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Brief communication: efficacy and safety of the dolutegravir/lamivudine dual therapy in antiretroviral treatment-experienced Chinese people living with HIV

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Abstract

This study aimed to evaluate the efficacy and safety of dolutegravir plus lamivudine (DTG/3TC) in antiretroviral treatment (ART)-experienced people living with HIV (PLWH). A total of 303 PLWH in Shanghai, China, who switched from triple ART to DTG/3TC between January 2019 and June 2022, with a minimum ART duration of 6 months, were retrospectively enrolled. More than 95% of PLWH maintained viral suppression with no significant changes in CD4 counts 12 months after switching. Patients transitioning from non-tenofovir (TDF)-based regimens demonstrated more pronounced improvements in lipid profiles, while those previously on TDF-based regimens showed greater enhancements in bone metabolism.

Keywords HIV, Dolutegravir, Lamivudine, Antiretroviral

Introduction

The efficacy and safety of the two-drug combination of dolutegravir (DTG) and lamivudine (3TC) have been assessed in both treatment-naïve and treatment-experienced people living with human immunodeficiency virus (HIV) (PLWH) [1–4]. The dual regimen of DTG/3TC is recommended by multiple guidelines for treatment-experienced PLWH [5–7]. Since 2003, the implementation of the National Free Antiretroviral Therapy Program has led to the provision of free antiretroviral therapy (ART) regimens to a majority of PLWH in China. These regimens mainly consist of tenofovir (TDF) or zidovudine (AZT) + 3TC + efavirenz (EFV) or nevirapine (NVP) or lopinavir/ritonavir (LPV/r), which were recommended as first-line and alternative ART regimens in China's national guidelines for HIV treatment [8]. However, during the course of ART, these patients have experienced a variety of drug-related adverse events, such as dyslipidemia, hepatotoxicity, osteotoxicity, nephrotoxicity, and neuropsychiatric symptoms.

In recent years, Chinese guidelines have also recommended the use of DTG/3TC dual therapy for the treatment of HIV infection [9]. To optimize or simplify ART, an increasing number of treatment-experienced patients in China have transitioned to DTG/3TC. This study aims to assess the efficacy and safety of DTG/3TC in ART-experienced Chinese PLWH.

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Methods

Study design and participants

We conducted a retrospective cohort study at Shanghai Public Health Clinical Center (SPHCC), a designated hospital providing the ART and long-term follow-up for PLWH in Shanghai, China. The study enrolled ART-experienced adult PLWH who had received previous ART for at least 6 months, without a history of treatment failure or prior HIV drug resistance, and who switched to DTG/3TC between January 2019 and June 2022. Among the 640 patients who switched to DTG/3TC, 303 were ultimately enrolled. A total of 337 patients were excluded for various reasons including previous ART duration < 6 months (n = 36), switching to another ART regimen within one year of starting DTG/3TC (n = 7), being on DTG/3TC for less than one year (n = 120), baseline HIV-RNA > 50 copies/mL (n = 1), the follow-up data was missing (n = 160), previous regimen other than two nucleoside reverse transcriptase inhibitors (NRTIs) with one protease inhibitor (PI) or one nonnucleoside reverse transcriptase inhibitor (NNRTI) or one integrase inhibitor (INSTI) (n = 13).

Outcome definitions and measures

Efficacy measures included the proportion of participants with virological suppression, which was defined as HIV-1 RNA level < 50 copies/mL, and the change in CD4 counts after 12 months of regimen switch. Safety indicators primarily include serum lipid, bone, and kidney metabolic markers from baseline to 12 months after regimen switch.

PLWH on ART at SPHCC were routinely followed-up every 3 months. CD4 counts were measured every 6 months by the flow cytometry using a BD FACS Canto II flow cytometry system (BD Multitest™ CD3/CD8/CD45/CD4, BD Biosciences), and plasma HIV-1 RNA levels were measured every year using RT-PCR (COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0, ABI7500). Blood biochemical tests are performed every 3 months.

Statistical analysis

Efficacy and safety outcomes were compared among enrolled patients before and after 12 months of regimen switch. In addition, subgroup analyses were performed based on prior ART regimens.

Data were analyzed using SPSS 24.0 (IBM Corp., Armonk, NY). Continuous variables were described as median (inter-quartile range, IQR), and compared using Mann–Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square (x^2) test or Fisher exact test. All tests were two tailed, and $p < 0.05$ is considered significant.

Table 1 Baseline demographics and laboratory characteristics of enrolled patients

Characteristics	n = 303
Gender, n (%)	
Male	293 (96.7)
Female	10 (3.3)
Age, year	
M (IQR)	40 (34–49)
Range	22–85
Prior duration of ART, year	
M (IQR)	4.4 (2.7–7.3)
Range	0.5–15
Prior ART regimen, n (%)	
Backbone agents	
Tenofovir	157 (51.8)
Zidovudine	80 (26.4)
Abacavir	47 (15.5)
Tenofovir alafenamide	19 (6.3)
Core agents	
INSTIs	128 (42.2)
NNRTIs	150 (49.5)
PIs	25 (8.3)
Reasons for switching, n (%)	
Simplification	152 (50.2)
Antiretroviral-related toxicities	142 (46.9)
Dyslipidaemia	77 (25.4)
Renal toxicity	28 (9.2)
Central nervous system adverse events	17 (5.6)
Osteotoxicity	10 (3.3)
Liver toxicity	6 (2.0)
Lipoatrophy	4 (1.3)
Other	9 (3.0)
CD4 counts, cells/μL (n = 158)	
M (IQR)	514 (375–759)
Range	106–1213
CD4/CD8 ratio	
M (IQR)	0.64 (0.42–0.89)
HIV-RNA, n (%)	
< 50 copies/mL	77 (25.4)
Unknown at baseline	226 (74.6)
< 50 copies/mL within one year prior to ART switch	177 (58.4)
≥ 50 copies/mL within one year prior to ART switch	5 (1.7)

M(IQR) median (interquartile range), *ART* antiretroviral therapy, *INSTIs* integrase inhibitors, *NNRTIs* nonnucleoside reverse transcriptase inhibitors, *PIs* protease inhibitors

Results

Baseline patient characteristics

The baseline characteristics of 303 enrolled PLWH at the time of switching regimens are detailed in Table 1.

Efficacy

HIV-RNA levels were measured at different follow-up visits. Sustained virological suppression was achieved in 96.7% (58/60), 97.5% (78/80), 95.9% (71/74) and 100% (85/85) of patients at 3, 6, 9, and 12 months after switching to DTG/3TC, respectively. Among those patients who did not achieve virological suppression, HIV-RNA were detected at low levels, 123 copies/mL and 496 copies/mL at month 3, 56 copies/mL and 67 copies/mL at month 6, and 284 copies/mL, 72 copies/mL and 96 copies/mL at month 9.

There were no significant changes in CD4 counts following the regimen switch, with a median change of 42 cells/μL (IQR, −63 to 91 cells/μL, $p=0.582$) at month 6 and 44 cells/μL at month 12 (IQR, −47 to106 cells/μL, $p=0.575$), respectively.

Safety

We compared the changes in serum lipid levels from baseline to 12 months after regimen switch in 239 patients with available data. The serum levels of total cholesterol (TC) ($p=0.289$), triglycerides (TG) ($p=0.373$), and high-density lipoprotein cholesterol (HDL-C) ($p=0.305$) did not change significantly. However, a significant elevation of low-density lipoprotein cholesterol (LDL-C) ($p<0.001$) was observed. See Fig. 1.

Subgroup analyses were further performed based on prior ART regimens, comparing the TDF-based group (n = 131) with the non-TDF-based group (n = 108), as well as the DTG-based group (n = 88) with the EFV-based group (n = 104). Changes in serum levels of TC ($p<0.001$), TG ($p<0.001$) and HDL-C ($p=0.001$) exhibited significant disparities between the non-TDF-based and TDF-based regimens, with a decrease in the former and an increase in the latter, respectively. LDL-C levels were similarly elevated in both TDF-based and non-TDF-based groups ($p=0.711$). There were no significant differences in the changes of TC ($p=0.370$), HDL-C ($p=0.313$) and LDL-C ($p=0.247$) levels between the DTG-based and the EFV-based groups. However, the DTG-based

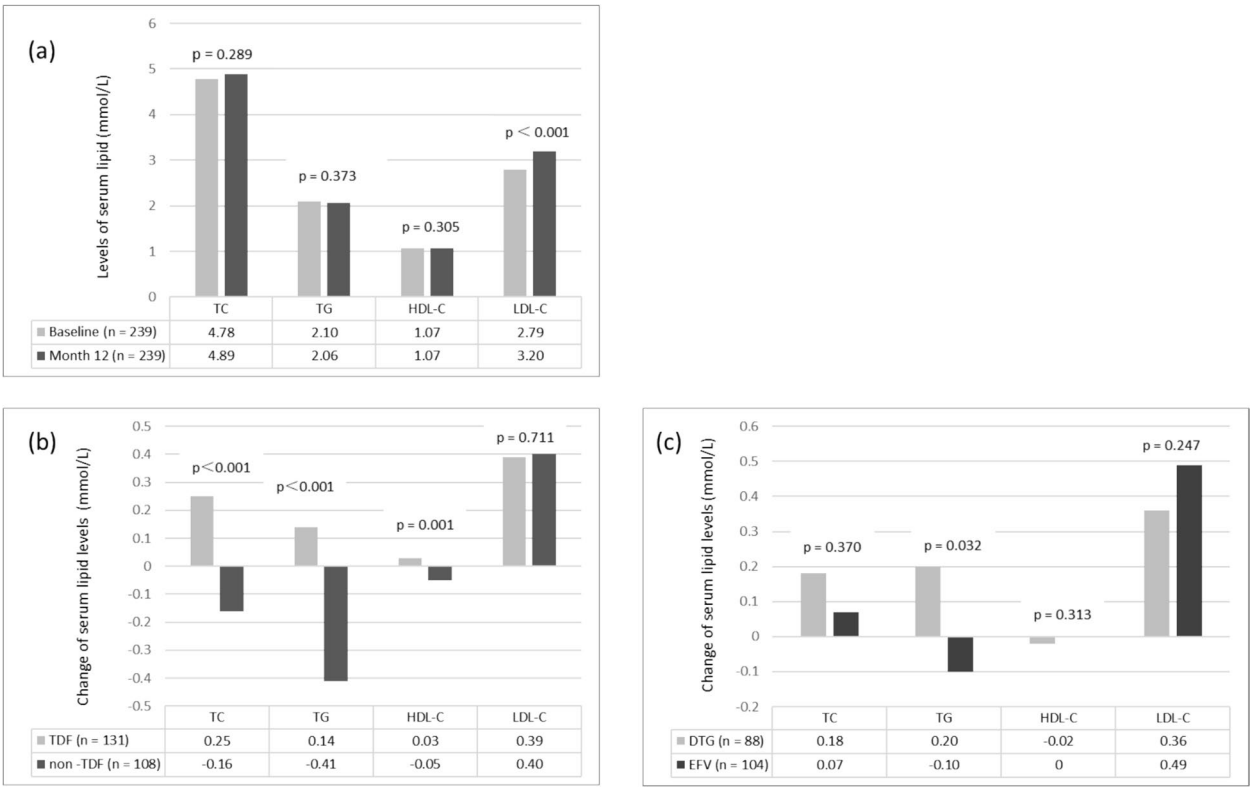

Fig. 1 Changes in serum lipid profiles. Comparison of serum lipid levels before and 12 months after switching to dolutegravir/lamivudine (DTG/3TC) (**a**). Comparison of changes in serum lipid profiles between individuals prior on tenofovir (TDF)-based and non-TDF-based regimens (**b**), as well as those previously exposed to efavirenz (EFV) and DTG regimens (**c**). *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol

group exhibited an increase while the EFV-based group showed a decrease in TG levels following switch to DTG/3TC ($p=0.032$). See Fig. 1.

The changes in serum levels of kidney and bone metabolic markers from baseline to month 12 following the switch were evaluated in 245 participants with available data. Serum creatinine levels increased from 80.9 μmol/L (IQR: 67.7–90.8) to 87.7 μmol/L (IQR:77.09–96.5) ($p<0.001$). The estimated glomerular filtration rate (eGFR, mL/min*1.73m^2) decreased from 97.8 (IQR:84.30–117.60) to 89.1 (IQR:77.40–101.10) ($p<0.001$). No significant changes were observed in the serum levels of cystatin C (0.70 mg/L vs. 0.68 mg/L, $p=0.239$). Alkaline phosphatase (ALP), a bone metabolic marker, showed a significant decrease from 89 U/L (IQR:74–106) to 72 U/L (IQR: 61–89) ($p<0.001$). Subgroup analyses were conducted based on previous ART regimens, comparing the TDF-based group (n = 133) with the non-TDF-based group (n = 112). ALP exhibited a more pronounced decrease in the TDF-based group compared to the non-TDF based group (−20 U/L vs. −12.5 U/L, $p<0.001$).

Discussion

To maintain viral suppression while preserving potential treatment options for future use is the primary principle of ART optimization [6]. This study found that the majority of PLWH maintained viral suppression after transitioning from triple ART to DTG/3TC dual therapy. A small number of participants experienced minor fluctuations in viral load, emphasizing the critical importance of closely monitoring viral load levels and providing patient education on improving medication adherence. Stable immunological levels were observed post-switch, possibly due to the PLWH included in this study having potentially reached a state of immune reconstitution plateau after a median duration of 4.4 years on ART.

PLWH had a higher cardiovascular diseases (CVD) risk than the general population [10]. The prevalence of dyslipidemia, a significant risk factor for CVD, is high among PLWH and increases after ART, mainly with elevated TG and low HDL-C, primarily due to specific classes of antiretroviral drugs: NRTIs, NNRTIs, and PIs [11, 12]. Different antiretroviral drugs exert differential effects on lipid profiles. In this study, dyslipidaemia was the most common reasons for switching to 3TC/DTG among antiretroviral-related adverse events. Overall lipid levels did not show significant changes after transitioning to DTG/3TC, except for an increase in LDL-C. However, subgroup analysis showed that switching to DTG/3TC lowered triglyceride levels for those not on TDF-based regimens, but raised them for those previously on TDF-containing ART, possibly due to the lipid-lowering effect of TDF [13]. The similar change of lipid profile was also observed in other study, showing that the increase in triglyceride and LDL-C was associated with the withdrawal of TDF [14]. Subgroup analysis revealed similar changes in TC, HDL-C, and LDL-C levels between the previous DTG-based and EFV-based groups. However, an increase in TG levels was observed in the former group while a decrease was noted in the latter, which may also be attributed to the lipid-lowering effect of TDF. Integrase inhibitors were known to have minimal impact on lipid profiles. One study showed that individuals with dyslipidemia experienced improved lipid profiles after transitioning from EFV to DTG [15].

We observed an increase in serum creatinine levels and a decrease in eGFR after switch, consistent with the known impact of DTG on tubular secretion of creatinine [16]. In contrast, there were no significant changes in levels of Cystatin C, a protein that is not cleared by tubular secretion. It has been suggested to be used in combination with creatinine to more accurately evaluate the glomerular renal function in PLWH receiving ART [17]. Elevated ALP levels are recognized as a serum biomarker for metabolic bone disease [18]. Our study found that ALP levels decreased more in the TDF-based group than in the non-TDF-based group, suggesting that switching to DTG/3TC may help improve bone metabolism in patients on TDF-based regimens.

The limitations of this study include its retrospective design, the relatively small sample size of the cohort, incomplete evaluation indicators for safety and effectiveness, as well as missing follow-up data.

Conclusions

The study supports the use of DTG/3TC as a switch option for treatment-experienced PLWH. After transitioning, individuals maintained virological suppression and stable immunological levels. Patients on non-TDF-based regimens had better lipid profiles, while those on TDF-based regimens had improved bone metabolism.

Abbreviations

DTG	Dolutegravir
3TC	Lamivudine
HIV	Human immunodeficiency Virus
ART	Antiretroviral therapy
PLWH	People living with HIV
TDF	Tenofovir
EFV	Efavirenz
NVP	Nevirapine
LPV/r	Lopinavir/ritonavir
AZT	Zidovudine
NRTIs	Nucleoside reverse transcriptase inhibitors
PI	Protease inhibitor
NNRTI	Nonnucleoside reverse transcriptase inhibitor
INSTI	Integrase inhibitor
CD4	Clustered Differentiation
IQR	Inter-quartile range
TC	Total cholesterol

TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
eGFR	Estimated glomerular filtration rate
ALP	Alkaline phosphatase
CVD	Cardiovascular diseases

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Author contributions
ZRF and LL contributed to the study conception and design. Patient enrollment and data collection were performed by WZY, YJY, WL, WJR, SYZ, CJ, QTK, SJJ, SW, TY, XSB. Analysis was performed by WZY. The first draft of the manuscript was written by WZY. All authors read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Ethics Committee of SPHCC (2020-S197-02). Informed consent was waived for data collected retrospectively.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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