Evaluation of the Efficacy and Tolerability of Dolutegravir Plus Lamivudine as a Switch Strategy in Treatment-experienced HIV-infected Patients

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Abstract

Background: Dual therapy containing dolutegravir (DTG) plus lamivudine (3TC) is a reasonable alternative antiretroviral therapy (ART) option in treatment-experienced patients, which could prevent long-term toxicity and reduce treatment cost. But so far, the effectiveness as safety data of this two-drug regimen is still limited.

Methods: This observational study included treatment-experienced HIV-infected patients who switched to a dual regimen containing DTG (50mg/QD) plus 3TC (300mg/QD). Efficacy (HIV RNA <50 copies/mL), safety, and metabolic changes based on laboratory and clinical findings at 48 weeks were analyzed.

Results: A total of 33 patients were included, who switched for the following reasons: treatment failure in 5 /33patients (15.2%), simplification in 10 patients (30.3%), and drug toxicity in 18 patients (54.5%). The patients were treated with ART for a median of 2.1 years (interquartile range = 1.0-4.2) before drug switching, and 28/33(84.8%) patients were virologically suppressed at baseline. After switching to DTG plus 3TC, all 33 patients (100%) showed HIV RNA <50 copies/mL after 48 weeks, and the CD4+ cell count was significantly increased (+82 cell/mm³, p=0.0071). We observed a significant increase in LDL-C (+0.77mg/dL, p<0.0001) after switch, however, triglycerides (-0.6mg/dL, p=0.0179) and cholesterol/HDL-C ratio (-0.327, p=0.0366) were found significantly decreased. A significant decrease in eGFR was also observed (-17.8 ml/min, p=0.0047). No patient discontinued due to adverse events.

Conclusions: The use of dual therapy containing DTG and 3TC is effective and well-tolerated in treatment-experienced patients under any prior ART, without significant adverse drug reaction.

Background

Advances in antiretroviral therapy (ART) have transformed HIV infection into a manageable chronic disease, which could significantly reduce HIV-associated morbidity and mortality[1]. The current ART regimen could effectively suppress the viral replication in nearly all treated patients and led to dramatic improvements in recovery of immune function, decreasing the risk of HIV transmission, and improvement in health-related quality of life of HIV-infected persons[2]. However, until now HIV cure remains elusive and a life-time treatment of ART is required for the patients. The challenges of such lifelong ART include long-term drug-related side effects, reduced medication adherence, and high costs[3].

ART has been associated with a standard three-drug regimen including two nucleoside reverse transcriptase inhibitors (NRTIs) and one other drug from either the non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase strand transfer inhibitor (INSTI) classes. In order to achieve and maintain viral suppression while reducing cumulative drug toxicities and cost, and improve long-term drug adherence and convenience, strategies with less than triple therapy have been explored including dual therapy and monotherapy using the newest potent antiretrovirals [4], and several coformulations have also been developed to make into once-daily single-tablet regimen.

As a second-generation of INSTI, dolutegravir (DTG) has been proved with highly effective virological suppression, minimal drug-drug interaction risk and a high genetic barrier to resistance in combination ART [5–7], and several studies have investigated the efficacy of DTG-based dual therapies. The combination of DTG with 3TC has been proved in several other studies with rapid and sustained virological suppression in ART-naïve patients [8, 9]. Besides, the combination of DTG and 3TC could be made into a single pill, which is more convenient and tolerated to support long-term adherence.

To our knowledge, the evidence of the applicability of the two-drug regimen of DTG plus 3TC is still insufficient, especially in patients with known or suspected resistance to the INSTI class or 3TC. Second, the side effects of DTG in this two-drug regimen, such as its impact on blood lipids, weight and liver function, are still worthy of our attention. Moreover, little is known about the performance of DTG plus 3TC in treatment-experienced patients in China. Therefore, we performed a prospective observational study of dual therapy of DTG plus 3TC as a switch strategy in treatment-experienced HIV infected patients from a tertiary hospital in Beijing, China. The main objectives of this study are to evaluate the virological efficacy, safety and tolerability of DTG plus 3TC for a follow-up period of 48 weeks. The drug-related adverse events, the impact on lab parameters and the influence of M184V/I mutation have also been evaluated.

Methods

Study design and population

We conducted a prospective study of HIV infected outpatients in a real-life clinical practice between *September 2016* and *May 2019* at the Center for Infectious Diseases of Beijing Youan Hospital, Capital Medical University in Beijing, China. This center is one of the most important HIV/AIDS health care centers in China, where more than 9000 HIV-infected patients on ART are followed regularly.

The Participants were included if they were HIV infected adults aged ≥ 18 years, negative for HbsAg, and begin or switched to a two-drug regimen of DTG 50 mg and 3TC 300 mg once daily. Participants were excluded if they were pregnant or breastfeeding, incapable of providing informed consent, and a history of adverse reactions to either of the two drugs. All patients were followed until they completed 48 weeks of treatment or discontinued. DTG plus 3TC was prescribed by attending physicians after obtaining the written informed consent from each participant.

The study was approved by the Clinical Research Ethics Committee of the Beijing Youan Hospital (LL-2019-038-K) in accordance with the tenets of the Declaration of Helsinki. All subjects provided written informed consent before the initiation of study procedures.

Assessments And Procedures

Patients in the present study were followed for 48 weeks after drug change. At baseline (before drug switch), the demographic and clinical characteristics were recorded, including age, sex, active co-infections, date of HIV diagnosis and ART initiation, previous ART lines, and reason for drug switch.

Laboratory data were also recorded at baseline and in follow-up visits at 48 weeks after the drug change including HIV viral load (VL), CD4 + cell counts, serum levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, liver enzymes and total bilirubin, serum creatinine and estimated glomerular filtration rate [eGFR], serum glucose, and complete blood cell count. eGFR was calculated according to the Modification of Diet in Renal Disease equation[10, 11].

The primary endpoint/outcome of the cohort was to assess the virological efficacy of DTG plus 3TC, defined as the proportion of patients with HIV RNA (viral loads, VL) < 50 copies/ml at 48 weeks after drug switching.

Patients with a VL > 50 copies/mL at 2 consecutive determinations after 24 weeks as well as those who discontinued the DTG plus 3TC regimen for any reason prior to week 48 were considered as virological failures. The secondary outcomes include the assessment of adverse events, tolerability, and changes in immunological and metabolic profiles.

Resistance Analyses

In this study, the baseline drug resistance before switch was assessed from both historical genotypes and retrospective proviral archive DNA genotyping from whole blood. The historical genotypic data were derived from Sanger sequencing of plasma HIV RNA tested during the ART period of the patients before the drug switch.

To probe for drug resistance in the viral archive of these virologically suppressed participants, HIV proviral DNA was retrospectively analyzed from baseline whole-blood samples using the fluorescent dideoxy-terminator method and the ABI Prism 3100 genetic analyzer (Applied Biosystem, CA, USA). Drug resistance genotyping was analyzed according to the most recent mutation list [12]. Viruses exhibiting either possible resistance or full resistance to a drug were considered to be resistant.

Statistical Analysis

The continuous variables were expressed as means $\pm$ standard deviations or medians (quantile: 1/4–3/4) depending on their distribution within the cohort, whereas the qualitative variables were expressed as frequencies or percentages. A paired *t*-test or the Wilcoxon test was used to identify significant changes in the parameters at baseline and 48 weeks after drug change. All data from enrolled patients were analyzed statistically using IBM SPSS Statistics 19 (SPSS Inc. Chicago, USA).

Results

Study Population

Overall, 33 patients were recruited in this study who switched from their conventional ART to DTG plus 3TC. The baseline characteristics are summarized in Table 1. 87.9% (29/33) of the patients were male, with a median age of 42 years (IQR: 37–55). Comorbid conditions included hyperlipidemia (40%), hypertension (35%), diabetes mellitus (9%), and cardiovascular disease (6%). The median duration of HIV infection was 3.08 years (IQR: 2.35–4.87), and the median of 2.13 years under ART (IQR: 1.05–4.23). 28 patients (84.8%) had baseline VL < 50 copies/ml, while median time of virological suppression was 21.0 months (IQR 15.3–35.7). 5 (15.2%) had experienced virological failure prior to drug switch.

Table 1
Baseline characteristics of the 33 patients enrolled in the study.

Characteristic	Value
Male, n (%)	29 (87.9)
Age (years), median (IQR)	42 (37–55)
Mode of HIV transmission, n(%)	
heterosexual	2(6.1)
MSM	30(90.9)
IVDU	1(3.0)
Duration of HIV infection (years)	3.08(2.35–4.87)
Nadir CD4 + cell count (cells/mm3)	
Baseline CD4 + cell count (cells/mm3)	515(363–595)
Duration of ART (years)	2.13(1.05–4.23)
Duration of plasma HIV RNA < 50 copies/ml (months)	21.0(15.3–35.7)
Duration of current ARV therapy (months)	7.9(5.7–17.2)
Pre-switch therapy, n (%)	
2 NRTIs + PI/r	3(9.1)
2 NRTIs + NNRTI	7(21.2)
2 NRTIs + INI	14(42.4)
NRTI + PI/r	8(24.2)
INI + PI/r	1(3.0)
Reasons for drug switch	
Treatment simplification	10(30.3)
Virological failure	5(15.2)
Toxicity	
Renal toxicity	7(21.2)
Liver toxicity	0(0)
Dyslipidemia	7(21.2)
Gastrointestinal toxicity	4(12.1)
Osteoporosis	1(3.0)

Characteristic	Value
Other	1(3.0)

Most patients (24/33) were taking a standard triple-drug regimen at the time of switching as the following: 7 patients with 2NRTIs + NNRTI (21.2%), 14 with 2NRTIs + INSTI (42.4%), and 3 with 2NRTIs + PI (9.1%). The most frequent combination of NRTI was tenofovir plus 3TC (16/33), and the third drug was mainly DTG (12/33), followed by efavirenz (6/33). Nine patients were already treated on a dual ART with 3TC + lopinavir/ritonavir (LPV/r) (8/33, 24.2%) and LPV/r + raltegravir (1/33, 3.0%). Previous exposure to INSTI was documented in 15(45.5%) of individuals.

The main reasons for changing to DTG + 3TC regimen were treatment failure for 5 patients (15.2%), simplification for 10 patients (30.3%), and drug toxicity of the previous regimen for 18 patients (54.5%). These drug toxicity with current ART included 6 patients with dyslipidemia, 1 patient with decreased bone density, 6 patients with renal toxicity, 4 patients with gastrointestinal toxicity, and 1 patient with other toxicities.

Drug Resistance

Historical genotypes were assessed from 78.8% (26/33) of the participants, and proviral genotypes using baseline HIV proviral DNA were obtained from 54.5% (18/33) of the enrolled patients. 42.4% (14/33) of the participants had both historical and proviral genotypes. Altogether, cumulative baseline resistance data (historical and/or proviral) were available for 90.9% (30/33) of the patients.

According to the accumulated drug-resistant mutations analysis, pre-existing primary NRTI resistance (-R), NNRTI-R, and PI-R mutations were observed in 18.2% (6/33), 36.4% (12/33), and 3.0% (1/33), respectively. Of note, the M184V/I resistance mutation to lamivudine was present in 18.2% (6/33) participants. 2 of the 6 patients didn't have virological suppression at baseline.

Efficacy In Virological Suppression

For the 5 patients without virologic suppression at baseline, the VL was undetectable at 12 weeks after switching for 4 patients and at 24 weeks for 1 patient, and the VL remained undetectable until the end of the follow-up period after 48 weeks. For the 28 virologically suppressed patients who changed medication for adverse drug reaction or drug simplification, viral suppression was well maintained below 50 copies/ml during follow-up. The proportion of suppressed patients who maintained undetectable VL at week 48 was 28/28 (100%; 95% CI = 88.4–100.0).

The median CD4 + count was 543 cells/ μ L (IQR 363–595) at baseline, and it significantly increased to 625 cells/ μ L (IQR 455–651) at 48 weeks from baseline ($p = 0.0017$). For the 6 patients with M184V/I resistance at baseline, the VL maintained suppressed at 48 weeks.

Safety And Tolerability

The laboratory parameters were analyzed for lipid profile, renal function, liver function, and complete blood cell counts before and after the regimen change. The impact of DTG plus 3TC in laboratory parameters at 48 weeks is shown in Table 2. During the 48-week follow-up, an increase in median LDL-cholesterol levels (+ 0.77 mg/dL, $p < 0.0001$) and a slight decrease in median triglyceride levels (-0.6 mg/dL, $p = 0.0179$) and the total cholesterol/HDL-cholesterol ratio (-0.327, $p = 0.0366$) were observed in the lipid profile, but the median changes in serum concentration of total cholesterol and HDL-cholesterol were not statistically significant (Table 2). For the patients who switched to DTG plus 3TC because of dyslipidemia ($n = 7$), a significant decrease in total cholesterol and total triglycerides were observed at 48 weeks of -1.6 and - 1.3 mg/dL, respectively ($p = 0.0039$; $p = 0.0040$) (Table 3).

Table 2
Analytical changes between baseline and 48 weeks of all patients.

Parameter	Baseline	IQR	48 weeks after	IQR	P value
Lipid profile					
Cholesterol (mg/dL)	4.6	4.073–6.775	4.74	3.865–5.308	0.1987
HDL-C (mg/dL)	0.96	0.89–1.19	1.06	0.9–1.19	0.3333
LDL-C (mg/dL)	2.35	1.8–3.08	3.12	2.74–3.87	< 0.0001
Triglycerides (mg/dL)	2.21	1.27–4.37	1.61	1.2–2.22	0.0179
TC: HDL-C	5.022	4.133–6.395	4.695	3.55–5.35	0.0366
Renal profile					
Creatinine (mg/dL)	71.6	60.2–77.3	86.8	75–97	0.0034
eGFR (mL/min/1.73 m ²)	106.4	78.16–118.2	88.6	75.71–107.9	0.0047
Liver function					
ALT, UI/L	20.4	13.9–34.1	21.7	14.9–37.4	0.5607
AST, UI/L	22	16.5–26.9	20.7	18.4–24.7	0.6889
Bilirubin, mg/dL	14.7	10.9–20.2	13.2	10.7–16.6	0.5503
Other tests					
Body weight (kg)	69.2	62.5–75.3	70.5	65.0–78.8	0.3214
Glucose, mg/dL	5.3	4.98–6.18	4.95	4.69–5.52	0.1888
Platelet count (*10 ³ /mL)	230	193–269.5	216	194.5–260.5	0.7141

Table 3
Analytical changes between baseline and 48 weeks of patients with drug toxicity at baseline.

Patients with laboratory abnormality	Parameter	Baseline	IQR	Week 48	IQR	P value
Renal toxicity	Creatinine (mg/dL)	113.2	106.5-122.6	96.1	94.3-117.1	0.013
	eGFR (mL/min/1.73 m ²)	77.4	67.8-83.3	87.1	84.2-90.9	0.039
Dyslipidemia	TC (mg/dL)	6.8	6.3-8.2	5.2	4.6-5.9	0.003
	HDL-C (mg/dL)	1.3	1.2-1.6	1.2	0.9-1.5	0.734
	LDL-C (mg/dL)	3.7	3.4-4.2	3.9	3.1-4.6	0.438
	TG (mg/dL)	3.4	2.4-13.8	2.1	1.5-3.3	0.004

The change to dual therapy also resulted in a significant increase in the median value of serum creatinine (+ 15.2 mg/dL, $p = 0.0034$), and a significant decrease in the mean eGFR value (-17.8 mL/min/1.73 m², $p = 0.0047$) (Table 2). The analysis of patients who switched to DTG plus 3TC because of renal toxicity ($n = 7$) showed a trend toward a decrease in creatine (-17.1 mg/dL, $p = 0.013$) and an increase in eGFR (+ 9.7 mL/min/1.73 m², $p = 0.039$) at 48 weeks.(Table 3)

As shown in Table 2, no significant change was found in body weight before and after drug change. Regarding liver function tests, no significant changes were observed in ALT, AST, and total bilirubin levels. There was also no significant adverse reaction observed when comparing the complete blood count and serum glucose at the time of drug change and the last follow-up after the drug change. No patient experienced serious adverse effects, AIDS-related events or died during the follow-up period. None of the enrolled participants discontinued study treatment due to adverse events.

Discussion

Our study reports the observational data on the effectiveness and safety of DTG plus 3TC dual therapy in a cohort of heavily treatment-experienced HIV patients. After 48 weeks of follow-up, all the enrolled patients achieved and maintained viral suppression, including 5 patients with previously nonsuppressed VL. The good efficacy was also observed in 6 patients with the presence of the M184V/I resistance mutation to 3TC. No participants discontinued because of intolerance with no serious adverse event was detected. The results of this study confirmed the efficacy and safety of DTG plus 3TC dual therapy in daily clinical practice, which could be a suitable option for patients who had extensive experience with ART, including those with multiple resistance mutations.

DTG in combination with 3TC has been chosen and evaluated as a two-drug regimen due to favorable characteristics of both drugs. The antiretroviral activity of 3TC against HIV is well established as a key component of antiretroviral regimens since its approval in 1995[13]. As a next-generation INSTI class, DTG is the most powerful antiretroviral drug ever marketed as a first-line strategy [14]. Moreover, the two drugs all showed excellent tolerability and safety [15]. The combination of DTG with 3TC has been proved in several other studies with rapid and sustained virological suppression in ART-naïve patients in the PADDLE[8] and GEMINI-1 and GEMINI-2[9] trials. In patients with sustained HIV virological suppression from the TANGO trial, switching to treatment with DTG plus 3TC was non-inferior to a TAF-based regimen at 48 weeks[16]. Several real-life studies also demonstrated that 3TC plus DTG was a safe and effective option for the simplification of ART in pretreated and virologically stable HIV-positive patients, being the same effectiveness as the triple therapy it replaces [17–19]. In addition, DTG and 3TC has also demonstrated cost-effective and projecting a lower cost with a high rate of virologic suppression [20].

Our results also demonstrated good efficacy of the DTG plus 3TC dual therapy with all patients achieving virological suppression after 48 weeks. Overall, DTG plus 3TC was well-tolerated with no study discontinuation due to serious adverse events in our study, which is also proved by other studies [8, 19]. It was notable that there were patients with virological failure and various drug toxicity from previous drugs in our study, the good efficacy and tolerability of DTG plus 3TC suggested that the dual therapy could be a reliable rescue regimen in highly treatment-experienced patients.

We observed a decline in renal function including decreased eGFR and increased serum creatinine. Although the changes in serum creatine and eGFR have been statistically significant at 48 weeks after the switching, they are proved not to be related to a real decrease in glomerular filtration [21]. These are substantially similar to previous findings using the same drug combination [9, 16]. This change could be due to the long-term use of DTG on organic cation transporter 2 (OCT2), which provides a mechanistic basis for the mild increases in serum creatinine[21, 22].

In our study, there was a variety of preexisting resistance among these treatment-experienced patients switching to DTG plus 3TC. Even in these patients, DTG plus 3TC still showed high efficacy with no virological failure at 48 weeks, which were consistent with another study by Borghetti et al[23]. DTG has been proved to be more powerful in pretreated patients because its high genetic barrier allows it to maintain antiviral activity against most mutated strains [24, 25]. The M184V/I mutation of HIV could develop resistance with 3TC. However, the M184V/I mutation could reduce HIV replication which leads to low viral fitness. The M184V/I variant also exhibited reduced mutation frequency compared with wild type [26]. These effects all indicate residual antiviral activity and support the use of 3TC in combination with other antiviral agents even if M184V/I has been documented[27]. Therefore, the DTG + 3TC could be a durable switch option for treatment-experienced patients with different kinds of drug-resistant. However, the presence of M184V/I mutation in patients was observed with an increased risk of virological failure using 3TC-based dual regimens[17, 28]. Emerging resistance to DTG and 3TC has also been found in

ART-naïve HIV patients[29]. Therefore, this dual regimen should be carefully evaluated and closely monitored by the clinicians in order to minimize the risk of virological failure.

This study has some limitations. First, this was an observational study with a limited sample size, which made it not possible for comparison with the standard NRTIs-based triple regimen. Second, the present study only collected routine clinical and laboratory data and therefore some data such as bone mineral density could be missing in the analysis, which could influence analysis of drug safety. Third, the study included patients with heterogeneous histories of ART regimens before switching, and the toxic effects associated with specific kinds of drugs could not be analyzed in improvement after the drug switch. These inclusion criteria could support the wide-ranging application of this dual regimen, but larger and prospectively designed randomized studies are certainly required for better evaluation of the dual therapy in the future.

Conclusions

In conclusion, the results of our study demonstrated that dual therapy of DTG and 3TC is an effective option for ART simplification in treatment-experienced HIV patients, with a high rate of virological suppression and low incidence of treatment discontinuation. The tolerability profile was also satisfactory with no case of serious adverse events.

Declarations

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Contributions

1. W., W. H., L. D., and L. S. conceived and designed the experiments; W. W., A. L., Z. L., B. S., and T. Z. collected the sample information and contributed to reagents and materials; W. H., S. W., Y.S., J. Y., and J. L. performed the experiments; W. H., S. W., B. S., and L. D. analyzed the data; and W. H., S. W., and L. D. wrote the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The data used in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from the Clinical Research Ethics Committee of the Beijing Youan Hospital (LL-2019-038-K).

Consent for publication

Not applicable.

Competing interests

The authors report no conflicts of interest relevant to this article.

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