ORIGINAL RESEARCH

Pharmacokinetics and Safety of Ainuovirine/Lamivudine/Tenofovir Combination Tablets in Young and Elderly Patients with Human Immunodeficiency Virus-1 Infection

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ABSTRACT

Introduction: Ainuovirine/lamivudine/tenofovir is a novel antiretroviral therapy regimen used to treat human immunodeficiency virus-1 (HIV-1) infection. This study aimed to compare the pharmacokinetics of ainuovirine/lamivudine/tenofovir in HIV-1-infected patients aged ≥ 65 (elderly patients) and ≤ 40 years (young patients).

Methods: This prospective, open-label, parallel controlled clinical study included 15 young and 15 elderly patients. Blood (1 mL) was collected 30 min before dosing and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 16, and 24 h after dosing, to measure the plasma concentrations of ainuovirine/lamivudine/tenofovir. Safety was assessed by monitoring the adverse events, physical examinations, and clinical laboratory tests.

Results: Plasma concentrations of each ainuovirine/lamivudine/tenofovir component reached peak levels 1–4 h after dosing and gradually decreased during the remaining observation period. Compared with the young group, ainuovirine had significantly higher $T_{1/2Ke}$, AUC_{0-24}, and AUC_{0-inf} (all $P < 0.05$) in the elderly group, whereas K_e ($P = 0.002$) was significantly lower. However, the C_{max} and T_{max} of ainuovirine did not differ significantly. Lamivudine and tenofovir also had a significantly higher C_{max} ($p = 0.004$ and $p = 0.008$, respectively) and AUC_{0-inf} ($P = 0.014$ and $P = 0.006$, respectively) in the elderly group, whereas there was no significant difference in T_{max}, K_e, and $T_{1/2Ke}$. Ainuovirine/lamivudine/tenofovir was well tolerated in both the young and elderly groups.

Conclusion: This study suggests that the ainuovirine/lamivudine/tenofovir regimen might be an effective and safe treatment regimen for HIV-1-infected patients aged ≥ 65 years and ≤ 40 years. Further studies are needed to confirm these results and develop optimal dosing regimens for elderly HIV-1-infected patients.

Keywords: Ainuovirine; Elderly; HIV-1 infection; Lamivudine; Pharmacokinetics

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Key Summary Points

Why carry out this study?

Studies have suggested that ainuovirine/lamivudine/tenofovir might be an effective and safe primary treatment regimen for human immunodeficiency virus-1 (HIV-1)-infected patients. However, the pharmacokinetics of ainuovirine/lamivudine/tenofovir in elderly and young HIV-1-infected individuals remains unclear.

This study aimed to compare the pharmacokinetics of ainuovirine/lamivudine/tenofovir in HIV-1-infected patients aged ≥ 65 (elderly patients) and ≤ 40 years (young patients).

What was learned from the study?

This study demonstrates that the ainuovirine/lamivudine/tenofovir regimen is an efficacious and well-tolerated treatment regimen for HIV-1-infected patients aged ≥ 65 years and ≤ 40 years.

This study was a single-center, prospective, open-label, parallel-controlled clinical study with a small sample size and short follow-up period. Larger, longer, and more rigorously designed clinical trials and real-world studies are needed to validate the results of this study and to further explore the applicability and benefits of this regimen in different populations.

INTRODUCTION

Human immunodeficiency virus-1 (HIV-1) infection is a global health challenge that affects millions of people worldwide. Since the first case of AIDS was reported, more than 79.3 million people worldwide have been infected with HIV-1 and 36.3 million have died from HIV-related illnesses [1, 2]. By 2022, a total of 39.0 million people were living with HIV-1 [3, 4]. Current guidelines recommend that people with HIV-1 infection receive antiretroviral therapy (ART) immediately after they are diagnosed [5, 6]. ART has improved the survival and quality of life of HIV-1-infected patients, but also poses challenges such as drug resistance, toxicity, and poor adherence [7, 8]. Therefore, it is important to develop new and improved ART regimens to overcome these challenges and meet the needs of different populations.

The main drug classes used for ART treatment include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INSTIs) and fusion/invasion inhibitors. Typically, ART regimens consist of a combination of two or three classes of drugs to enhance efficacy and reduce the incidence of drug resistance [9]. Ainuovirine/lamivudine/tenofovir is a novel ART regimen comprising two NRTIs (lamivudine and tenofovir) and an NNRTI (ainuovirine) approved by the Chinese health authorities for the treatment of HIV [10]. A preclinical study demonstrated that ainuovirine exhibited potent antiviral activity against various HIV strains in vitro, as well as synergistic effects with lamivudine and tenofovir [11]. In addition, a phase III clinical trial found that the ainuovirine/tenofovir/lamivudine group was not inferior to the efavirenz/tenofovir/lamivudine group in terms of viral suppression at both 48 and 96 weeks and had a better tolerability and safety profile, particularly in terms of liver function, lipids, neuropsychiatric symptoms, and skin rashes [12]. This trial suggests that ainuovirine/lamivudine/tenofovir is an effective and safe primary treatment regimen for HIV-infected patients.

With an increase in the aging population in China, the incidence of HIV-1 infection in the elderly is increasing year by year [13]. Elderly HIV-1-infected patients may have decreased renal function, increased body fat, decreased lean body mass, altered drug metabolism and clearance, and are at a high risk of

cardiovascular disease, osteoporosis, diabetes mellitus, and cognitive impairment [14–16], thus affecting the absorption, distribution, metabolism, and excretion processes of drugs in the body. In addition, studies have found that people living with HIV aged > 50 years have more concomitant medications and are at a higher risk of potential drug–drug interactions compared to people living with HIV aged $\leq$ 50 years [17, 18]. Tyrberg et al. also found higher steady-state levels of plasma Darunavir and Atazanavir in people aged $\geq$ 65 years living with HIV treated with darunavir compared to controls aged $\leq$ 49 years [19]. It is not clear whether there are differences in the pharmacokinetics of ainuovirine/lamivudine/tenofovir treatment between elderly and young HIV-1-infected people. Therefore, we compared the pharmacokinetic parameters and safety profile of ainuovirine/lamivudine/tenofovir in HIV-1-infected patients aged 65 and 40 years.

METHODS

Study Design

This was a single-center, prospective, open-label, parallel-controlled clinical study to evaluate the pharmacokinetics and safety profile of ainuovirine 150 mg/lamivudine 300 mg/tenofovir 300 mg in HIV-1-infected patients. The participants were divided into two groups based on age (elderly group, $\geq$ 65 years; young group, 18–40 years). The study was conducted at the Guiyang Public Health Treatment Center (China) from October 2022 to February 2023, in accordance with the Declaration of Helsinki of 1964 and its later amendments. The study protocol, amendments, and written consent forms were reviewed and approved by the Ethics Committee of the Guiyang Public Health Treatment Center prior to study initiation (ID 202152). All the participants provided written informed consent for participation and publication.

Study Population

The inclusion criteria for this study were patients (1) aged 18–40 years or $\geq$ 65 years, regardless of gender; (2) diagnosed with HIV-1 infection, and received initial treatment with ainuovirine/lamivudine/tenofovir for at least 7 days; (3) able to understand and comply with the study protocol requirements, and able to voluntarily sign a written informed consent form.

Patients were excluded if they met any of the following conditions: (1) frailty or other conditions that may jeopardize the safety of the subjects; (2) patients who received drugs and/or foods that may potentially have affected CYP2C19 activity (mango, grapefruit, pomelo, etc.) in the past 7 days, or missed at least one dose of the study drug in the past 7 days; (3) history of drug abuse, recent alcohol or drug dependence, or participated in other drug or therapeutic device clinical trials within the 30 days prior to enrollment in this study; (4) used systemic immunosuppressive therapy or immunomodulators within the 30 days prior to treatment in this study, or could not avoid using them during the clinical trial; (5) cirrhosis and severe liver dysfunction, or creatinine $\geq$ upper limit of normal range and a glomerular filtration rate calculated by Chronic Kidney Disease-Epidemiology Collaboration creatinine formula $\leq$ 60 (ml/min/1.73 m^2); (6) any grade 3 or 4 manifestations according to the Division of AIDS grading table; (7) subjects who had active tuberculosis and were undergoing treatment at screening, or who had taken or were taking antifungal, corticosteroid, or anti-tuberculosis drugs within the 14 days prior to screening; (8) history of allergy or hypersensitivity to any component or excipient of the study drug; (9) pregnant or lactating women, women of childbearing age who did not take effective contraceptive measures, men with active heterosexual behavior who did not undergo vasectomy and did not take birth control measures, or men and women who were unwilling to continue taking contraceptive measures during the trial period and up to at least 30 days after its end; (10) undergoing any

surgery or operation that would change the pharmacokinetics of the experimental drug.

Pharmacokinetic Sampling

Intravenous blood samples (1 mL) were obtained 30 min before the administration of the study drug and at various time points (0.5, 1, 1.5, 2, 3, 4, 8, 12, 16, and 24 h) after dosing to measure the pharmacokinetics (PK) parameters of ainuovirine, lamivudine, and tenofovir. Patients fasted for 2 h after administration. Lunch was taken after 4 h and dinner was taken after about 10 h.

Safety Assessments

Safety was assessed by monitoring all adverse events (AEs), physical examinations, and clinical laboratory tests (routine blood, blood biochemistry, and urine tests) during the study period and 30 days after the PK test. In addition, a medical evaluation was performed for any AEs that occurred.

Sample Size

The study sample size was calculated on the basis of the expected result that the maximum concentration ($C_{max,ss}$) in elderly subjects was 30% higher than that in young subjects (526 ± 143 ng/ml) under steady-state conditions. The study set a two-sided $\alpha = 0.05$ and $\beta = 0.2$ for sample size calculation. Therefore, this study requires a sample size of 14–15 for both elderly and young subject groups. Each group comprised 15 participants.

Bioanalytical Methods

The concentrations of ainuovirine, lamivudine, and tenofovir in human (sodium heparin) plasma samples were determined using high-performance liquid chromatography–tandem mass spectrometry by Yu Jing Technology (Shanghai) Co., Ltd. (Shanghai, China). Lamivudine, ainuovirine, and tenofovir had quantification ranges of 20.0–5000 ng/mL, 4.0–1000 ng/mL, and 4.0–1000 ng/mL, respectively.

Isocratic chromatographic separation of ainuovirine, lamivudine, and tenofovir was achieved on a Waters ACQUITY UPLC HSS T3 (2.1×100 mm, 1.8 μm) analytical column. The mobile phase consisted of 0.1% formic acid in water and 2% methanol delivered at a flow rate of 0.4 mL/min. The gradient elution program was as follows: 0–0.6 min, 2–20% B; 0.6–2 min, 20–45% B; 2–2.01 min, 45–95% B; 2.01–4 min, 95–95% B; and 4–5.5 min, 95–2% B. The volume of the sample was 10 μL and the autosampler tray was kept at 40 °C.

The following setup was used for analysis: capillary voltage, 1.0 kV; source temperature, 150 °C; the desolvation gas flow rate and temperature were 1000 L/h and 550 °C, respectively. The analytes were detected and quantified in multiple reaction-monitoring (MRM) modes. The m/z values for the precursor-to-product ion conversions of ainuovirine, lamivudine, and tenofovir are shown in Table 1.

In addition, the between-run precisions (coefficient of variation [%CV]) of ainuovirine, lamivudine, and tenofovir were 17.31%, 15.28%, and 11.76%, respectively. The between-run precisions (%CV) for ainuovirine, lamivudine, and tenofovir were 11.09%, 11.84%, and 10.42%, respectively.

Pharmacokinetic and Statistical Analysis

Non-compartmental pharmacokinetic analysis was performed using Phoenix WinNonLin (Certara) to calculate the PK parameters for ainuovirine, lamivudine, and tenofovir. The C_{max}, time to C_{max} (t_{max}), area under the plasma concentration–time curve (AUC_{0-24}, AUC_{0-inf}), elimination rate constant (Ke), and elimination half-life ($T_{1/2Ke}$) were obtained directly from the observed concentration–time data.

Data were analyzed using the SPSS 21 software. Categorical variables were described as percentages (%) and compared using the chi-square test. Normally distributed data were described with mean $\pm$ standard deviation and compared with the Student's t test. Non-normally distributed data were described as median

Table 1 Ion transitions and other optimized parameters for ainuovirine, lamivudine, and tenofovir

Compound name	Dwell time (min)	Ion transition cone voltage (eV)	Collision energy (eV)	Acquisition time (min)	Internal standard
Ainuovirine	3.04	326.1 > 256.0*	20	20	Ainuovirine-d_5
		326.1 > 298.1	30	18	
Lamivudine	1.37	230.1 > 112.0*	30	40	Ainuovirine-d_5
		230.1 > 95.1	30	10	
Tenofovir	1.31	288.0 > 176.1*	50	28	Ainuovirine-d_5
		288.0 > 159.0	50	22	
Ainuovirine-d_5	3.04	331.1 > 299.1	30	18	Ainuovirine-d_5

*Indicates the ion pair used for quantification

(25th percentile, 75th percentile) and compared using nonparametric tests. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Demographic and Baseline Characteristics

Thirty patients with HIV were enrolled in this study. Of these, 15 were young patients (aged 30 ± 6.93 years) and 15 were elderly patients (aged 68.53 ± 3.80 years). The mean weights and heights of the young patients were 61.47 ± 14.63 kg and 164.87 ± 8.40 cm, while the mean weights and heights of the elderly patients were 58.83 ± 9.32 kg and 154.4 ± 27.14 cm, with no statistical difference between the two groups ($P > 0.05$). The blood platelet count, estimated glomerular filtration rate, and serum albumin were significantly lower in the elderly patients than those in the young patients ($P < 0.05$). In the elderly group, two patients were prescribed hypolipidemic drugs and hypoglycemic drugs, and four patients were prescribed hypotensive drugs during the same period. No concomitant drugs were taken in the young patients. All patients received a single oral dose of ainuovirine (150 mg/lamivudine 300 mg/tenofovir 300 mg) and completed all study assessments. Demographic and baseline characteristics are shown in Table 2.

Pharmacokinetics

The mean plasma concentration–time profiles of ainuovirine/lamivudine/tenofovir are shown in Fig. 1. The plasma levels of each component of ainuovirine/lamivudine/tenofovir, a combination medicine used to treat HIV, reached their highest point within 1–4 h after drug administration and then gradually declined during the rest of the observation period (Fig. 1).

Ainuovirine

The C_{max} (698.18 ± 270.16 vs. 586 ± 235.04 ng/ml) and T_{max} (3.0 (1.0, 4.0) vs. 2.0 (1.5, 4) h) of the elderly group were similar to those of the young group ($P > 0.05$, Table 3). The AUC_{0-24} and AUC_{0-inf} of ainuovirine were significantly increased in elderly patients (9098.71 ± 3572.91 and $22{,}933.07 \pm 19{,}026.61$ ng h/ml, respectively) compared to young patients (6235.32 ± 2065.53 and 8989.11 ± 3439.60 ng h/ml, respectively) ($P < 0.05$). The K_e value of the elderly group was smaller than that of the young group (0.031 ± 0.017 vs. 0.053 ± 0.018, respectively, $P = 0.002$), while the $T_{1/2Ke}$ of the elderly group was twice as high as that of the young group (29.98 ± 17.82 vs. 14.64 ± 5.16, $P < 0.05$).

Table 2 Baseline characteristics

Baseline characteristics	Elderly group (*n* = 15)	Young group (*n* = 15)	*P* value
Sex			
Female	4 (26.7%)	12 (80%)	1
Male	11 (73.3%)	3 (20%)	1
Age, years	68.53 ± 3.80	30 ± 6.93	< 0.001
WHO disease staging			
Stage 1	4 (26.67%)	11 (73.33%)	1
Stage 2	5 (33.33%)	2 (13.33%)	1
Stage 3	0 (0%)	1 (6.67%)	1
Stage 4	6 (40%)	1 (6.67%)	1
Weight (g)	58.83 ± 9.32	61.47 ± 14.63	0.057
Height (cm)	154.4 ± 27.14	164.87 ± 8.40	0.524
Hemoglobin (g/L)	138.27 ± 20.33	151.33 ± 19.88	0.043
Blood platelet count	160.93 ± 63.76	217.67 ± 33.03	0.006
Glutamic pyruvic transaminase (U/L)	20.87 ± 14.40	26.00 ± 13.61	0.163
Glutamic oxalacetic transaminase (U/L)	27.93 ± 14.72	32.73 ± 19.76	0.404
Blood glucose (μmol/L)	6.13 ± 1.70	5.23 ± 0.70	0.073
eGFR (mL/min/1.73 m^2)	91.28 ± 12.16	122.83 ± 13.99	< 0.001
Serum albumin (g/L)	42.21 ± 3.71	44.68 ± 2.50	0.041
Cholesterol (mmol/L)	4.11 ± 0.98	3.95 ± 0.78	0.62
Low density lipoprotein (mmol/L)	2.19 ± 0.57	2.4 ± 3.00	0.848
High density lipoprotein (mmol/L)	1.05 ± 0.35	0.93 ± 0.25	0.289
Triglyceride (mmol/L)	1.91 ± 1.24	2.24 ± 0.69	0.561
Total bilirubin (μmol/L)	12.19 ± 4.72	15.61 ± 6.54	0.075
Serum creatinine (μmol/L)	69.07 ± 15.74	66.91 ± 14.68	0.647
HIV RNA (copies/ml)			
< 2000	1 (6.67%)	1 (6.67%)	1
2000–10,000	5 (33.33%)	4 (26.67%)	1
10,000–20,000	1 (6.67%)	4 (26.67%)	1
≥ 20,000	8 (53.33%)	6 (40%)	1

eGFR estimated glomerular filtration rate, *HIV* human immunodeficiency virus-1, *WHO* World Health Organization
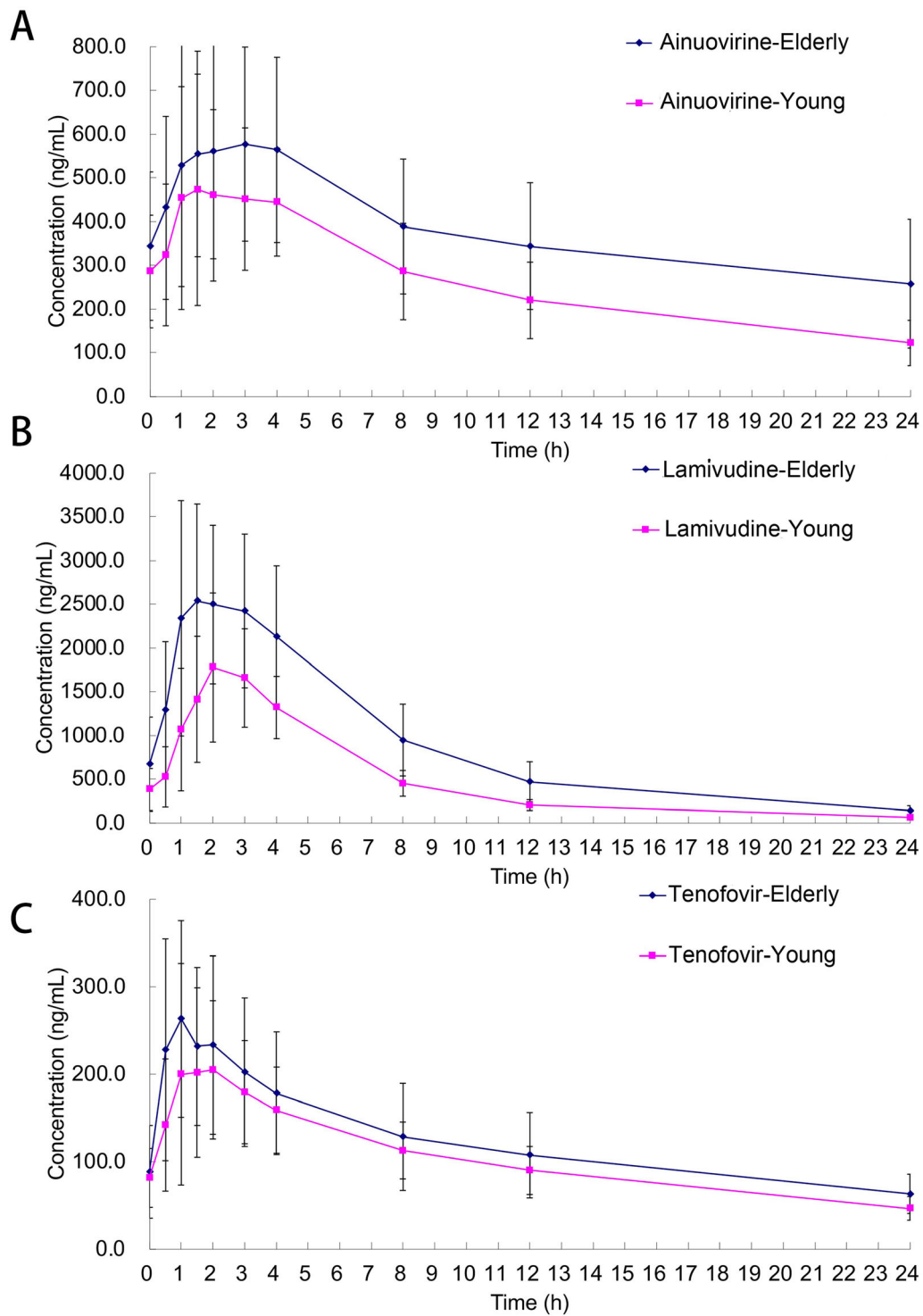eGFR was calculated by Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine formula

Fig. 1 Mean (± standard deviation) concentration–time profiles of ainuovirine/lamivudine/tenofovir. **a** Ainuovirine, **b** lamivudine, **c** tenofovir

Table 3 Comparison of pharmacokinetic parameters after oral administration of ainuovirine/lamivudine/tenofovir in the elderly and young groups

Drug	PK parameter	Elderly group ($n = 15$)	Young group ($n = 15$)	P value
Ainuovirine	C_{max} (ng/ml)	698.18 ± 270.16	586 ± 235.04	0.235
	T_{max} (h)	3.0 (1.0, 4.0)	2.0 (1.5, 4)	0.935
	K_e	0.031 ± 0.017	0.053 ± 0.018	0.002
	$T_{1/2Ke}$	29.98 ± 17.82	14.64 ± 5.16	0.005
	AUC_{0-24} (ng h/ml)	9098.71 ± 3572.91	6235.32 ± 2065.53	0.013
	AUC_{0-inf} (ng h/ml)	22,933.07 ± 19,026.61	8989.11 ± 3439.60	0.014
Lamivudine	C_{max} (ng/ml)	3011.88 ± 1100.60	2009.86 ± 693.90	0.004
	T_{max} (h)	2.30 ± 1.21	2.60 ± 1.04	0.472
	K_e	0.118 ± 0.027	0.118 ± 0.021	0.923
	$T_{1/2Ke}$	6.38 ± 2.47	6.05 ± 1.22	0.648
	AUC_{0-24} (ng h/ml)	21,238.89 ± 7299.89	11,652.82 ± 2745.43	< 0.001
	AUC_{0-inf} (ng h/ml)	22,630.62 ± 7312.37	12,222.69 ± 2876.82	< 0.001
Tenofovir	C_{max} (ng/ml)	337.87 ± 81.61	262.61 ± 93.16	0.008
	T_{max} (h)	1.0 (0.5, 2)	1.5 (1.0, 2.0)	0.174
	K_e	0.044 ± 0.015	0.056 ± 0.012	0.15
	$T_{1/2Ke}$	12.03 (5.65, 17.05)	12.54 (10.9, 13.32)	0.775
	AUC_{0-24} (ng h/ml)	2952.67 ± 1113.01	2465.11 ± 703.87	0.163
	AUC_{0-inf} (ng h/ml)	4713.69 ± 1659.63	3347.68 ± 924.13	0.006

C_{max} maximum concentration, *PK* pharmacokinetics, *Ke* elimination rate constant, t_{max} time to maximum concentration, $T_{1/2Ke}$ elimination half-life, AUC_{0-24} area under the concentration–time curve over the dosing interval, AUC_{0-inf} area under the concentration versus time curve from zero to infinity

Lamivudine

Elderly patients showed a significant increase in the C_{max}, AUC_{0-24}, and AUC_{0-inf} of lamivudine (3011.88 ± 1100.60 ng/ml, 21,238.89 ± 7299.89 ng h/ml, and 22,630.62 ± 7312.37 ng h/ml, respectively) in comparison to young patients (2009.86 ± 693.90 ng/ml, 11,652.82 ± 2745.43 ng h/ml, and 12,222.69 ± 2876.82 ng h/ml, respectively) (all $P < 0.05$). However, the elderly group were similar to the young group in terms of T_{max} (2.30 ± 1.21 vs. 2.60 ± 1.04 h), K_e (0.118 ± 0.027 vs. 0.118 ± 0.021), and $T_{1/2Ke}$ (6.38 ± 2.47 vs. 6.05 ± 1.22), with no statistically significant differences (all $P > 0.05$).

Tenofovir

Tenofovir was rapidly absorbed (median $T_{max} = 1.0$ h for the elderly group and 1.5 h for the young group; $P > 0.05$). Elderly patients had a higher C_{max} (337.87 ± 81.61 vs. 262.61 ± 93.16 ng/ml, $P = 0.008$) and AUC_{0-inf} (4713.69 ± 1659.63 vs. 3347.68 ± 924.13 ng h/ml, $P = 0.006$) than young patients, but no differences were observed in AUC_{0-24} (2952.67 ± 1113.01 vs. 2465.11 ± 703.87 ng h/ml, $P = 0.163$). In addition, there were no statistically significant differences in K_e (0.044 ± 0.015 vs. 0.056 ± 0.012, $P = 0.15$) or $T_{1/2Ke}$ (12.03 (5.65, 17.05) vs. 12.54 (10.9, 13.32), $P = 0.775$) between the elderly group and the young group.

Table 4 Comparison of physical examinations after 30 days of oral administration of ainuovirine/lamivudine/tenofovir combination tablets in young and elderly patients with human immunodeficiency virus-1 infection

Characteristics	Elderly group ($n = 15$)	Young group ($n = 15$)	P value
Hemoglobin (g/L)	143.87 ± 16.37	158.2 ± 18.05	0.031
Blood platelet count	160.07 ± 52.91	223.53 ± 45.4	0.001
Glutamic pyruvic transaminase (U/L)	16.53 ± 5.82	22.73 ± 12.58	0.099
Glutamic oxalacetic transaminase (U/L)	23.87 ± 6.98	21.4 ± 4.45	0.258
Blood glucose (μmol/L)	5.76 ± 1.56	5.15 ± 0.46	0.164
Serum albumin (g/L)	45.13 ± 2.90	49.11 ± 2.18	< 0.001
Cholesterol (mmol/L)	4.11 ± 0.98	4.06 ± 0.737	0.758
Low density lipoprotein (mmol/L)	2.25 ± 0.63	2.4 ± 0.65	0.544
High density lipoprotein (mmol/L)	1.07 ± 0.28	1.09 ± 0.28	0.85
Triglyceride (mmol/L)	2.24 ± 1.21	1.78 ± 1.39	0.343
Total bilirubin (μmol/L)	6.45 ± 2.32	7.93 ± 2.51	0.106
Serum creatinine (μmol/L)	76 ± 14.84	68.49 ± 16.48	0.2

Safety

No abnormalities were observed in the physical examinations and laboratory tests for either the young or elderly groups 30 days after oral administration of ainuovirine/lamivudine/tenofovir (Table 4).

Ainuovirine/lamivudine/tenofovir was well tolerated and no unexpected safety signals were observed. After treatment, the overall incidence of AEs in the young group was 20%, while that in the elderly group was 33.33%; the difference between the two groups was not statistically significant ($P > 0.05$, Table 5). There were two drug-related AEs in the elderly group (sleep disorders and cough) and two in the young group (sleep disorders and chest stuffiness). There were no statistically significant differences in drug-related AEs between the two groups ($P > 0.05$). Sleep disorders were more severe in the elderly group (grade 3–4) than in the young group (grade 1–2). All drug-related AEs were improved after treatment in elderly group and improved without treatment in young group.

DISCUSSION

Human immunodeficiency virus (HIV) is a major global health concern. The goal of ART is to reduce the viral load, improve morbidity and mortality, and prevent transmission. Ainuovirine/lamivudine/tenofovir is a novel ART regimen containing ainuovirine (150 mg), lamivudine (300 mg), and tenofovir (300 mg) administered orally once daily as a simple, effective, and safe treatment option for HIV-1-infected patients. Ainuovirine is a novel NNRTI that blocks viral replication by binding to HIV reverse transcriptase and inhibiting its catalytic reaction [20]. Lamivudine and tenofovir are NRTIs that bind competitively to natural nucleosides and inhibit HIV reverse transcriptase activity, thereby impeding provirus synthesis [21, 22]. Elderly HIV-1-infected patients are a special population that may have different pharmacokinetic and pharmacodynamic responses to antiretroviral drugs owing to changes in physiology and metabolism. Therefore, the assessment of the pharmacokinetic profile of ainuovirine/lamivudine/tenofovir in elderly patients is necessary to determine

Table 5 Adverse event summary

	Elderly group (n = 15)		Young group (n = 15)		P value
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	
Participants with any AE, n (%)	2 (13.33%)	3 (20%)	3 (20%)	0	0.409
Sleep disorders		1 (6.67%)[†,$]	1 (6.67%)[#]		
Cough	1 (6.67%)[$]		1 (6.67%)[*]		
Chest stuffiness		1 (6.67%)[**,$]	1 (6.67%)[#]		
Diarrhea	1 (6.67%)[#]				
Prostatic hyperplasia		1 (6.67%)[$]			
Drug-associated AE, n (%)	1 (6.67%)	1 (6.67%)	2 (13.3%)	0	
Sleep disorders		1 (6.67%)[$]	1 (6.67%)[#]		
Cough	1 (6.67%)[$]				
Chest stuffiness			1 (6.67%)[#]		

[*]The subject developed cough symptoms as a result of COVID-19 infection

[**]The subject was hospitalized with symptoms of panic and chest tightness due to coronary artery disease and cardiac function class II

[†]The subject had been diagnosed with insomnia prior to the start of the study and had a combination of heartburn, chest tightness, hospitalized for consideration of coronary artery disease, and class II cardiac function

[#]These subjects recovered without treatment

[$]These subjects recovered after treatment

whether dose adjustment or monitoring is required. There is a paucity of data regarding the pharmacokinetics of ainuovirine/lamivudine/tenofovir in elderly patients. This study is the first to compare the pharmacokinetics and safety of the ainuovirine/lamivudine/tenofovir regimen in HIV-1-infected patients aged 65 and 40 years. The results showed no significant differences in the T_{max} between the two groups for any of these drugs, suggesting that these three drugs were absorbed at a similar rate and were not influenced by age. This is consistent with the results of a previous study [23] comparing the pharmacokinetics of the tenofovir acetate–emtricitabine combination regimen in women, which found that the rate of absorption of tenofovir in the plasma was independent of age. Meanwhile, elderly patients had a smaller K_e and higher $T_{1/2Ke}$, $AUC_{0–24}$, and $AUC_{0–inf}$ for ainuovirine than young patients. This indicates that ainuovirine has a reduced clearance rate in elderly patients, leading to higher drug exposure. Ainuovirine is mainly excreted by the bile/feces (70.91%), and the renal pathway accounts for 23.32% [15]. It has been speculated that elderly people may have a reduced digestive function or renal function, leading to a lower clearance rate of ainuovirine. In this study, we found that although there was no significant difference, the clearance rate tenofovir was lower in the elderly group compared with that in the young group, which presumably as a result of the decline in eGFR. Interestingly, the clearance rate of lamivudine did not decrease significantly in older patients, possibly because lamivudine was primarily cleared by the renal tubule organic cationic transport system, which was not measured in older patients in our study. Generally, exposure to tenofovir and lamivudine was higher in the elderly group. This finding is consistent with those of previous studies that reported higher exposure to these drugs in elderly patients [10, 24, 25]. Therefore, dose adjustment or careful monitoring of drug concentrations may

be necessary in elderly patients to ensure the safe and effective use of these drugs.

In terms of safety, ainuovirine/lamivudine/tenofovir was well tolerated in both groups, with no unexpected safety signals. The incidence of AEs was 20% and 33.33% in the young and elderly groups, respectively; however, there was no statistical difference between the two groups. Similarly, a previous phase III clinical trial conducted in China, which compared the efficacy and safety of the ainuovirine/lamivudine/tenofovir regimen with the efavirenz/tenofovir/lamivudine regimen in treatment-naïve HIV-1-positive adults, found that the former was not inferior to the latter in inhibiting viral replication and had better tolerability and safety, particularly in terms of liver function, lipids, neuropsychiatric symptoms, and skin rashes [12]. Moreover, we found a similar incidence of drug-related AEs between the two groups; however, sleep disorders were more severe in the elderly patients than in the young patients. It should be noted that this elderly patient also had concomitant hypertension, diabetes, and coronary heart disease and had been diagnosed with insomnia before the start of the study. These factors may lead to the aggravation of sleep disorders in patients. These conditions also emphasize the issue of comorbidities and combined medications in elderly patients. Therefore, potential interactions and effects of ainuovirine/lamivudine/tenofovir with other drugs should be assessed when prescribing this regimen to elderly patients.

There are some limitations in this study. First, this study was a single-center clinical study with a small sample size and short follow-up period. Second, in order to better investigate the pharmacokinetics, we performed some pre-screening to exclude patients with disease that might affect drug metabolism. Therefore, further real-world data with larger sample size and longer follow-up time is needed to validate the results of this study.

CONCLUSION

This study suggests that the ainuovirine/lamivudine/tenofovir regimen might be an effective and safe HIV-1 treatment regimen for HIV-1-infected patients aged ≥ 65 years and ≤ 40 years. This study also observed that the exposure level to each drug in the treatment plan was higher in middle-aged and elderly patients; however, the incidence of AEs did not increase, indicating the safety of the treatment plan containing ainuovirine in elderly patients. Moreover, during the clinical application process, attention should be paid to whether elderly patients have increased clinical complications due to comorbidities and combined medications. In addition, this study was a single-center, prospective, open-label, parallel-controlled clinical study with a small sample size and short follow-up period. Larger, longer, and more rigorously designed clinical trials and real-world studies are needed to validate the results of this study and to further explore the applicability and benefits of this regimen in different populations.

Declarations

Center (China) from October 2022 to February 2023, in line with the Declaration of Helsinki of 1964 and its later amendments. The study protocol, amendments, and written consent forms were reviewed and approved by the Ethics Committee of Guiyang Public Health Treatment Center before study initiation (ID 202152). All the participants provided written informed consent for participation and publication.

REFERENCES

1. Abbas Q, Nisa M, Khan MU, et al. Brief cognitive behavior therapy for stigmatization, depression, quality of life, social support and adherence to treatment among patients with HIV/AIDS: a randomized control trial. BMC Psychiatry. 2023;23(1): 539. https://doi.org/10.1186/s12888-023-05013-2.

2. Bekolo C, Ndeso S, Gougue C, et al. The effect of the Universal Test and Treat policy uptake on CD4 count testing and incidence of opportunistic infections among people living with HIV infection in Cameroon: a retrospective analysis of routine data. Dialog Health. 2023;2:100120.

3. HIV/AIDS JUNPo. Fact sheet 2023. Global HIV Statistics. https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. Accessed 31 Aug 2023.

4. Karim QA, Archary D, Barre-Sinoussi F, et al. Women for science and science for women: gaps, challenges and opportunities towards optimizing pre-exposure prophylaxis for HIV-1 prevention. Front Immunol. 2022. https://doi.org/10.3389/fimmu.2022.1055042.

5. Stanley SK, Kaplan JE, Fauci A, et al. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. MMWR Recomm Rep. 1998;47(RR-5):39–82.

6. Rojo P, Carpenter D, Venter F, Turkova A, Penazzato M. The HIV drug optimization agenda: promoting standards for earlier investigation and approvals of antiretroviral drugs for use in adolescents living with HIV. J Int AIDS Soc. 2020;23:e25576.

7. Campbell GR, Spector SA. Current strategies to induce selective killing of HIV-1-infected cells. J Leukoc Biol. 2022;112(5):1273–84.

8. Cao W, Hsieh E, Li T. Optimizing treatment for adults with HIV/AIDS in China: successes over two decades and remaining challenges. Curr HIV/AIDS Rep. 2020;17:26–34.

9. Koay WLA, Kose-Otieno J, Rakhmanina N. HIV drug resistance in children and adolescents: always a challenge? Curr Epidemiol Rep. 2021;8:97–107.

10. AIDS and Hepatitis C Professional Group, Society of Infectious Diseases, Chinese Medical Association, Chinese Center for Disease Control and Prevention. Chinese guidelines for the diagnosis and treatment of HIV/AIDS. Infect Dis Immun. 2022;2(3):145–67.

11. Huang XS, Luo RH, Hu XL, et al. The new NNRTI ACC007 combined with lamivudine and tenofovir disoproxil fumarate show synergy anti-HIV activity in vitro. Curr HIV Res. 2020;18(5):332–41.

12. 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. 2023;36:100769.

13. Joska JA, Dreyer AJ, Nightingale S, Combrinck MI, De Jager CA. Prevalence of HIV-1 infection in an elderly rural population and associations with neurocognitive impairment. AIDS. 2019;33(11): 1765–71.

14. Bjørklund G, Shanaida M, Lysiuk R, et al. Natural compounds and products from an anti-aging perspective. Molecules. 2022;27(20):7084.

15. Marzolini C, Livio F. Prescribing issues in elderly individuals living with HIV. Expert Rev Clin Pharmacol. 2019;12(7):643–59.

16. Murray M, Lin J, Buros Stein A, et al. Relationship of polypharmacy to HIV RNA suppression in people aged≥ 50 years living with HIV. HIV Med. 2021;22(8):742–9.

17. Tseng A, Szadkowski L, Walmsley S, Salit I, Raboud J. Association of age with polypharmacy and risk of drug interactions with antiretroviral medications in HIV-positive patients. Ann Pharmacother. 2013;47(11):1429–39.

18. Marzolini C, Back D, Weber R, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. J Antimicrob Chemother. 2011;66(9):2107–11.

19. Tyrberg E, Edén A, Eriksen J, et al. Higher plasma drug levels in elderly people living with HIV treated with darunavir. PLoS ONE. 2021;16(2):e0246171.

20. Sluis-Cremer N, Tachedjian G. Mechanisms of inhibition of HIV replication by non-nucleoside reverse transcriptase inhibitors. Virus Res. 2008;134(1–2):147–56.

21. Holec AD, Mandal S, Prathipati PK, Destache CJ. Nucleotide reverse transcriptase inhibitors: a thorough review, present status and future perspective as HIV therapeutics. Curr HIV Res. 2017;15(6): 411–21.

22. Popović-Djordjević J, Quispe C, Giordo R, et al. Natural products and synthetic analogues against HIV: a perspective to develop new potential anti-HIV drugs. Eur J Med Chem. 2022;233:114217.

23. Thurman AR, Schwartz JL, Cottrell ML, et al. Safety and pharmacokinetics of a tenofovir alafenamide fumarate-emtricitabine based oral antiretroviral regimen for prevention of HIV acquisition in women: a randomized controlled trial. EClinicalMedicine. 2021;36:100893.

24. De Sousa MM, Chetty M. Are standard doses of renally-excreted antiretrovirals in older patients appropriate: a PBPK study comparing exposures in the elderly population with those in renal impairment. Drugs R&D. 2019;19(4):339–50.

25. Tan M, Johnston S, Nicholls J, Gompels M. Dual therapy with renally adjusted lamivudine and dolutegravir: a switch strategy to manage comorbidity and toxicity in older, suppressed patients? HIV Med. 2019;20(9):634–7.

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