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Original Article

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Long-Term Effectiveness and Tolerability of Dolutegravir/Lamivudine in Korea: A 3-Year Follow Up Study

Jae Eun Seong [1], Sang Min Ahn [2], Min Han [2], Yong Seop Lee [2], Jung Ah Lee [2], Jin Young Ahn [2], Su Jin Jeong [2], Nam Su Ku [2], Jun Yong Choi [2], Joon-Sup Yeom [2], and Jung Ho Kim [2]

[1]Division of Infectious Diseases, Department of Internal Medicine, Seoul Medical Center, Seoul, Korea
[2]Division of Infectious Diseases, Department of Internal medicine and AIDS Research Institute, Yonsei University College of Medicine, Seoul, Korea

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ABSTRACT

Background: Several studies have demonstrated the real-world efficacy and tolerability of dolutegravir/lamivudine (DTG/3TC). However, data from Asian countries—particularly regarding long-term use—remain limited.
Materials and Methods: We conducted a retrospective cohort study of adult people living with human immunodeficiency viruses (PLWH) who were treated with DTG/3TC at a tertiary hospital in Korea. Individuals with a 36-month observation period from the initiation of DTG/3TC were included in the study, as well as those who switched to other regimens during follow-up were also analysed. Both treatment-naive individuals and those who switched to DTG/3TC from other regimens were included. Baseline characteristics, DTG/3TC maintenance rates, effectiveness, and changes in metabolic parameters over 36 months were evaluated.
Results: Between July 2020 and April 2024, 305 PLWH received DTG/3TC, of whom 134 had an observation period of 36 months or longer. Most PLWH were male (94.0%), with a median age was 45.5 years. No participant switched from DTG/3TC to other regimens during the 36-month follow-up period. In the treatment-naïve group, HIV RNA levels remained <50 copies/mL from 6 to 36 months after starting DTG/3TC treatment. In the switching group, 99.2% maintained <50 copies/mL at 36 months. Among the treatment-naïve individuals, the CD4+ T cell count increased from a median of 494 cells/μL at baseline to 795 cells/μL at 36 months. During the 36-month follow-up, no significant changes were observed in lipid profiles or body weights in either the treatment-naïve or switching groups, apart from an increase in high-density lipoprotein cholesterol in the switching group.
Conclusion: DTG/3TC demonstrated sustained viral suppression and maintained CD4 count, with no significant adverse effects on lipid profiles or body weight.

Keywords: Dolutegravir; Lamivudine; Anti-HIV agents; HIV

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Corresponding Author: Jung Ho Kim, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: +82-2-2228-1986; Fax: +82-2-393-6884
Email: qetu1111@yuhs.ac

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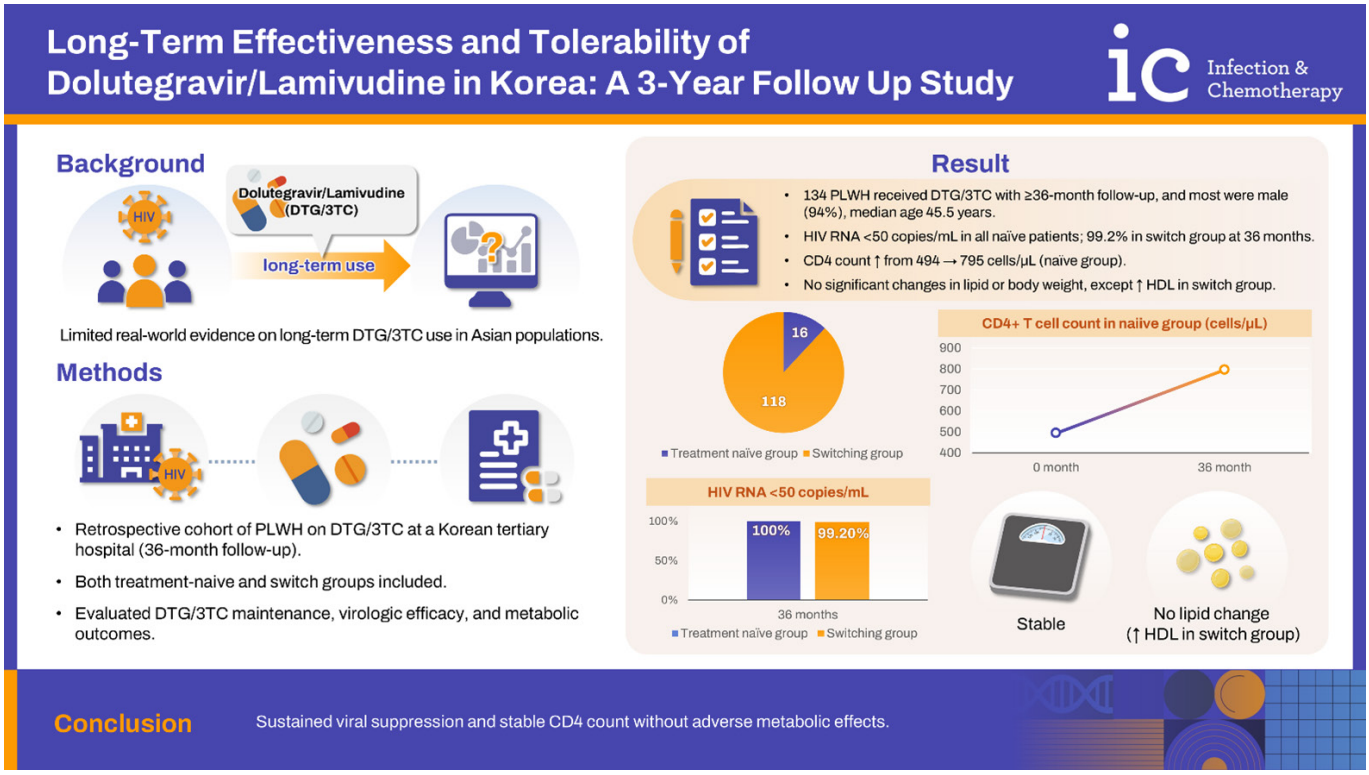
GRAPHICAL ABSTRACT



INTRODUCTION

As antiretroviral therapy (ART) has been developed and refined over recent decades, the life expectancy of people living with human immunodeficiency viruses (HIV) (PLWH) has significantly increased [1]. The integrase strand transfer inhibitor (INSTI) has been identified as a key component of ART due to its potent effect [2]. In particular, second-generation INSTIs are known for their high potency and strong generic barrier [3-5]. The second-generation INSTI have facilitated the development of two-drug regimens (2DR). Dolutegravir/lamivudine (DTG/3TC), a leading 2DR with DTG as the core agent, has demonstrated efficacy in both treatment-naïve and switching populations in a large Phase 3 trial [6, 7]. Consequently, DTG/3TC is now recommended as a first-line treatment in guidelines issued by the United States Department of Health and Human Services (DHHS) [8], the International Antiviral society [9], the European AIDS Clinical Society [10], and others. Since its introduction, numerous real-world data sets have been published on the effectiveness and tolerability of DTG/3TC in real-world settings [11-13]. Additionally, relevant studies have been conducted in Asia, including in Korea [14, 15].

A key concern is the long-term use of these therapies [16]. As no cure currently exists, PLWH require lifelong medication. It is therefore crucial to assess the maintenance of DTG/3TC after initiation and the sustainability of its effectiveness as indicators of combinational ART performance. Furthermore, given the increasing importance of cardiovascular disease management in PLWH [17, 18], changes in lipid profiles and body weight represent important endpoints [19, 20]. Therefore, evaluating how metabolic parameters such as lipid profiles and weight changes after long-term use of DTG/3TC is particularly relevant, particularly in light of the weight gain associated with second-generation INSTIs [5, 21]. Although long-term outcomes of DTG/3TC have been reported in Western cohorts [11, 22], corresponding data from Asia remain limited. Existing studies from Japan and Korea are limited by short follow-up periods and small sample sizes [14, 15]. Moreover, metabolic consequences such as weight gain and lipid alterations—important concerns with second-generation INSTIs—have not been adequately assessed in Asian populations. Given reported metabolic differences in HIV treatment responses between Asian and Western cohorts [23, 24], further long-term real-world data from Asia are warranted.

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As evidenced by data compiled in 2022, there are an estimated 39 million PLWH globally, including 6.5 million in the Asia-Pacific region [25]. The '2022 HIV/AIDS Annual Report' in Korea indicates that 1,066 new cases of HIV/acquired immunodeficiency syndrome (AIDS) were reported in 2022 [26]. Given the number of people infected with HIV in Asia and the increasing use of DTG/3TC in this region, further investigation is warranted.

Therefore, this study aimed to evaluate the adherence, persistence, efficacy, and tolerability of DTG/3TC in Asia. To this end, we conducted a three-year follow-up study of individuals with HIV initiating DTG/3TC therapy at a tertiary hospital in Korea.

MATERIALS AND METHODS

1. Study design and population

This retrospective cohort study used data from a tertiary hospital in Korea collected between July 2020 and April 2024. The study included PLWH aged ≥19-years who were treated with a DTG/3TC-specific combination regimen. Among them, only individuals with an observation period >36 months were included, regardless of whether they remained on DTG/3TC or switched to another regimen during the observation period. Individuals who were on DTG/3TC but had not yet reached 36 months or were lost to follow-up due to discontinuation of hospital visits were excluded. Both treatment-naïve individuals and those who switched from other ARTs to DTG/3TC were included.

2. Ethics statement

This study was approved by the Institutional Review Board (IRB) of Severance Hospital (IRB approval number: 4-2024-0655). The IRB waived the requirement for written consent due to the retrospective nature of the study.

3. Study outcomes and covariates

The primary objective of this study was to assess the treatment maintenance rate among PLWH who initiated DTG/3TC treatment and maintained the same regimen for a 36-month follow-up period. Furthermore, this study aimed to determine the reasons for the changes from DTG/3TC to other regimens.

The secondary objective was to assess the long-term effectiveness of DTG/3TC over 36 months. To assess the effectiveness of the treatment, we monitored the rate of HIV-1 RNA levels <50 copies/mL and the change in CD4 count at baseline and at 6, 12, 18, 24, 30, and 36 months after the initiation of DTG/3TC.

The third objective was to evaluate the long-term tolerability of DTG/3TC. Tolerability profile included changes in weight, glucose level, lipid profile, aspartate aminotransferase/alanine aminotransferase, and blood urea nitrogen (BUN)/creatinine levels. These alterations were also evaluated at the same six-month interval along with the viral load.

Additional covariates examined included sex, age, body mass index, sexual orientation, social history, drug adherence, and underlying diseases, including recently diagnosed sexually transmitted infections. The drug adherence rate was assessed based on the attending physician's evaluation of patient compliance documented during outpatient visits. All virological analyses were conducted by the Virology Unit Laboratory and Department of Diagnostic Laboratory Medicine at Severance Hospital.

4. Statistical analysis

If the values were not normally distributed, median and interquartile range were used. The Chi-square test or Fisher's exact test was used to compare two categorical variables between the treatment-naïve and switching groups. The unpaired t-test or Mann–Whitney *U* test was used to compare continuous variables. A repeated-measures analysis of variance was employed to ascertain whether there were any significant differences between the values observed before and after DTG/3TC administration. The statistical analysis demonstrated that there was a significant difference between the two groups over time, with a *P*-value of <0.05. All statistical analyses were performed using SPSS Statistics for Windows (version 26.0, IBM, Armonk, NY, USA).

RESULTS

1. Demographic and clinical characteristics

Between July 2020 and April 2024, 305 PLWH initiated DTG/3TC therapy at a specific tertiary hospital in Korea. Among them, 134 PLWH with an observation period exceeding 36 months were included in the analysis. Of these, 16 and 118 PLWH were included in the treatment-naïve and treatment-switching groups, respectively. The median duration of DTG/3TC for the entire cohort was 1,230.5 days, compared to 1,341.5 days in the naïve group and 1,228.5 days in the switching group.

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Table 1 shows the baseline characteristics of the study participants, including their comorbidities. The majority of participants were male (n=126, 94.0%), with a median age of 45.5 years. The median age of the treatment-naïve group was 32 years, which was significantly younger than the switching group (48 years). The median HIV RNA titre prior to initiating DTG/3TC therapy was 27,200 (5,150–61,950) copies/mL in the treatment-naïve group. The median CD4 T cell count prior to initiating DTG/3TC was 493.5 (359.5–560.75) in the treatment-naïve group and 663 (489.5-855.75) in the switching group.

Antiretroviral resistance testing was conducted in 15 (93.8%) treatment-naïve and 46 (39.0%) switching participants. As a result, 4 in the naïve group (25.0%) and 13 in the switching group (11.0%) were found to harbour at least one resistant mutation (**Supplementary Table 1**).

In the switching group, the mean duration of ART prior to initiating DTG/3TC was 2,817 days. Among the regimens used prior to the initiation of DTG/3TC therapy in the switching group, abacavir/DTG/3TC was the most prevalent (78.8%, 93 cases) (**Supplementary Table 2**). Most patients switched regimens for treatment simplification, while eight patients transitioned to DTG/3TC due to adverse effects such as dyspepsia, nausea, weight gain, or insomnia from previous regimens.

2. Effectiveness

Figure 1 shows the effectiveness of DTG/3TC over a 36-month follow-up period in both the treatment-naïve group and the switching group. The treatment-naïve group demonstrated sustained HIV RNA levels of <50 copies/mL from 6 to 36 months after the initiation of DTG/3TC. The switching group exhibited a 99.2% (117/118) rate of

Table 1. Baseline characteristics of patients treated with dolutegravir/lamivudine

Characteristic	Total (n=134)	Treatment-naïve (n=16)	Switching group (n=118)	*P*-value
Demographics				
Male, n (%)	126 (94.0)	16 (100)	110 (93.2)	0.237
Age, years, median (IQR)	45.5 (34-56)	32 (28-45.5)	48 (38-58)	
BMI, kg/m^2, median (IQR)	23.4 (21.74-25.84)	23.03 (22.26-24.26)	23.59 (21.7-25.91)	0.741
Sexual orientation[a]	Respondents: 86	Respondents: 12	Respondents: 74	
Heterosexual, n (%)	30 (34.9)	4 (33.3)	26 (35.1)	0.237
MSM, n (%)	46 (53.5)	6 (50.0)	40 (54.1)	0.797
Bisexual, n (%)	6 (7.0)	1 (8.3)	5 (6.8)	0.845
Lifestyle factors				
Alcohol use, n (%)	64 (74.4)	12 (100)	52 (70.3)	0.158
Smoking, n (%)	46 (53.5)	6 (50.0)	40 (54.1)	0.605
Clinical data				
HIV RNA, copies/mL, median (IQR)	0.0 (0.0-0.0)	27,200 (5,150-61,950)	0.0 (0.0-0.0)	0.008
Initial CD4+ T cell, cells/μL, median (IQR)	616 (472.25-811.25)	493.5 (359.5-560.75)	663 (489.5-855.75)	0.003
Initial CD8+ T cell, cells/μL, median (IQR)	731 (553.75-993.75)	756.5 (623-1,150)	718 (550-960)	0.673
Treatment duration, week, median (IQR)	175.8 (170.6-183.6)	191.6 (171.7-197.8)	175.5 (170.6-181.9)	0.006
Resistance test performed, n (%)	61 (45.5)	15 (93.8)	46 (39.0)	
Comorbidities				
Hypertension, n (%)	29 (21.6)	2 (12.5)	27 (22.9)	0.506
Diabetes mellitus, n (%)	24 (18.0)	2 (12.5)	22 (18.6)	0.774
Dyslipidemia, n (%)	50 (37.3)	1 (6.25)	49 (41.5)	0.017
Cardiovascular disease, n (%)	4 (3.0)	1 (6.25)	3 (2.5)	0.519
Osteoporosis, n (%)	8 (6.0)	0	8 (6.8)	0.312
Osteopenia, n (%)	22 (16.4)	3 (18.8)	19 (16.1)	0.873
Chronic kidney disease, n (%)	9 (6.7)	1 (6.25)	8 (6.8)	0.312
Chronic lung disease, n (%)	1 (0.7)	0	1 (0.8)	0.690
Tuberculosis, n (%)	19 (14.2)	1 (6.25)	18 (15.3)	0.485
Syphilis, n (%)	42 (31.3)	2 (12.5)	40 (33.9)	0.061
Solid tumor, n (%)	4 (3.0)	1 (6.25)	3 (2.5)	0.330
Hematologic malignancy, n (%)	3 (2.3)	0	3 (2.5)	0.690
Psychiatric illness, n (%)	12 (9.0)	2 (12.5)	10 (8.5)	0.350
Hepatitis C antibody positive, n (%)	1 (0.7)	0	1 (0.8)	0.065
Recently diagnosed STD, n (%)	5 (3.7)	1 (6.25)	4 (3.4)	0.330

Data are presented as the median (interquartile range) or number (%) of patients unless otherwise indicated.
[a]Sexual orientation: Twelve people in the treatment-naïve group and 74 in the switching group answered the question.
IQR, interquartile range; BMI, body mass index; MSM, Men who have sex with men; HIV, human immunodeficiency virus; STD, sexually transmitted disease.

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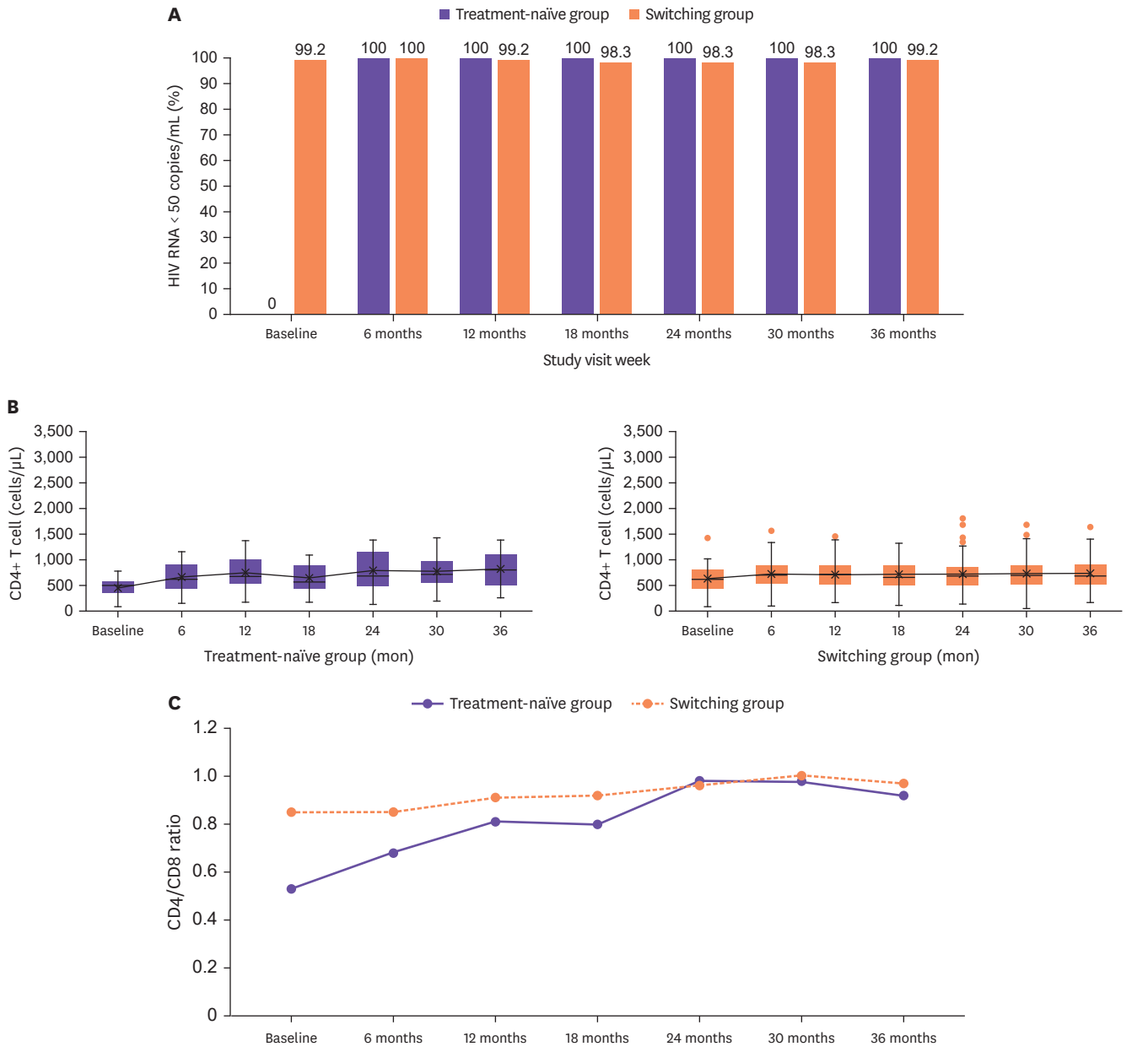

Figure 1. Effectiveness of dolutegravir/lamivudine in the treatment-naïve and switching groups.
(A) Proportion of patients achieving HIV-1 RNA <50 copies/mL in treatment-naïve and switching groups. (B) Comparison of CD4⁺ T-cell counts between treatment-naïve and switching groups. (C) Comparison of CD4/CD8 ratios between treatment-naïve and switching groups.

HIV RNA <50 copies/mL at the 36-month follow-up.

In the treatment-naïve group, there was a statistically significant increase in the CD4 T cell count from a median of 494 cells/μL at baseline to 795 cells/μL at 36 months (*P*=0.005). In the switching group, there was no notable change in the CD4 cell count from a median of 663 cells/μL at baseline to 677 cells/μL at 36 months (*P*=0.336). In the treatment-naïve group, the CD4/CD8 ratio increased significantly over the 36-month follow-up period (*P*<0.001).

3. Tolerability and safety

Figure 2 presents the tolerability of DTG/3TC over a 36-month follow-up period in both the treatment-naïve group and the switching group. During the 36-month follow-up period, no discernible changes were observed in the lipid profiles or body weights in either group. However, in the switching group, there was a significant increase in high-density lipoprotein (HDL) cholesterol levels, from a median of 45 mg/dL at baseline to a median of 49 mg/dL at 36 months (*P*=0.001).

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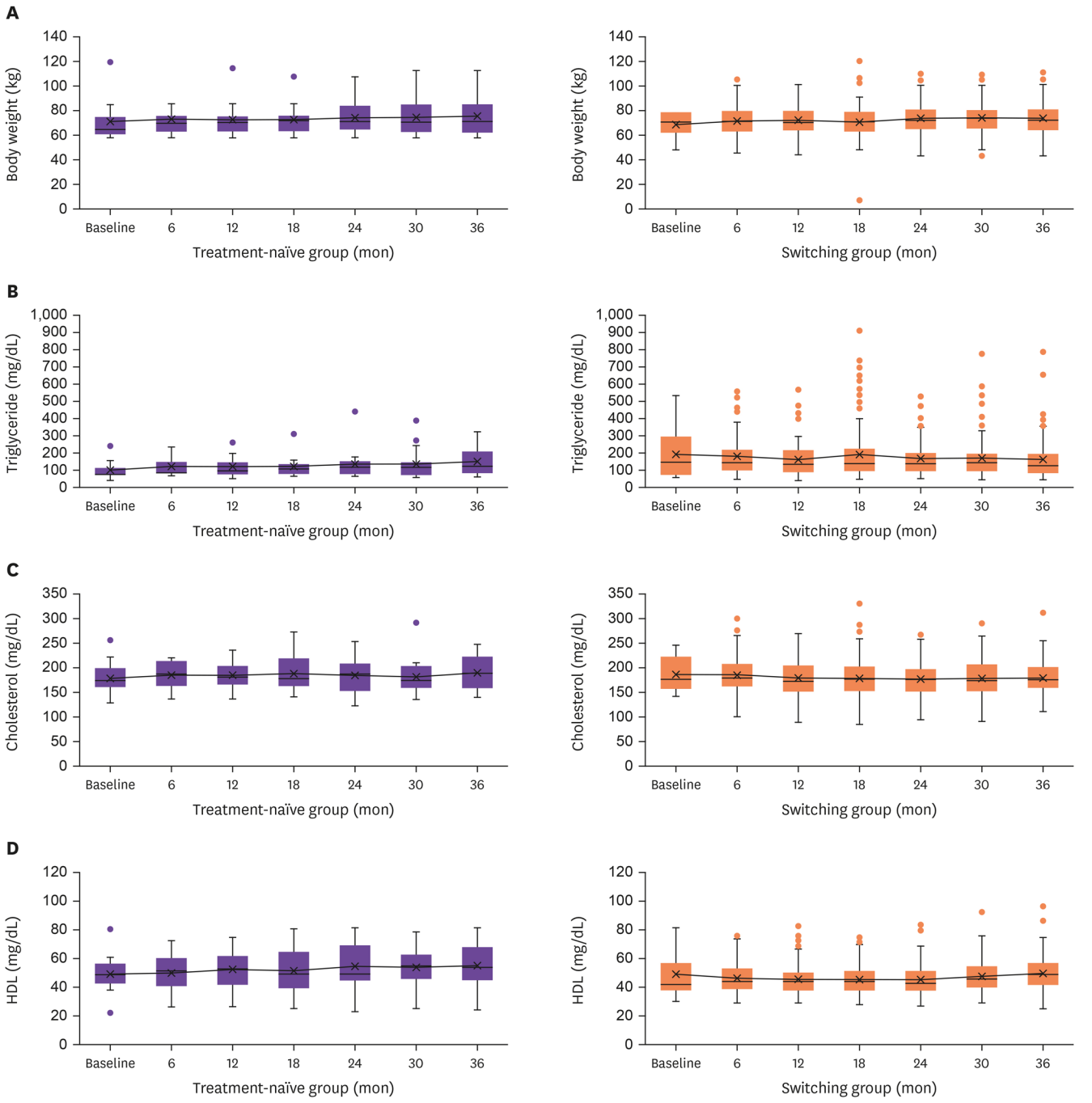

Figure 2. Tolerability of Dolutegravir/Lamivudine for the treatment-naïve and switching groups.
(A) Comparison of body weight between treatment-naïve and switching groups. (B) Comparison of triglyceride levels between treatment-naïve and switching groups. (C) Comparison of total cholesterol levels between treatment-naïve and switching groups. (D) Comparison of HDL cholesterol levels between treatment-naïve and switching groups. (E) Comparison of LDL cholesterol levels between treatment-naïve and switching groups. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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Additionally, there were no significant changes observed in glucose levels and liver function profile in either group, with the exception of an increase in total bilirubin in the switching group (from a median of 0.7 mg/dL at baseline to median 0.9 mg/dL at 36 months; $P<0.001$).

BUN levels demonstrated a statistically significant change in both groups. In the treatment-naïve group, the median BUN level increased from 11.6 mg/dL at baseline to 14.3 mg/dL at 36 months ($P=0.003$). The creatinine level demonstrated a statistically significant change only in the treatment-naïve group, with a median value

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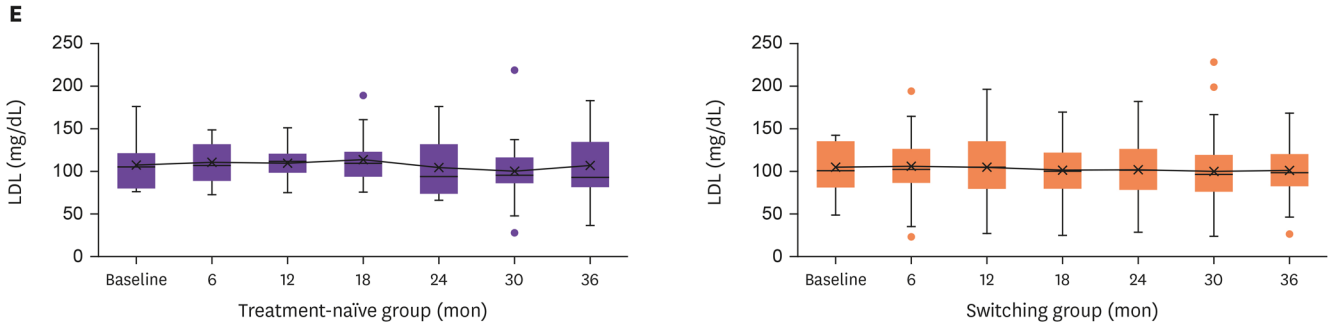

Figure 2. (Continued) Tolerability of Dolutegravir/Lamivudine for the treatment-naïve and switching groups.
(A) Comparison of body weight between treatment-naïve and switching groups. (B) Comparison of triglyceride levels between treatment-naïve and switching groups. (C) Comparison of total cholesterol levels between treatment-naïve and switching groups. (D) Comparison of HDL cholesterol levels between treatment-naïve and switching groups. (E) Comparison of LDL cholesterol levels between treatment-naïve and switching groups. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

of 0.87 mg/dL at baseline and 0.97 mg/dL at 36 months (P<0.001). The values for each parameter are presented in the **Supplementary Tables 3** and **4**.

During the three-year study, three participants developed a rash, one participant developed pruritus, and one participant developed abdominal discomfort; however, none discontinued DTG/3TC. With the exception of one participant who exhibited an adherence rate of 70%, the remaining participants demonstrated drug adherence rates exceeding 95%. In addition, no participant switched from DTG/3TC to other ARTs during the 36-month follow-up period after initiating DTG/3TC.

DISCUSSION

A study of PLWH who had been receiving DTG/3TC for three years in Korea revealed that none opted to switch to an alternative regimen. The results demonstrated favourable outcomes in terms of viral suppression, CD4, and CD4/CD8 ratios, with no significant concerns with tolerability.

The DTG/3TC maintenance rate was 100% in our 3-year study, which included 134 PLWH. This high retention rate without discontinuation is comparable to that observed in a prospective cohort study of 218 PLWH who switched to DTG/3TC in 2015, with a maintenance rate of 77.1% up to 5 years [3]. The high adherence to DTG/3TC is presumably attributed to the absence of significant adverse effects. The finding that abacavir/DTG/3TC was the most common prior regimen among PLWH who switched to DTG/3TC suggests that the main reason for switching was concern about potential cardiovascular adverse effects associated with abacavir use [27], with a preference for avoiding such risks and pursuing greater long-term safety. The available data indicate only a few cases of mild adverse effects, none of which were warranted discontinuation.

A 2-year study of 187 PLWH in Japan initiated in 2020 revealed that HIV RNA levels in the naïve group declined within 3 months following the initiation of DTG/3TC therapy, subsequently maintaining a level <20 copies/mL. The switching group demonstrated levels comparable to those observed prior to switching, indicating the effectiveness of this approach [14]. Furthermore, a 48-week DTG/3TC study conducted in China from 2020 to 2022 revealed that 96.4% of the 137 PLWH in the DTG/3TC group exhibited undetectable viral loads at 48 weeks [3]. In our 3-year study, 133 of 134 participants maintained HIV RNA levels <50 copies/mL over the 36-month follow-up period. One participant with HIV exhibited detectable HIV RNA levels at the 36-month follow-up with a confirmed viral load of 159,000 copies. The patient had not taken any antiretroviral medications for 5 months before the 36-month follow-up. Following resumption of DTG/3TC, the patient demonstrated a declining viral load at the 42-month follow-up.

The CD4/CD8 ratio is a crucial indicator of immune restoration [28]. A low CD4/CD8 ratio can be interpreted as a secondary phenomenon indicating dysregulation and activation of the immune system. This may be associated with adverse outcomes, such as mortality and premature aging [29-31]. In our study, the CD4/CD8 ratio exhibited an upward trajectory in both the treatment-naïve and switching groups over 36 months (**Supplementary**

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Tables 5 and 6). In another study conducted in China, the median increase in CD4 cell count and CD4/CD8 cell ratio was 143.5 cells/μL and 0.35, respectively, at 48 weeks compared to baseline after initiation of DTG/3TC. These findings further support the potential of DTG/3TC as an effective treatment regimen for Asian PLWH.

ART has been shown to affect several physiological parameters, including weight, glucose, and lipid profile [32, 33]. In a multi-country study involving 716 PLWH receiving DTG/3TC were assessed, including 71 Asian individuals. The mean weight change from the baseline to week 144 was 6.8 kg in the DTG/3TC group. One person discontinued treatment because of weight gain [2]. In our study, the treatment-naïve group exhibited weight gain primarily concentrated in the first 6 months following initiation of therapy, with minimal changes observed over the subsequent 36-month follow-up period. In the switching group, no significant weight changes were observed throughout the 36-month follow-up. These findings suggest that the initial weight gain may reflect a "return to health" phenomenon [34], whereas the long-term impact of DTG/3TC on weight appears to be minimal.

In a multi-country study, the lipid profile demonstrated an increase of 0.365, 0.180, and 0.158 mmol/L in total cholesterol, HDL, and LDL cholesterol, respectively, while creatinine exhibited a 0.14 mg/dL elevation from baseline [13]. In this study, the treatment-naïve group showed an increase in triglyceride levels from a baseline of 80 mg/dL to 119 mg/dL at 36 months, but this change was not statistically significant. In the switching group, triglyceride levels decreased from 140 mg/dL to 123 mg/dL over the same period; the change was also not statistically significant. Meanwhile, in the switching group, HDL levels showed a statistically significant increase from a median of 45 mg/dL to 49 mg/dL over the 36-month follow-up period. Serum creatinine levels increased significantly in the treatment-naïve group. This finding is consistent with previous reports that second-generation INSTIs, including DTG, may increase serum creatinine levels without causing actual renal impairment [35].

This study has limitations, including its reliance on data from a single country and institution, as well as the comparatively small number of PLWH included in the analysis. Another limitation of this study is that potential confounding factors, such as metabolic liver disease (*e.g.*, nonalcoholic fatty liver disease) or concomitant medication use (*e.g.*, statins), were not systematically assessed. Therefore, the results should be interpreted with caution, as these unmeasured variables may have affected the long-term outcomes. Additionally, this study's retrospective design without a control group treated with other regimens or a placebo is a limitation. Nevertheless, the 2023 UNAIDS Global HIV & AIDS Statistics report indicates that there are 39.0 million PLWH globally, of whom 6.5 million are identified in Asia and the Pacific, representing 16.6% of the global total [25]. Given the considerable number of PLWH in Asia, a key strength of this study lies in its comprehensive 36-month follow-up, contributing valuable long-term data to the regional evidence base.

In conclusion, the results of our three-year follow-up study conducted in Korea demonstrated the effectiveness of DTG/3TC in maintaining viral suppression and CD4 counts. Furthermore, no notable adverse effects on lipid profiles or body weight were observed in either the treatment-naïve or switching groups. The findings of this study regarding the long-term effectiveness and tolerability of DTG/3TC in an Asian setting may provide valuable evidence to inform future use of this regimen across broader populations in the region.

ORCID iDs
Jae Eun Seong
https://orcid.org/0009-0001-5555-4911
Sang Min Ahn
https://orcid.org/0000-0003-0641-4493
Min Han
https://orcid.org/0009-0003-1763-5643
Yong Seop Lee
https://orcid.org/0000-0002-0116-6710
Jung Ah Lee
https://orcid.org/0000-0001-9891-5134
Jin Young Ahn
https://orcid.org/0000-0002-3740-2826
Su Jin Jeong
https://orcid.org/0000-0003-4025-4542
Nam Su Ku
https://orcid.org/0000-0002-9717-4327
Jun Yong Choi
https://orcid.org/0000-0002-2775-3315
Joon-Sup Yeom
https://orcid.org/0000-0001-8940-7170
Jung Ho Kim
https://orcid.org/0000-0002-5033-3482

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Conflict of Interest
JYC is editorial board of *Infect Chemother*; however, he did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

Author Contributions

Conceptualization: JHK. Data curation: JES. Formal analysis: JES. Investigation: JES, SMA, JAL, JYA. Methodology: YSL. Supervision: JHK. Validation: MH, SJJ, NSK, JSY. Writing - original draft: JES, JHK. Writing - review & editing: YSL, SMA, JAL, JYA, MH, SJJ, NSK, JSY.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Treatment resistance tests for the treatment-naïve and switching groups

Supplementary Table 2

Previously treated antiretroviral therapy

Supplementary Table 3

Laboratory parameters at baseline, 6, 12, 18, 24, and 30 months for the treatment-naïve groups

Supplementary Table 4

Laboratory parameters at baseline, 6, 12, 18, 24, and 30 months for the switching groups

Supplementary Table 5

CD4, CD8, and CD4/8 ratio at baseline, 6, 12, 18, 24, and 30 months for the treatment-naïve groups

Supplementary Table 6

CD4, CD8, and CD4/8 ratio at baseline, 6, 12, 18, 24, and 30 months for the switching groups

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