EFV group

Table 5. Adverse events in ANV group and EFV group at week 12 and week 24

Adverse events	Week 12						*P*	Week 24						*P*
	ANV group (n = 274)			EFV group (n = 541)				ANV group (n = 274)			EFV group (n = 541)			
Severity	mild	moderate	Severe	mild	moderate	Severe		mild	moderate	Severe	mild	moderate	Severe	
Any adverse event, *n* (%)	11 (4)	6 (2.2)	0	109 (25)	21 (4.8)	4 (0.9)	< 0.001	5 (1.8)	2 (0.7)	3 (1)	13 (3)	9 (2.1)	2 (0.5)	0.28
Dizziness	6 (2.2)	1 (0.4)	-	63 (14.4)	12 (2.7)	1 (0.2)	< 0.001	-	-	-	7 (1.6)	2 (0.5)	-	
Abnormal dreams	3 (1)	-	-	2 (0.5)	-	-	-	2 (0.7)	-	-	-	1 (0.2)	-	0.28
Insomnia	1 (0.4)	1 (0.4)	-	12 (2.7)	3 (0.7)	-	0.06	1 (0.4)	-	1 (0.4)*	3 (0.7)	3 (0.7)	-	
Anxiety/depression	-	-	-	1 (0.2)	1 (0.2)	-	-	-	-	1 (0.4)	1 (0.2)	-	-	
Rash	1 (0.4)	3 (1)	-	14 (3.2)	3 (0.7)	3 (0.2)[&]	0.03	1 (0.4)	1 (0.4)	-	-	2 (0.5)	-	
Facial numbness	-	-	-	-	1 (0.2)	-		-	-	-	-	-	-	
Palpitation	-	1 (0.4)	-	2 (0.5)	-	-		-	-	-	-	-	-	
Weakness	-	-	-	4 (0.9)	1 (0.2)	-		-	-	-	-	-	-	
Diarrhea	-	-	-	-	-	-		1 (0.4)	1 (0.4)	-	-	-	-	
Nausea/abdominal distension	-	-	-	6 (1.4)	-	-		-	-	-	-	1 (0.2)	2 (0.5)	
Decreased vision	-	-	-	-	-	-		-	-	1 (0.4)*	-	-	-	
Osteopenia/osteoporosis	-	-	-	-	-	-		-	-	-	2 (0.5)	-	-	
Other	-	-	-	5 (1.1)	-	-		-	-	-	-	-	-	

*Remission or improvement after treatment; [&]2 patients remitted after treatment.

had HIV-1 RNA levels below the LOQ (P = 0.002) at week 24. Compared with the EFV group, ANV exhibited superior HIV RNA suppression efficacy and favorable lipid profile changes. In terms of safety, the results of this study showed that the incidence of AEs in the EFV group was higher (30.7% *vs.* 6.2%, P < 0.001), especially in the early stage of treatment (week 12). To the best of our knowledge, this is the first multicenter, real-world study in China to evaluate the efficacy, safety and lipid profiles of treatment-naïve PLWH treated with ANV-based regimen in China.

The most prominent AEs caused by EFV were CNS-related AEs, such as dizziness (17.4%), insomnia (3.4%), and cutaneous AEs, such as rash (3.9%). We speculated that these AEs may significantly affect ART adherence in intolerant patients during the early treatment period, thereby resulting in a relatively low EFV efficacy (76.04%). Simultaneously, ANV appears to be "CNS friendly," with much lower incidences of AEs, such as dizziness (2.5%) and insomnia (0.7%) than those with EFV, even though the CNS-related AEs were also the main AEs of ANV. This result is consistent with a previous prospective study that ANV improves the patient's symptom experience, such as dizziness, nervousness and anxiety, compared to the EFV regimen (*17*). After 24 weeks of treatment, the AEs of EFV significantly reduced, indicating improved tolerance. However, it is noteworthy that the early AEs may prompt some patients to switch treatment regimens, thus affecting treatment efficacy. Studies have shown that HIV RNA suppression in the early stages of treatment is associated with a good prognosis and reduces the risk of HIV transmission to the uninfected partners (*18*).

Notably, our results found that HIV RNA inhibition rates were similar regardless of EFV doses of 400 or 600 mg, which was in line with previous non-inferiority studies (*19,20*). In this study, although 400 mg of EFV achieved a non-inferior efficacy to 600 mg, AEs were not reduced, suggesting that for patients with extreme intolerance, it may still be necessary to switch treatment regimens. In addition, we speculate that there may be another reason for the efficacy of EFV drug resistance. The prevalence of drug resistance to EFV has increased from 1.6% in 2004–2007 to 6.3% in 2020–2022 in China (*21-24*). Owing to limited resources, baseline drug resistance is generally not tested in treatment-naïve PLWH in China, which may lead to treatment failure. Preliminary *in vitro* studies have shown that ANV can overcome the HIV-1 resistance mutations K103N and V106M (*6*), which are non-polymorphic resistance mutation sites selected by EFV. Overall, our real-world study showed that ANV significantly improved tolerability while achieving viral suppression.

Regarding lipid changes, patients in the ANV group showed decreases in the mean changes in TC, TG, and LDL-C at weeks 12 and 24, whereas these lipid parameters were all increased in patients treated with

EFV. The advantage of ANV in changing lipid profiles still exists after excluding the confounding factors in subgroup analyses. These results suggest that ANV might be less associated with increase of cardiovascular disease (CVD) risk, which is consistent with the results of phase III with a study period of 96 weeks (*7*). An increase in CVD risk is proportional to dyslipidemia, indicated by increase in LDL-C, TC, and TG levels (*25*). However, these results seem more likely that ANV does not lead to lipid deterioration than EFV. Therefore, we further analyzed the proportion of PLWH with improved lipid profiles and worsened lipid profiles. The percentage of patients with improved lipid profiles was significantly higher in the ANV group (37.44 %) than in the EFV group (29.55%), whereas the percentage of patients with worsened lipid profiles was significantly lower in the ANV group (23.53 %) than in the EFV group (35.18%). For the treatment-naïve PLWH, EFV caused a significant proportion of lipid deterioration even at the early treatment periods of week 12 or week 24, and this metabolic disorder may become more serious with the extension of treatment time (*17*). On the other hand, the favorable lipid changes by ANV may provide a better option for the initial ART of treatment-naïve PLWM.

Weight gain, central obesity, and lipodystrophy in PLWH during ART have attracted increasing attention. PLWH initiating ART gain excess weight, which is associated with a higher risk of metabolic disease (*26*). In our study, ANV had no significant effect on body weight no mater in treatment-naïve or treatment-experienced PLWH. This may also be due to the short follow-up period after ANV treatment, which typically requires extended reobservation.

Our study has some limitations. First, this is a retrospective study and a bias might still exist though we have balanced all the factors that can be collected. Second, the follow-up period was only 24 weeks, and the long-term effects of ANV on lipid profiles may be different. Third, there may have been other unavoidable confounding factors or biases. Therefore, the results should be interpreted with caution and further prospective studies are warranted.

In conclusion, the ANV-based regimen was well tolerated and more lipid-friendly while achieving viral suppression and immune reconstitution in treatment-naïve PLWH. This study, together with the previous study in treatment-experienced PLWH, comprehensively demonstrated the good efficacy and advantages on lipid metabolism of ANV in PLWH. ANV deserves more attention in treatment-naïve PLWH. However, further prospective studies with longer follow-up periods are required to validate our conclusions.

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References

1. Yoshimura K. Current status of HIV/AIDS in the ART era. J Infect Chemother. 2017; 23:12-16.
2. Wang N, Lan G, Zhu Q, *et al.* HIV Epidemiology, Care, and Treatment Outcomes Among Student and Nonstudent Youths Living With HIV in Southwest China Between 1996 and 2019: Historical Cohort Study. JMIR Public Health Surveill. 2023; 9:e38881.
3. Farahani M, Mulinder H, Farahani A, Marlink R. Prevalence and distribution of non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: a systematic review and meta-analysis. Int J STD AIDS. 2017; 28:636-650.
4. Naghavi M. Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the Global Burden of Disease Study 2016. Bmj. 2019; 364:l94.
5. Cha YJ, Lim KS, Park MK, Schneider S, Bray B, Kang MC, Chung JY, Yoon SH, Cho JY, Yu KS. Pharmacokinetics and tolerability of the new second-generation nonnucleoside reverse- transcriptase inhibitor KM-023 in healthy subjects. Drug Des Devel Ther. 2014; 8:1613-1619.
6. Huang XS, Luo RH, Hu XL, Chen H, Xiang SY, Tang CR, Zhang CT, Shen XN, Zheng YT. The New NNRTI ACC007 Combined with Lamivudine and Tenofovir Disoproxil Fumarate Show Synergy Anti-HIV Activity *In Vitro*. Curr HIV Res. 2020; 18:332-341.
7. Su B, Gao G, Wang M, *et al.* 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. Lancet Reg Health West Pac. 2023; 36:100769.
8. Wang C, Yu X, Ke Y, Fu Y, Luo Y, Li Y, Bi Y, Chen X, Li L, Zhao X, Chen Z. Efficacy and effect on lipid profiles of switching to ainuovirine-based regimen versus continuing efavirenz-based regimen in people with HIV-1: 24-week results from a real-world, retrospective, multi-center cohort study. Antimicrob Agents Chemother. 2024; e0166823.
9. Grunfeld C. Dyslipidemia and its Treatment in HIV Infection. Top HIV Med. 2010; 18:112-118.
10. Willig AL, Overton ET. Metabolic Complications and Glucose Metabolism in HIV Infection: A Review of the Evidence. Curr HIV/AIDS Rep. 2016; 13:289-296.
11. Waters DD, Hsue PY. Lipid Abnormalities in Persons Living With HIV Infection. Can J Cardiol. 2019; 35:249-259.
12. Guo F, Hsieh E, Lv W, Han Y, Xie J, Li Y, Song X, Li T. Cardiovascular disease risk among Chinese antiretroviral-

naïve adults with advanced HIV disease. BMC Infect Dis. 2017; 17:287.
13. Jun-Ren ZHU, Run-Lin GAO, Shui-Ping Z, Guo-Ping LU, Dong Z, Jian-Jun LI. 2016 Chinese guidelines for the management of dyslipidemia in adults. Journal of Geriatric Cardiology. 2018; 15:1-29.
14. Dai L, Su B, Liu A, Zhang H, Wu H, Zhang T, Shao Y, Li J, Ye J, Bai S, Guo X, Sun L. Adverse events in Chinese human immunodeficiency virus (HIV) patients receiving first line antiretroviral therapy. BMC Infect Dis. 2020; 20:158.
15. Hongo H, Nagao T, Nakamura K, Kitaichi T, Maeno Y, Tokunaga T, Fukuda A, Koga I. Safety and Effectiveness Analysis of Dolutegravir in Patients with HIV-1: Interim Report of Post-Marketing Surveillance in Japan. Advances in Therapy. 2021; 38:4480-4504.
16. Gebrezgabher BB, Kebede Y, Kindie M, Tetemke D, Abay M, Gelaw YA. Determinants to antiretroviral treatment non-adherence among adult HIV/AIDS patients in northern Ethiopia. AIDS Res Ther. 2017; 14:16.
17. Ma S, Xie X, Fu Y, Gan L, Yang X, Kong L, Li J, Long H. Clinical benefits of novel non-nucleoside reverse transcriptase inhibitors: A prospective cohort study. Immun Inflamm Dis. 2024; 12:e1217.
18. Robbins RN, Spector AY, Mellins CA, Remien RH. Optimizing ART adherence: update for HIV treatment and prevention. Curr HIV/AIDS Rep. 2014; 11:423-433.
19. Carey D, Puls R, Amin J, *et al.* Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. Lancet Infect Dis. 2015; 15:793-802.
20. Carey D. Efavirenz 400 mg daily remains non-inferior to 600 mg: 96 week data from the double-blind, placebo-controlled ENCORE1 study. J Int AIDS Soc. 2014; 17:19523.
21. Lin B, Sun X, Su S, Lv C, Zhang X, Lin L, Wang R, Fu J, Kang D. HIV drug resistance in HIV positive individuals under antiretroviral treatment in Shandong Province, China. PLoS One. 2017; 12:e0181997.
22. Chen M, Wu M, Zeng L, Zhang Y, Huobu-Mo M, Li J, Li C, Xiao H. Virologic status and pattern of drug resistance mutation among ART-experienced HIV-infected patients in Butuo County, China. J Glob Antimicrob Resist. 2023; 32:98-103.
23. Dong K, Ye L, Leng Y, Liang S, Feng L, Yang H, Su L, Li Y, Baloch S, He F, Yuan D, Pei X. Prevalence of HIV-1 Drug Resistance among Patients with Antiretroviral Therapy Failure in Sichuan, China, 2010-2016. Tohoku J Exp Med. 2019; 247:1-12.
24. Liu X, Wang D, Hu J, Song C, Liao L, Feng Y, Li D, Xing H, Ruan Y. Changes in HIV-1 Subtypes/Sub-Subtypes, and Transmitted Drug Resistance Among ART-Naïve HIV-Infected Individuals - China, 2004-2022. China CDC Wkly. 2023; 5:664-671.
25. Galindo J, Amariles P, Mueses-Marín HF, Hincapié JA, González-Avendaño S, Galindo-Orrego X. Effectiveness and safety of generic version of abacavir/lamivudine and efavirenz in treatment naïve HIV-infected patients: a nonrandomized, open-label, phase IV study in Cali-Colombia, 2011-2012. BMC Infect Dis. 2016; 16:532.
26. Lam JO, Leyden WA, Alexeeff S, Lea AN, Hechter RC, Hu H, Marcus JL, Pitts L, Yuan Q, Towner WJ, Horberg MA, Silverberg MJ. Changes in Body Mass Index Over Time in People With and Without HIV Infection. Open Forum Infect Dis. 2024; 11:ofad611.

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