

# Reasons, Efficacy and Safety of Switching to Dolutegravir-Based Regimens Among Virologically Suppressed PLWH: A Retrospective Cohort Study of 96 Weeks

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**Purpose:** The study aimed to explore the reasons, efficacy, and safety of switching to dolutegravir (DTG) based regimens in virologically suppressed people living with HIV (PLWH) in tertiary hospitals in China. Therefore, the study could provide a valuable reference for the rational clinical use of DTG.

**Methods:** PLWH's basic information, treatment details, and reasons for switching were collected, through the electrical clinical medical record system and telephone follow-up. Data included the proportion of PLWH with HIV RNA <50 copies/mL, changes in immunological indicators, and metabolic metrics at week 48 and week 96.

**Results:** 319 PLWH were included in the analysis. The three major reasons for switching were neurological toxicity (16.30%), simplification (13.79%), and renal toxicity (11.29%). Our study showed high rates of virologic suppression in the per-protocol analysis (week 48: 99.69%; week 96: 99.29%) after switching to DTG-based regimens. The median CD4+ T cell count increased from 579 cells/ $\mu$ L (IQR 420.5–758) to 642 cells/ $\mu$ L (IQR 466.5–854) at week 96 ( $p < 0.0001$ ). An improvement was observed in liver function (ALT:  $p < 0.0001$ ; AST:  $p < 0.0001$ ) and fasting glucose ( $p < 0.0001$ ). However, there was an elevation in creatinine (Cr) ( $p < 0.0001$ ) and a slight decrease in the estimated glomerular filtration rate (eGFR) ( $p < 0.0001$ ). Regarding lipid profile, triglyceride (TG) levels declined, while total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels increased. Further analysis revealed that the increase in TC and LDL-C was associated with the withdrawal of tenofovir disoproxil fumarate (TDF). This observed increase in lipid parameters only concerned the PLWH who switched from a TDF-containing regimen to a non-TDF regimen.

**Conclusion:** This study confirmed the virologic efficacy of switching to DTG-based regimens in virologically suppressed PLWH over a 96-week period. The findings also expanded the evidence of immune reconstitution and metabolic safety associated with this switch.

**Keywords:** HIV, dolutegravir, switching, virologically suppressed, lipids profile

## Introduction

Treatment optimization has always been the primary focus of managing HIV-1. To achieve better virus suppression and reduce long-term toxicity, researchers are constantly exploring new or substitution drugs. One such pharmaceutical option is dolutegravir (DTG), which is used to combat Human Immunodeficiency Virus type-1 (HIV-1) infection. As a second-generation integrase strand transfer inhibitor (INSTI) of HIV-1, DTG fits loosely into the intasome binding pocket and can retain its binding ability even with conformational changes in the pocket structure.<sup>1</sup> This ability to subtly readjust its binding position enhances the genetic barrier to resistance, resulting in high virologic efficacy.<sup>2</sup> Additionally, DTG is generally well tolerated, with rare severe side effects and a low potential for drug-drug interactions.<sup>3,4</sup>

The World Health Organization (WHO) and other guidelines have recommended DTG as a core drug for both naïve and treatment-experienced PLWH.<sup>5–7</sup> In China, DTG was approved by the National Medical Products Administration in 2015 for the treatment of PLWH. However, DTG was not included in the Chinese medical insurance

reimbursement catalog until 2021. Despite partial costs covered by medical insurance, PLWH still has to bear a portion of the financial burden, which severely hinders the widespread application of DTG. Limited data exists regarding its use in China. Therefore, it's necessary for us to retrospectively analyze the results of switching to DTG-based regimens.

In this study, we presented data on virologically suppressed PLWH and explored the factors that led to switching to DTG-based regimens. A retrospective study over a period of 96 weeks was conducted to assess the virologic efficacy, immunologic profile, and metabolic profile of using DTG as a switch strategy.

## Methods

### Study Design

We conducted a retrospective analysis of treatment-experienced PLWH who switched to DTG-based regimens and assessed their outcomes over a 96-week period. We enrolled PLWH in Beijing Ditan Hospital from 2018 to 2023 who underwent a therapeutic switch to DTG-based regimens with a follow-up period of 96 weeks. PLWH's basic information, treatment details, reasons for switching, and laboratory indicators were collected through the electrical clinical medical record system and telephone follow-up. All PLWH met the following inclusion criteria: (a) being at least 18 years old; (b) being on stable (at least 6 months) antiretroviral therapy (ART) with viral suppression (HIV-RNA < 50 copies/mL) at the time of switching to DTG-based regimens (week 0); (c) having a follow-up period of at least 48 weeks; (d) having follow-up data.

The primary endpoint was the rate of virologic control (defined as HIV-RNA < 50 copies/mL) at week 48 and week 96. Secondary outcomes of the study were: 1. The reasons for switching to DTG. 2. Immune changes (CD4+ T cell count, CD8+ T cell count and CD4/CD8 ratio). 3. Metabolic changes (liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST)); fasting glucose (GLU); renal function: urea, creatinine (Cr), uric acid (UA), estimated glomerular filtration rate (eGFR); blood lipids: total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and total cholesterol / high-density lipoprotein cholesterol (TC/HDL-C).

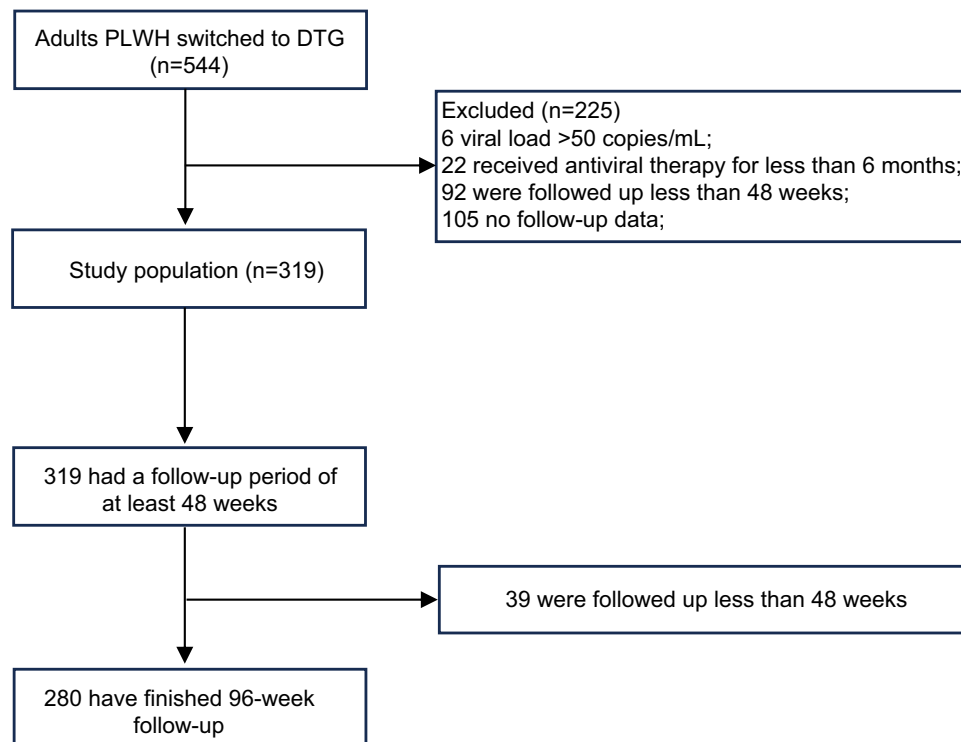
### Definitions

The HIV diagnosis and AIDS definitions followed the definition of WHO. Viral suppression was defined as having an undetectable viral load, of less than 50 copies/mL.

Virological failure was defined as a viral load > 50 copies/mL confirmed on two consecutive occasions or a single viral load determination > 400 copies/mL. The definitions for abnormal cholesterol levels were based on the Chinese Guidelines for Lipid Management (2023). A normal level of TC was defined as less than 5.2 mmol/L. Borderline high TC was defined as equal to or greater than 5.2 mmol/L but less than 6.2 mmol/L. A high level of TC was defined as equal to or greater than 6.2 mmol/L. A normal level of LDL-C was defined as less than 3.4 mmol/L. Borderline high LDL-C was defined as equal to or greater than 3.4 mmol/L but less than 4.1 mmol/L. A high level of LDL-C was defined as equal to or greater than 4.1 mmol/L.

### Statistical Analysis

Data were displayed as median values and interquartile range (IQR), or simple percentages (%), according to the variable type, continuous or categorical, respectively. The change from week 0 was assessed by raw absolute difference (eg, week 0–96 = week 96 value–week 0 value) or percentage of median relative difference (eg, MRD% (week 0–96) =  $100 \times (\text{week 96 value} - \text{week 0 value}) / \text{week 0 value}$ ). The normality of variable distribution was assessed by the Kolmogorov–Smirnov test. Longitudinal analysis was assessed by the paired Wilcoxon test for continuous variables. For all analyses,  $P < 0.05$  was considered statistically significant. All data were analyzed with GraphPad Prism 7 (GraphPad Software, La Jolla, CA, USA).



**Figure 1** Study profile.

**Abbreviation:** DTG, dolutegravir.

## Results

### Population Characteristics at the Time of the Switch

Between 2018 and 2023, 579 individuals were screened for eligibility, of which 319 met the inclusion criteria (Figure 1). The characteristics of 319 PLWH at the time of switching were summarized in Table 1. The majority of PLWH were

**Table 1** Characteristics of the Study Population at the Start of Switching (Week 0) (N=319)

Characteristic	n (%) or Median (IQR), Unless Otherwise Specified
Male, n (%)	302 (94.67)
Age (years)	35 (30–41)
Time on cART (years)	3.83 (2.17–6.67)
Previous virological failure (at least one)	14 (4.39)
Pre-switch ART regimen	
2NRTIs+NNRTIs	193 (60.5)
2NRTIs+INSTIs	76 (23.82)
2NRTIs+PI	50 (15.67)
Post-switch ART regimen	
DTG+3TC	158 (49.53)
DTG+3TC+TDF	63 (19.75)
DTG+FTC+TAF	53 (16.61)
DTG+3TC+ABC	33 (10.34)
DTG+3TC+AZT	12 (3.76)

**Abbreviations:** IQR, interquartile range; ART, antiretroviral therapy; NRTIs, integrase strand transfer inhibitors; NNRTIs, non-nucleosidic reverse transcriptase inhibitors; INSTIs, integrase strand transfer inhibitors; PI, protease inhibitor; DTG, dolutegravir; 3TC, Lamivudine; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; TAF, tenofovir alafenamide fumarate; ABC, abacavir; AZT, Zidovudine.

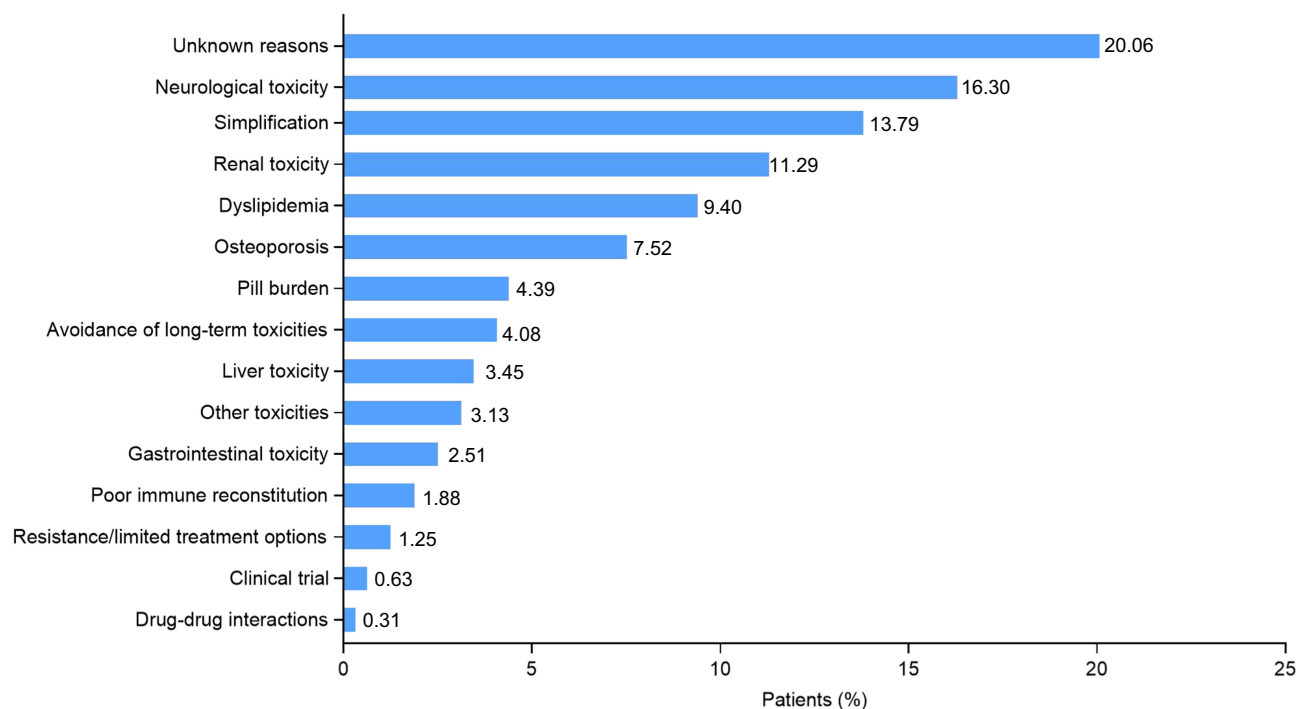
male (94.67%), and the median age was 35 years (IQR 30–41). Prior to switching to DTG-based regimens, the median duration of ART was 3.83 years (IQR 2.17–6.67). A total of 14 individuals among 319 PLWH had experienced virological failure. Out of the 319 PLWH, 193 individuals (60.5%) were on a regimen of two nucleoside reverse transcriptase inhibitors (2NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), with the majority of these individuals (182) receiving efavirenz (EFV). Additionally, 76 individuals (23.82%) were on a regimen of 2NRTIs plus INSTI. The remaining 50 individuals (15.67%) received a regimen of 2NRTIs plus a protease inhibitor (PI). After switching, PLWH received the following combinations: DTG+3TC (49.53%), DTG+3TC+TDF (19.75%), DTG+FTC+TAF (16.61%), DTG+3TC+ABC (10.34%), and DTG+3TC+AZT (3.76%). In other words, 158 individuals (49.53%) switched to a DTG-based two-drug regimen (DTG-2DR), while 161 individuals (50.47%) switched to a DTG-based three-drug regimen (DTG-3DR).

## The Reasons for Switching

The most common reason for switching, among known causes in our study, was neurological toxicity (16.30%). Other frequent causes included simplification (13.79%), renal toxicity (11.29%), dyslipidemia (9.40%), osteoporosis (7.52%), and pill burden (4.39%) (Figure 2). Totally, most PLWH switched to DTG-based regimens due to adverse reactions, while a minority were seeking an optimal treatment proposal.

## Efficacy

No missing data were recorded at week 48, therefore the intention-to-treat analysis (ITT, where missing equal failure) and the per-protocol analysis (PP, where missing equal excluded) yielded the same results. The virologic suppression rate at week 48 was 99.69% (318/319). However, at week 96, there were missing virologic data for a total of 39 PLWH. Among them, the follow-up time for 24 PLWH did not reach 96 weeks, so their viral load at week 96 could not be assessed. Additionally, 15 PLWH were lost to follow-up at week 96, as transferred elsewhere for care. In the ITT analysis at week 96, the rate of virologic suppression was 87.15% (278/319). In the PP analysis, the rate of virologic suppression



**Figure 2** The reasons for switching. Unknown (n=64), neurological toxicity (n=52), renal toxicity (n=36), simplification (n=35), dyslipidemia (n=30), osteoporosis (n=24) and convenience (n=21), avoidance of long-term toxicities (n=13), liver toxicity (n=11), other toxicities (n=10), gastrointestinal toxicity (n=8), poor immune reconstitution (n=6), resistance/limited treatment options (n=4), pill burden (n=2), clinical trial (n=2) and drug-drug interactions (n=11).

was 99.29% (278/280). One PLWH had an HIV-RNA of 59 copies/mL at week 48 but achieved virologic suppression again at week 96. Furthermore, two PLWH experienced low-level viremia at week 96 (HIV-RNA 55 copies/mL and 90 copies/mL) (Figure 3A).

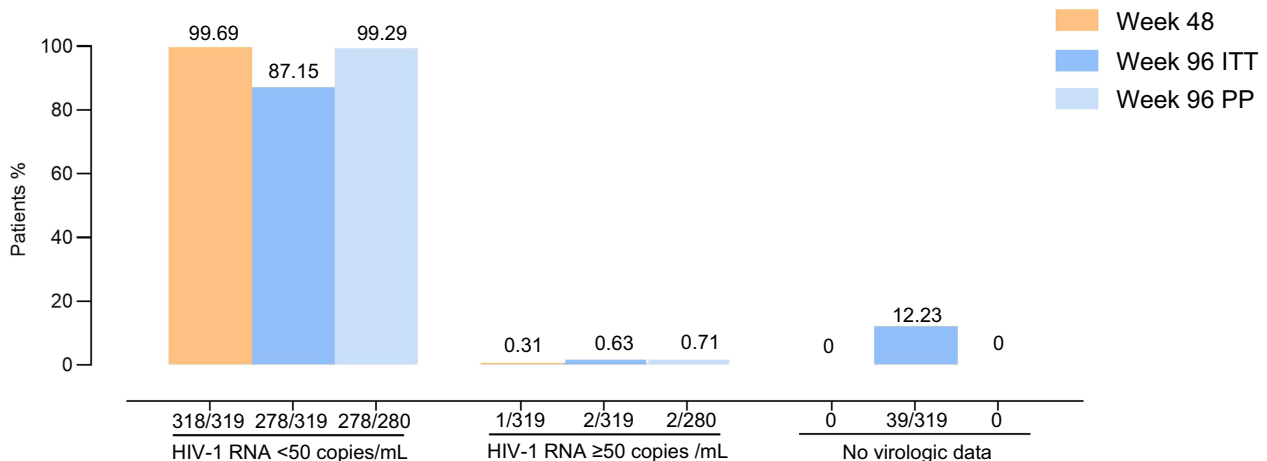
Meanwhile, the CD4+ T cell count showed a gradual improvement over the follow-up weeks. The CD4+ T cell absolute count and proportion increased by 31 cells/ $\mu$ L, +6.4% ( $p < 0.0001$ ), and 65 cells/ $\mu$ L, +12.49% ( $p < 0.0001$ ) at week 48 and week 96 compared to week 0, respectively. However, the CD8+ cell count did not change over time (week 0–48:  $p = 0.1619$ ; week 0–96:  $p = 0.22135$ ). A modest increase in the CD4/CD8 ratio was observed (week 0–48: +5.882%,  $p < 0.001$ ; week 0–96: +13.68%,  $p < 0.001$ ) (Table 2, Figure 3B).

## Safety

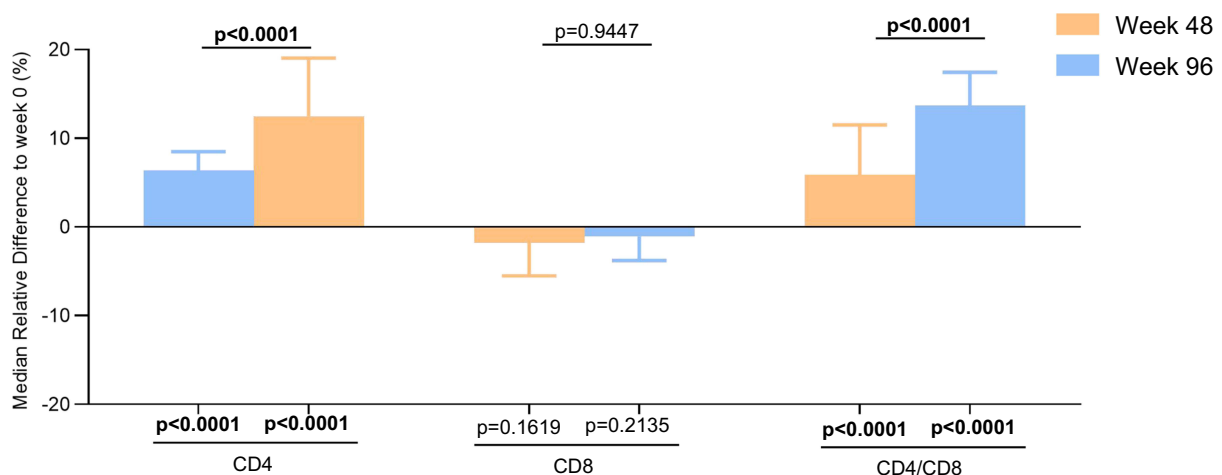
### Liver Function and Fasting Glucose

A significant reduction in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was observed from week 0 to week 96 (ALT:  $-10.32\%$ ,  $p < 0.0001$ ; AST:  $-12.69\%$ ,  $p < 0.0001$ ) (Table 2, Figure 4A). Additionally, there was a parallel decline in fasting glucose (GLU) (week 0–96:  $-4.519\%$ ,  $p < 0.0001$ ) (Table 2, Figure 4A).

A



B



**Figure 3** Virologic and immunologic response. (A) Virologic control (HIV-RNA < 50 copies/mL), virologic failure (HIV-RNA  $\geq$  50 copies/mL), and missing virologic data at week 48 and week 96. ITT: intention-to-treat analysis—missing equal failure; PP: per-protocol analysis—missing equal excluded. No missing data were recorded at week 48, thus the ITT and the PP analyses are equal (yellow bar). At week 96 missing data were recorded; thus, the figure shows bars for both the ITT analysis (blue bar) and the PP analysis (light blue bar). (B) Changes of CD4+ T cell count, CD8+ T cell count, and CD4/CD8 ratio at week 48 and week 96 (week 0:  $n = 317$ ; week 48:  $n = 283$ ; week 96:  $n = 257$ ).

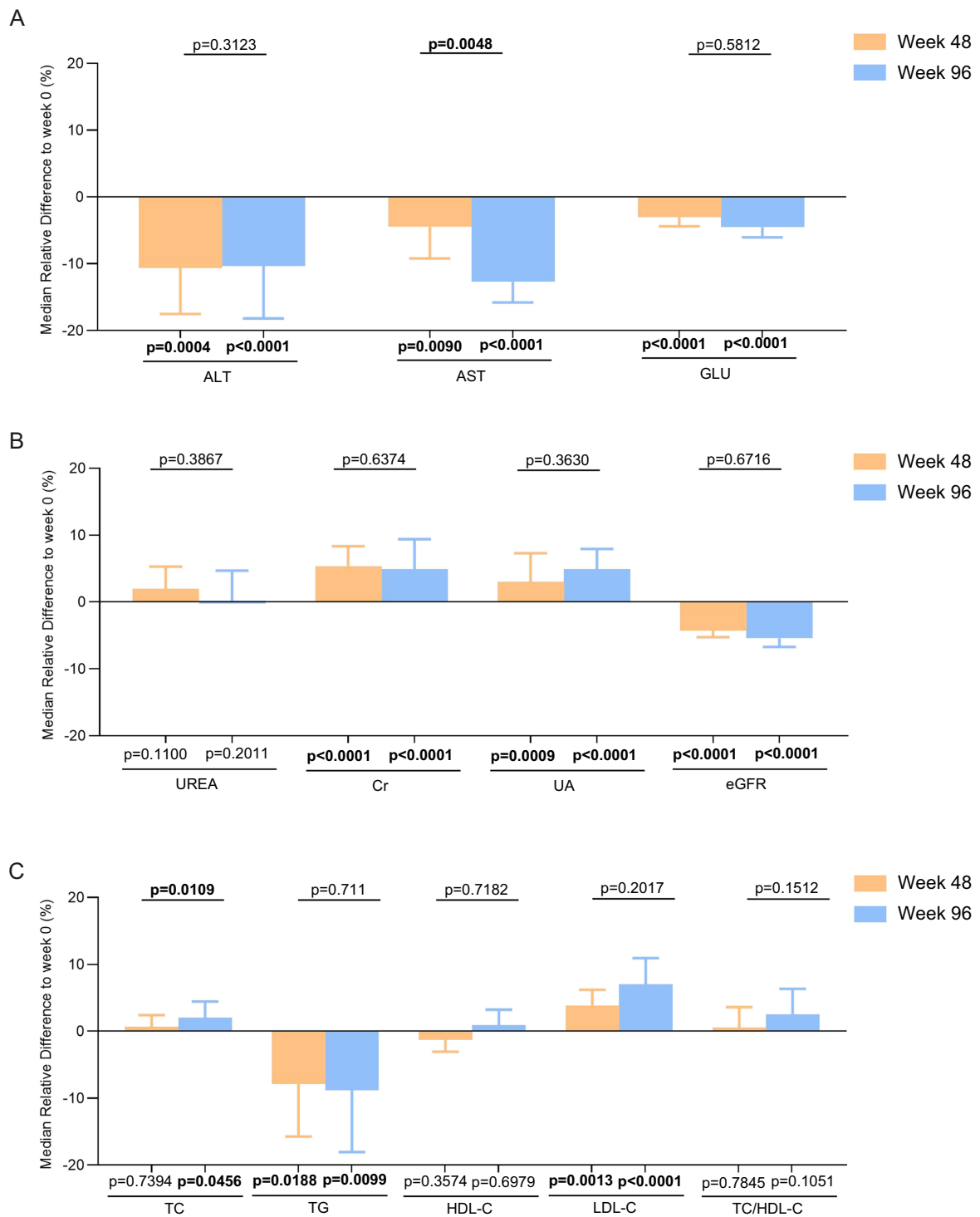
**Note:** Bold indicates statistically significant associations,  $p < 0.05$ .

**Table 2** Immunological and Metabolic Changes at Pre-Switching (Week 0) and Post-Switching (Week 48 and Week 96)

Characteristic	Week 0	Week 48	Week 96	Week 0–48			Week 0–96		
				Absolute Difference	MRD%	p value	Absolute Difference	MRD%	p value
CD4 count (cells/ $\mu$ L)	579(420.5–758)	605(425–795)	642(466.5–854)	31(–42.5–114.5)	6.4(–8.321–23.78)	<b>&lt;0.0001</b>	65(–30–183)	12.49(–5.345–36.86)	<b>&lt;0.0001</b>
CD8 count (cells/ $\mu$ L)	873(663.5–1126)	859(636–1115)	864(680.5–1079)	–14(–206–137.5)	–1.763(–18.57–18.19)	0.1619	–10(–218–142)	–1.076(–21.65–17.64)	0.2135
CD4/CD8	0.67(0.415–0.935)	0.68(0.46–0.96)	0.72(0.50–0.995)	0.03(–0.03–0.1248)	5.882(–4.01–23.17)	<b>&lt;0.0001</b>	0.08(–0.01–0.17)	13.68(–0.862–31.78)	<b>&lt;0.0001</b>
ALT (mg/dL)	26.75(18.68–42.00)	23.7(17.43–36.4)	22.6(17.3–34.4)	–2.7(–12.53–4.95)	–10.64(–36.17–26.68)	<b>0.0004</b>	–2.2(–15.3–5.6)	–10.32(–43.73–27.01)	<b>&lt;0.0001</b>
AST (mg/dL)	22.8(18.5–28.95)	21.55(18.23–27.28)	20.4(17.0–25.9)	–1.1(–6.7–3.4)	–4.461(–25.35–16.02)	<b>0.009</b>	–2.5(–8.1–2.2)	–12.69(–29.46–10.53)	<b>&lt;0.0001</b>
GLU (mmol/L)	5.695(5.323–6.03)	5.47(5.17–5.86)	5.43(5.135–5.78)	–0.17(–0.55–0.17)	–3.011(–9.145–2.988)	<b>&lt;0.0001</b>	–0.27(–0.61–0.1)	–4.519(–10.37–1.883)	<b>&lt;0.0001</b>
UREA (mmol/L)	4.78(3.998–5.608)	4.96(4.13–5.69)	4.97(4.04–5.845)	0.09(–0.65–0.96)	1.975(–13.21–20.93)	0.11	–0.005(–0.725–0.923)	0.181(–14.35–21.31)	0.2011
Cr (mg/dL)	80.9(70.53–91.85)	85.6(77.08–95.0)	85.2(78.65–94.45)	4.2(–3.7–12.3)	5.378(–4.009–15.6)	<b>&lt;0.0001</b>	4.3(–3.9–13.15)	4.887(–4.397–17.7)	<b>&lt;0.0001</b>
UA ( $\mu$ mol/L)	361(307–421)	376(320.3–442)	377(329–435.5)	11.5(–33.25–58.25)	3.039(–8.672–17.07)	<b>0.0009</b>	18(–29.25–71.25)	4.884(–6.286–21.1)	<b>&lt;0.0001</b>
eGFR (mL/min/1.73m <sup>2</sup> )	106.2(92.58–117.7)	100.1(86.6–111.1)	100.6(89.1–110.3)	–4.6(–13.06–2.95)	–4.329(–12.21–2.825)	<b>&lt;0.0001</b>	–5.4(–14.15–2.4)	–5.445(–13.46–2.222)	<b>&lt;0.0001</b>
TC (mmol/L)	4.44(3.883–5.080)	4.33(3.8–5.05)	4.44(3.96–5.235)	0.03(–0.523–0.543)	0.703(–11.3–12.21)	0.7394	0.09(–0.34–0.66)	2.062(–7.388–14.46)	<b>0.0456</b>
TG (mmol/L)	1.56(1.053–2.663)	1.46(0.97–2.58)	1.46(0.915–2.44)	–0.085(–0.68–0.4625)	–7.906(–35.99–35.79)	<b>0.0188</b>	–0.1(–0.76–0.4)	–8.824(–39.48–35)	<b>0.0099</b>
HDL-C (mmol/L)	1.04(0.9–1.25)	1.05(0.88–1.24)	1.06(0.87–1.25)	–0.015(–0.13–0.1125)	–1.287(–11.76–10.64)	0.3574	0.01(–0.11–0.1)	0.943(–10.67–10.42)	0.6979
LDL-C (mmol/L)	2.61(2.12–3.08)	2.68(2.2–3.25)	2.76(2.195–3.2)	0.09(–0.263–0.473)	3.798(–9.332–22.83)	<b>0.0013</b>	0.18(–0.2–0.53)	7.042(–8.462–21.93)	<b>&lt;0.0001</b>
TC/HDL-C	4.171(3.438–5.157)	4.154(3.492–5.039)	4.273(3.431–5.337)	0.024(–0.549–0.538)	0.564(–12.06–14.2)	0.7845	0.103(–0.425–0.593)	2.564(–10.56–15.83)	0.1051
TC									
Group 1	4.43(3.88–5.065)	4.55(3.995–5.353)	4.56(4.04–5.34)	0.165(–0.365–0.6275)	4.208(–7.807–16.37)	<b>0.0027</b>	0.175(–0.208–0.805)	3.624(–4.685–18.34)	<b>&lt;0.0001</b>
Group 2	4.04(3.63–4.68)	3.74(3.37–3.99)	3.96(3.52–4.32)	–0.033(–0.823–0.07)	–7.639(–19.7–1.99)	<b>&lt;0.0001</b>	–0.14(–0.49–0.28)	–3.944(–11.58–7.734)	0.3169
Group 3	4.66(4.125–5.455)	4.56(4.115–5.14)	4.58(3.98–5.46)	–0.205(–0.848–0.345)	–4.374(–16.74–8.373)	0.103	–0.175(–0.683–0.518)	–4.051(–14.9–9.576)	0.3161
LDL-C									
Group 1	2.665(2.12–3.12)	2.825(2.298–3.423)	2.9(2.28–3.37)	0.175(–0.168–0.578)	6.387(–6.468–24.63)	<b>&lt;0.0001</b>	0.195(–0.093–0.603)	7.971(–3.411–22.02)	<b>&lt;0.0001</b>
Group 2	2.47(2.13–2.83)	2.29(2.01–2.65)	2.43(2.11–2.85)	–0.06(–0.435–0.135)	–2.548(–18.35–5.588)	<b>0.0434</b>	0(–0.36–0.445)	0(–16.83–20.75)	0.5572
Group 3	2.56(2.075–2.97)	2.74(2.22–3.3)	2.57(2.17–3.17)	0.07(–0.288–0.525)	2.559(–12.5–23.94)	0.2002	0.18(–0.388–0.538)	6.58(–15.15–26.57)	0.3161

**Notes:** Bold indicates statistically significant associations,  $p < 0.05$ . The table summarizes raw values of and changes between week 0, week 48 and week 96. On the left side the table reports the medians (first quartile–third quartile) values at the three time-points for the variables of interest. On the right side the table reports three columns, one for each comparison (week 48 versus week 0, week 96 versus week 0). For each comparison the table reports three columns, one for the absolute difference between time-points (eg, week 0–48), another for the percentual median relative difference (MRD %) between time-points (eg,  $100 \times [\text{week 48 value} - \text{week 0 value}] / \text{week 0 value}$ ), and a third for the p-values coming from the paired Wilcoxon test between time-points (paired Wilcoxon test between week 48 and week 0). p-values  $< 0.05$  are highlighted in bold.

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLU, fasting glucose; Cr, creatinine; UA, uric acid; eGFR, estimated glomerular filtration rate; TC, Total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; TC/HDL-C, total cholesterol /high-density lipoprotein cholesterol.



**Figure 4** Metabolic profile during the follow-up. The bars show the median relative difference from week 0 for the considered metabolic parameters at both week 48 and week 96. The p-value shown under each bar comes from the paired Wilcoxon test between week 0 and the considered time-point; the p-value above between the week 48 bar and the week 96 bar comes from the paired Wilcoxon test between week 48 and week 96. Vertical lines show the 95% CI. **(A)** Changes in liver function and fasting glucose from week 0 to week 48 and 96 (week 0: n = 314; week 48: n = 288; week 96: n = 259). **(B)** Changes in renal function from week 0 to week 48 and 96 (week 0: n = 315; week 48: n = 287; week 96: n = 257). **(C)** Changes in lipids from week 0 to week 48 and 96 (week 0: n = 311; week 48: n = 283; week 96: n = 253).

**Note:** Bold indicates statistically significant associations, p<0.05.

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLU, fasting glucose; Cr, creatinine; UA, uric acid; eGFR, estimated glomerular filtration rate; TC, Total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; TC/HDL-C, total cholesterol /high-density lipoprotein cholesterol.

## Renal Function

No pronounced changes in urea were found over time (week 0–96:  $p=0.2011$ ). However, creatinine (Cr) elevated from 80.9 mg/dL (IQR 70.53–91.85) at week 0 to 85.2 mg/dL (IQR 78.65–94.45) at week 96 ( $p<0.0001$ ), with an MRD% (percentual median relative difference) of +4.887%. A similar trend was observed in uric acid (UA) which changed from 361  $\mu\text{mol/L}$  (IQR 307–421) at week 0 to 377  $\mu\text{mol/L}$  (IQR 329–435.5) at week 96 ( $p<0.0001$ ), with an MRD% of +4.884%. The median estimated glomerular filtration rate (eGFR) slightly decreased from 106.2 mL/min/1.73m<sup>2</sup> (IQR 92.58–117.7) at week 0 to 100.6 mL/min/1.73m<sup>2</sup> (IQR 89.1–110.3) at week 96 ( $p<0.0001$ ), with an MRD% of –5.445% (Table 2, Figure 4B). Notably, no significant changes were detected between week 48 and week 96 in terms of the indicators of renal function (UREA:  $p=0.3867$ , Cr:  $p=0.6374$ , UA:  $p=0.3630$ , eGFR:  $p=0.6716$ ) (Table 2, Figure 4B), suggesting that the renal function of PLWH reduced in the first year after switching and then remained relatively stable in the second year.

## Blood Lipids

Regarding lipid profile, no significant change was found in total cholesterol (TC) between week 48 and week 0 ( $p=0.7394$ ). Nonetheless, there was a mild median increase of 0.09 mmol/L in TC (MRD%=+2.062%,  $p=0.0456$ ) and 0.18 mmol/L in low-density lipoprotein cholesterol (LDL-C) (MRD%=+7.042%,  $p<0.0001$ ) at week 96 (Table 2, Figure 4C). PLWH experienced a significant 8.824% reduction in triglyceride (TG) at week 96 ( $p=0.0099$ ). There were no statistical changes in high-density lipoprotein cholesterol (HDL-C) ( $p=0.6979$ ) and TC/HDL-C ratio ( $p=0.1051$ ) at week 96. Median values and changes from week 0 were presented in Table 2.

Further analysis was performed to investigate the cause of the increase in TC and LDL-C. It was speculated that the rise in blood lipids could be attributed to the discontinuation of tenofovir disoproxil fumarate (TDF), considering the positive impact of TDF on lipid parameters. Thus, the individuals were divided into different groups based on their pre-switch and post-switch ART regimens. Group 1 consisted of individuals who switched from a TDF-containing regimen to a non-TDF regimen (201/319). Group 2 included those who switched from a TDF-containing regimen to another TDF-containing regimen (58/319). Group 3 comprised individuals who switched from a non-TDF regimen to another non-TDF regimen (55/319). Group 4, which had a small sample size (5/319), was excluded from the analyses.

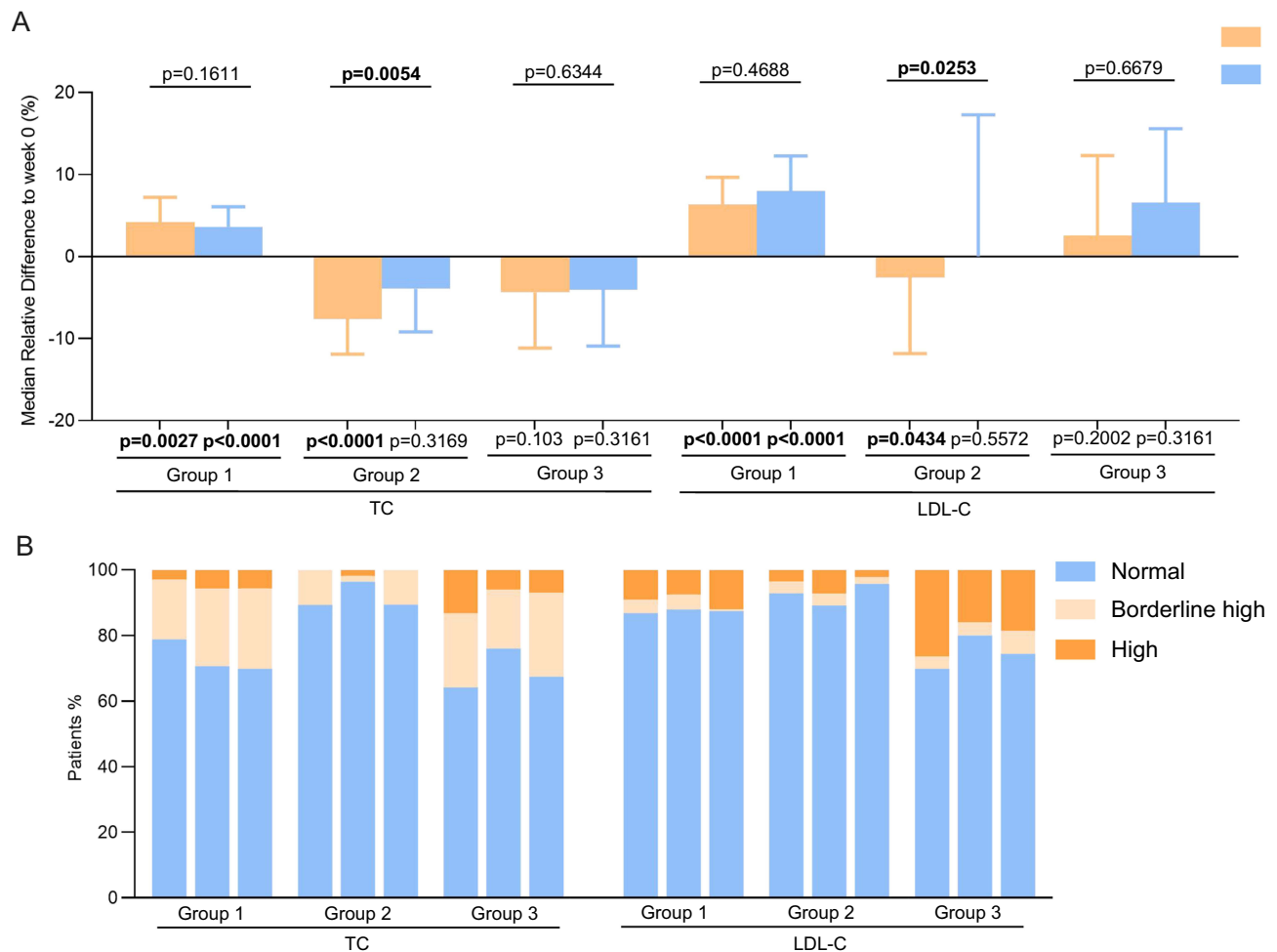
In Group 1, there was a significant increase in TC and LDL-C at week 96 (TC:  $p<0.0001$ ; LDL-C:  $p<0.0001$ ). Conversely, Group 2 showed a decrease in TC and LDL-C at week 48 (TC:  $p<0.0001$ ; LDL-C:  $p=0.0434$ ), but no significant change at week 96 (TC:  $p=0.3169$ ; LDL-C:  $p=0.5572$ ). Group 3 did not experience any significant changes in TC or LDL-C over time (TC:  $p=0.3161$ ; LDL-C:  $p=0.3161$ ) (Figure 5A). Furthermore, the severity grading of dyslipidemia indicated a mild increase in Group 1 and a decrease in both Group 2 and Group 3 (Figure 5B). Notably, Group 2 consistently maintained lower levels of TC and LDL-C compared to Group 1 and Group 3 throughout the observation period (Table 2).

## Discussion

The results of this retrospective, observational study supported the use of DTG-based regimens as effective maintenance therapies in virologically suppressed PLWH. DTG-based regimens provided long-lasting virological suppression and promoted immunological recovery. Furthermore, there was some improvement in metabolic changes.

In our study, PLWH had a long treatment history before transitioning to DTG-based regimens, with a median time since ART initiation of 3.83 years (IQR 2.17–6.67). It was worth noting that the majority of PLWH (53.61%) were compelled to switch drugs due to intolerable adverse reactions. Previous studies have reported that PLWH was plagued by severe EFV-related adverse events, particularly neurological toxicity and dyslipidemia.<sup>8,9</sup> Moreover, TDF was found to potentially cause renal impairment and reduce bone mineral density.<sup>10,11</sup> Gastrointestinal toxicity<sup>12</sup> and dyslipidemia, especially an increase in TC and TG,<sup>13</sup> were common side effects of Lopinavir/ritonavir (LPV/r). In our study, 182 individuals (57.05%) received EFV, 230 individuals (72.10%) received TDF, and 50 individuals (15.67%) received LPV/r in their pre-switch regimens. Overall, for most PLWH, the decision to switch drugs was made after experiencing serious adverse events, rather than for preventing severe side effects. It is crucial for PLWH, especially those at a high risk of





**Figure 5** The reason for the increase of TC and LDL-C. **(A)** Changes in TC and LDL-C from week 0 to week 48 and week 96 (Group 1, week 0: n=198; week 48: n=174; week 96: n=159; Group 2, week 0: n=56; week 48: n=55; week 96: n=47; Group 3: week 0: n=53; week 48: n=50; week 96: n=43). **(B)** Changes with non-missing fasting lipid data in TC and LDL-C from week 0 to week 48 and week 96 by the Chinese Guidelines for Lipid Management (2023).

**Note:** Bold indicates statistically significant associations,  $p < 0.05$ .

**Abbreviations:** TC, Total cholesterol; LDL-C, low-density lipoprotein.

diabetes, cardiovascular diseases, or other underlying diseases, to switch to drugs with effective viral suppression and rare severe side effects in a timely manner.

DTG showed high rates of virologic suppression in PLWH based on the PP analysis at week 48 and week 96, achieving a rate of virologic suppression close to 100%. Nonetheless, in the ITT analysis, the rate of virologic suppression at week 96 was 87.15% (278/319), with 39 PLWH missing virologic data. Consequently, the statistical power of the analyses involving week 96 was slightly reduced due to incomplete follow-up of all participants. Increasing the sample size or obtaining as much data as possible could enhance the statistical power of the analyses. Additionally, the CD4+ T cell count and CD4/CD8 ratio showed consistent improvement, as reported in other studies.<sup>14–16</sup> Overall, these findings suggested that switching to DTG-based regimens effectively maintains viral suppression and continuously improves the immunity of PLWH.

Consistent with previous studies,<sup>17</sup> the liver function of PLWH was beneficial, even though DTG was primarily metabolized by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and only a minor substrate for cytochrome P450 (P450) 3A4 (CYP3A4) in the liver.<sup>3,4</sup> This was partly explained by that DTG had no inhibition or induction of the UGT1A1 and CYP enzymes at clinically relevant concentrations.<sup>3</sup> However, clinical trials excluded PLWH with severe hepatic impairment. Therefore, further research is needed to investigate the potential liver toxicity of DTG in PLWH with severe hepatic impairment.

Despite renal excretion of DTG being negligible,<sup>3,18</sup> a slight decrease in renal function at week 48 was observed in our study, with overall stability from week 48–96. In fact, early investigations revealed that DTG mediated a modest, non-progressive increase in Cr by inhibiting organic cation transporter (OCT) 2, resulting in a reduction in tubular secretion of Cr without affecting actual eGFR.<sup>3,19</sup> However, in our data, glomerular filtration rate (eGFR) was estimated by serum Cr. Therefore, serum Cr-based estimated GFR (eGFR<sub>Cr</sub>) of PLWH received DTG could be lower than actual eGFR. Serum Cystatin C is another marker for estimation of GFR (eGFR<sub>CysC</sub>). Produced by nucleated cells at a constant rate, Cystatin C is freely filtered without tubular secretion or reabsorption and catabolized in the proximal tubule. Therefore, it is more reliable to use Cystatin C levels for assessing glomerular filtration rate (eGFR<sub>CysC</sub>) than merely serum Cr when evaluating renal function (eGFR<sub>Cr</sub>) in DTG-treatment PLWH.<sup>20,21</sup> Thus, it is necessary to regularly monitor Cystatin C levels and combine more renal biomarkers, such as microalbumin and  $\beta$ 2-microglobulin in urine to accurately assess renal function.

Data from the EuroSIDA study revealed that cardiovascular events accounted for approximately one-third of non-AIDS-defining events.<sup>22</sup> Atherogenic dyslipidemia (elevated TC and decreased HDL-C), recognized as a risk factor for cardiovascular disease, was found to be the most common pattern of lipid abnormalities in PLWH.<sup>23,24</sup> This dyslipidemia has become an important factor affecting the prognosis and quality of life of PLWH.<sup>25,26</sup> Previous studies demonstrated a favorable lipid profile among treatment-experienced PLWH switching to DTG-2DR and DTG-3DR, or at least no detrimental effects.<sup>27–31</sup> The TANGO trial,<sup>14</sup> a large clinical study on treatment simplification, showed that switching from triple TAF-based regimens to DTG+3TC brought about declines of 4.5% in TC, 5.5% in LDL-C, and 11.2% in TG. While the SALSA study<sup>15</sup> found that the lipid profile remained generally unchanged from baseline. In the case of DTG-3DR, the NEAT022 study showed that TC and other lipid fractions (except HDL-C) prominently improved after switching from a boosted PI-based regimen to a DTG-based regimen.<sup>16</sup> Consistent with the results of the NEAT022 study, the CHARACTERISE study also reported a slightly improved lipid profile.<sup>31</sup> However, our study observed an increase in the proatherogenic lipid fractions (TC and LDL-C), despite a significant improvement in TG. This variation could be partly explained by the high proportion of individuals (63.01%, 201/319) switching away from TDF-containing regimens, considering the previously described metabolic effects of TDF.<sup>32,33</sup> As expected, further analysis confirmed that the increase in TC and LDL-C was related to the withdrawal of TDF. Thus, it appears necessary to closely monitor lipid parameters in PLWH who switch away from TDF-containing regimens.

Our study had several limitations. Firstly, it was a single-center study and potential bias existed in our population of PLWH. Secondly, this study was a retrospective study with some pertinent data missing. And we did not have detailed ART adherence information. Finally, we only collected routine laboratory data, with bone density measures and urine protein biomarkers not included in our study.

## Conclusion

The primary reason for PLWH to switch ART regimens was adverse reactions. After switching to DTG-based regimens, HIV viral suppression was consistently maintained and the parameters of immunity and metabolism were partly improved. These findings reinforce the reliability of DTG-based regimens as an effective switching strategy for PLW. DTG-based treatments prove to be successful options for individuals who are virologically suppressed and may potentially improve patient adherence. There's a need to enhance doctor-patient communication to help patients in selecting more effective treatments in a timely manner.

## Ethical Approval

This study was approved by the Committee of Ethics at Beijing Ditan Hospital, Capital Medical University, Beijing, China (No. 2021-22-01). Written informed consent was obtained from all participants before study initiation. The study complied with the Declaration of Helsinki.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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