Uptake and outcomes of generic dolutegravir based antiretroviral therapy in Georgia

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Abstract

Background: In July 2018 the World Health Organization updated antiretroviral therapy guidelines to recommend dolutegravir (DTG) as preferred first line drug. DTG was introduced in Georgia in 2017 and since 2018 has been prescribed as preferred first line option. Aim: We aimed to describe uptake of DTG in Georgia and evaluate outcomes of DTG-based antiretroviral therapy.

Materials and Methods: Study included all patients initiating DTG based treatment between July 1, 2017 and June 10, 2019. Data on patient demographic, epidemiological, clinical and laboratory parameters were extracted from the national AIDS health information system. Virologic response was evaluated in patients receiving DTG-based antiretroviral therapy at least for 6 months period. Viral suppression was defined as viral load (VL) <200 copies/ml. Missing VL data among patients on DTG based treatment for more than 12 months and discontinuation of therapy were defined as a failure (VL >200 copies/ml). Factors associated with achieving viral suppression were evaluated in multivariable Cox proportional hazards regression analysis.

Results: A total 635 patients initiated DTG-based therapy, among them the median age was 40 (IQR: 32-48) years, 459 (72.3%) were men, 326 (51.3%) were infected through heterosexual contact, 169 (26.6%) through injection drugs use and 123 (19.4%) through sex between men. Overall 487 (76.7%) patients received DTG as part of their first line regimen and 148 (23.3%) – as part of second line treatment. Per quarter uptake of DTG increased by 300% from 31 persons initiating DTG-based antiretroviral therapy in Jul-Sep 2017 to 124 persons in Apr-Jun 2019. Tenovovir/emtricitabine + DTG was most commonly prescribed combination (n=510, 80.3%), followed by zidovudine/lamivudine + DTG (n=55, 8.7%), abacavir/lamivudine + DTG (n=29, 4.6%), dual-drug combination of ritonavir boosted protease inhibitor + DTG (n=41, 6.5%). Of 635 patients initiating DTG-based treatment 13 patients died and 11 patients switched to other ART. Remaining 611 patients were followed for the median 7.8 (IQR: 3.2-11.7) months. A total of 369 patients were evaluable for virologic outcomes, including 363 patients remaining on DTG-based ART and 6 patients completely discontinuing ART. Among 369 patients assessed for virologic outcomes 339 (91.9%) patients had viral suppression at the last viral load measurement. Viral suppression rate was 92.9% among persons on first-line treatment and 88.8% among persons on second-line treatment. In multivariate analysis receiving first-line treatment was significantly associated with achieving viral suppression (Hazard ratio: 1.58, 95% CI: 1.20-2.08, p<0.001), while time since HIV diagnosis per additional year was inversely associated with the outcome of interest (Hazard ratio: 0.92, 95% CI: 0.89-0.95, p<0.0001).

Conclusions: DTG has been successfully introduced in Georgia and the uptake has been increasing over time. Early results show effectiveness of DTG both in first- and second-line treatments. Treatment uptake, retention and viral suppression should be further monitored to inform national ART program. (TCM-GMJ April 2020; 5(1):P18-P22)

Keywords: Antiretroviral therapy; Dolutegravir; Georgia; Eastern Europe.

Introduction

Improvements in efficacy and safety of antiretroviral therapy (ART) to treat infection caused by human immunodeficiency virus (HIV) significantly increased life-expectancy of people living with HIV across the globe (1). Owing to the breakthrough pricing agreements, resource-limited countries have now access to new high-quality medicines such as generic formulation of newer generation integrase strand transfer inhibitor (INSTI) Dolutegravir (DTG) (2).

Due to its potency and favorable safety profile, DTG has become standard of care in resource-rich settings and is now rapidly rolling-out in low- and middle-income countries (3). In July 2018 the World Health Organization (WHO) updated ART guidelines to recommend DTG as a preferred first-line treatment option and preferred second-line drug among those failing non-DTG based regimen (4). Currently there are limited real-life data on the use of DTG in resource-limited settings. Georgia has established effective HIV care model that ensures high engagement in the continuum of care and universal access to antiretroviral therapy that translat-
ed into dramatic reduction in AIDS-related mortality (5-7). DTG in Georgia was introduced in 2017 for selected patient groups and since 2018 it has been recommended as preferred first-line option. The objective of this study was to describe uptake of DTG in Georgia and evaluate outcomes of DTG based ART.

**Methods**

A retrospective cohort study included all adult (age≥18 years) HIV patients initiating DTG based treatment in the country between July 2017 and June 2019.

Provision of ART in Georgia is governed by the national clinical practice guidelines. Since 2015 treatment is recommended for all HIV patients regardless of CD4 cell count or disease stage. DTG for the first-line treatment is recommended in combination with fixed-dose combination of two nucleoside reverse transcriptase inhibitors (NRTI) - tenofovir/emtricitabine (TDF/FTC), alternative NRTIs include abacavir/lamivudine (ABC/3TC) and zidovudine/lamivudine (AZT/3TC). In second-line treatment DTG can be used with the same NRTIs or as a dual combination with ritonavir-boosted protease inhibitors (PI/r) Lopinavir (LPV), Atazanavir (ATV) or Darunavir (DRV).

Data on patient demographic, epidemiological, clinical and laboratory parameters were extracted from the national AIDS health information system (AIDS HIS), which is the secure web-based system collecting real-time data from all HIV care providers in the country. Virologic outcomes were evaluated in patients receiving DTG-based ART for at least 6 months period. Virologic outcome of interest was viral suppression defined as viral load (VL) <200 copies/ml at the last viral load measurement. Missing VL data among patients who were on DTG based treatment for more than 12 months and who discontinued therapy were categorized as virologic failure (VL >200 copies/ml).

Descriptive statistics were used to describe uptake DTG. Factors associated with achieving viral suppression were evaluated in multivariable Cox proportional hazards regression analysis. All statistical analyses were performed using SAS v9.4. P value <0.05 was defined ad statistically significant.

**Results and discussion**

A total 635 patients initiated DTG-based therapy during the study period, among them the median age was 40 (IQR: 32-48) years, 459 (72.3%) were men, 326 (51.3%) were infected through heterosexual contact, 169 (26.6%) through IDU and 123 (19.4%) through sex between men (Table 1). Majority of participants were diagnosed late (CD4 cell count at diagnosis <350).

The most commonly prescribed DTG-based regimen was combination of TDF/FTC + DTG (n=510, 80.3%). Dual PI + DTG regimen was prescribed to 41 (6.5%) patients on second-line treatment. Overall 487 (76.7%) patients received DTG as part of their first line regimen (including 174 treatment-naïve patients initiating first regimen with DTG and 313 patients switching to DTG after initial NNRTI based regimen) and 148 (23.3%) – as part of second line treatment (Table 1).

Uptake of DTG has been increasing over time, particularly after spring 2018 when national guidelines were updated to recommend DTG as preferred first-line option. Per quarter uptake of DTG increased by 300% - from 31 persons initiating DTG-based ART in Jul-Sep 2017 to 124 persons in Apr-Jun 2019 (Figure 1).

Patients were followed for the median 7.8 (IQR: 3.2-11.7) months. Over the follow-up 17 (2.7%) patients discontinued therapy and 13 (2.0%) died, thus 605 (95.3%) patients remained on DTG (Figure 2). A total 369 patients were evaluable for virologic outcomes, among them 339 (91.9%) patients had viral suppression at the last viral load measurement. Viral suppression rate was 92.9% among persons on first-line treatment and 88.8% among persons on second-line treatment (Figure 3). Among 118 treatment-naïve patients 112 were virally suppressed (94.9%). Analysis by treatment regimens showed lowest response rate among persons receiving dual combination of DTG with PI/r of 80.8% - the regimen used in heavily pretreated patients.

In multivariate regression analysis patients receiving first line ART were more likely to achieve viral suppression (Hazard ratio [HR]: 1.58, 95% CI: 1.20-2.08, p=0.001), while time since HIV diagnosis per additional year was inversely associated with the outcome of interest (HR: 0.92, 95% CI: 0.89-0.95, p<0.0001). Non-IDUs were more likely to achieve viral suppression in univariate analysis (HR: 1.31, 95% CI: 1.02-1.68, p=0.04), but statistical significance was not retained in multivariate model (HR: 0.88, 95% CI: 0.65-1.18, p=0.39).

DTG has been rapidly rolling out in Georgia consistent with latest national and international recommendations. Optimization of treatment with this new highly efficacious, tolerable and durable medication has potential to speed-up achievement of global treatment targets to end the AIDS epidemic (8). Recent modeling study also shows that availability of generic formulations of new drugs, including DTG, can save US$ 3 billion on HIV treatment in low- and middle-income countries by 2025 globally (9). Therefore promoting wider use of DTG including through demonstrating its effectiveness in real-world settings is very important.

While most of the data on effectiveness of DTG originated from resource-rich settings (10), it is important to document effectiveness of the drugs in resource-limited countries to support increasing uptake of DTG. To the best of our knowledge there is only one published real-world study evaluating generic DTG in resource-limited settings. Kumarasamy and colleagues showed safety, tolerability and efficacy of generic DTG in the cohort of 564 patients from India (11).

Our study demonstrated excellent efficacy with more
than 90% of participant achieving viral suppression after median 7.8 months of follow-up. Persons on first-line ART were more likely to achieve viral suppression as confirmed in multivariate analysis underlining that treatment-experienced persons may need additional adherence support. The lowest response rate (80.8%) was shown in patients receiving two drug combination of boosted PI and DTG — regimen usually used in heavily pre-treated patients with multiple drug resistance mutations. Nevertheless, this should not preclude prescription of DTG in second-line treatment as superiority of DTG over boosted lopinavir has been clearly documented in a recent randomized control trial when used in combination with 2 NRTIs (12). In the post-hoc analysis of the same trial DTG retained superiority even in the presence NRTI mutations (13). In addition, 88.8% viral suppression observed in our study compares favorably to our previous report showing suppression rates between 79-83% among patients receiving Atazanavir and Lopinavir based second line regimens (14).

Study has limitation. First of all it was focused on efficacy outcome and missed to evaluate real-world safety of generic DTG in Georgian settings. The most commonly reported adverse events associated with DTG are neural system toxicity manifested by headaches, dizziness and sleep disturbances (15). Neurotoxicity has been identified as the main reason for discontinuing DTG treatment in a number of cohort studies (16-18). In our study treatment discontinuation rate was low with only 2.7% patients stopping DTG. Recent cohort collaboration from Europe and Australia showed that the toxicity was the main reason for stopping DTG within 6 months of starting the drug (18), therefore we can assume that majority of discontinuations were due to toxicity, although this has not be evaluated.

Weight gain associated with DTG is another emerging issue. Recent studies show that weight gain and treatment emergent obesity are worse with DTG (19). This issues along with neurotoxicity needs to be closely monitored as treatment uptake further increases.

The most concerning issue related to DTG is the potential embryofetal toxicity. Surveillance study from Botswana reported that exposure to DTG at the time of conception or early in the pregnancy is associated with increases risk of neural tube defects (20). In follow-up study in Botswana Zash and colleagues reported decrease in the frequency DTG-associated neural tube defects, but it was still higher than reported with other antiretroviral drugs (21). No cases of neural tube defects were identified in Brazil among 382 women, who received DTG at the time of conception (22). Initiating DTG after the first trimester appears to be safe and effective, as DTG more rapidly achieves viral suppression without exhibiting serious toxicities (23, 24). Based on the available evidence Georgian national guidelines do not recommend DTG during first trimester of pregnancy or among women of childbearing potential, who do not use effective contraception (25). Guidelines will be revised as more evidence becomes available.

Overall study had short duration evaluating early results of DTG introduction. Sample size was not large limiting statistical power to assess associations in certain cases such as association between individual drug regimens with viral suppression. Longer follow-up with larger number of participant will be required to assess long-term effectiveness, including efficacy and safety, of generic DTG in routine clinical practice.

Conclusions

DTG has been successfully introduced in Georgia and the uptake has been increasing over time. Early results show effectiveness of DTG both in first- and second-line treatments. Results of our study support roll-out of generic DTG in lower- and middle-income countries. Treatment uptake, retention, viral suppression and safety should be further monitored to inform national ART program.

References

NRTI resistance and second-line NRTI use. (Abstract No: 144). Conference on Retroviruses and Opportunistic Infections (CROI 2019); 2019; Seattle, USA.


Table 1. Study population characteristics (n=635)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=635)</th>
<th>1st line ART (n=487)</th>
<th>2nd line ART (n=148)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median years (IQR)</strong></td>
<td>40 (32-48)</td>
<td>39 (31-47)</td>
<td>44 (36-50)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Gender, n (%)</strong></td>
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<tr>
<td>Women</td>
<td>176 (27.7)</td>
<td>134 (27.5)</td>
<td>42 (28.4)</td>
<td>0.84</td>
</tr>
<tr>
<td>Men</td>
<td>459 (72.3)</td>
<td>353 (72.5)</td>
<td>106 (71.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Mode of HIV transmission, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Injection drugs use (IDU)</td>
<td>169 (26.6)</td>
<td>103 (21.1)</td>
<td>66 (44.6)</td>
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</tr>
<tr>
<td>Heterosexual contact</td>
<td>326 (51.3)</td>
<td>258 (53.0)</td>
<td>68 (46.0)</td>
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<tr>
<td>Male-to-male sex</td>
<td>123 (19.4)</td>
<td>112 (23.0)</td>
<td>11 (7.4)</td>
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<tr>
<td>Other/unknown</td>
<td>17 (2.7)</td>
<td>14 (2.9)</td>
<td>3 (2.0)</td>
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</tr>
<tr>
<td><strong>CD4 cell count at diagnosis, median (IQR)</strong></td>
<td>290 (124-452)</td>
<td>321 (162-480)</td>
<td>194 (62-346)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>CD4 cell count &lt;350</strong></td>
<td>384 (60.5)</td>
<td>272 (55.9)</td>
<td>112 (75.7)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Time since HIV diagnosis, median years (IQR)</strong></td>
<td>3.8 (1.2-8.0)</td>
<td>3.2 (0.9-7.0)</td>
<td>6.7 (3.1-10.3)</td>
<td>&lt;0.0001</td>
</tr>
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<td><strong>ART regimen, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>TDF/FTC + DTG</td>
<td>510 (80.3)</td>
<td>435 (89.3)</td>
<td>75 (50.7)</td>
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<td>AZT/3TC + DTG</td>
<td>55 (8.7)</td>
<td>24 (4.9)</td>
<td>31 (20.9)</td>
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<td>ABC/3TC + DTG</td>
<td>29 (4.6)</td>
<td>28 (5.7)</td>
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<tr>
<td>ATV/r + DTG</td>
<td>17 (2.7)</td>
<td>17 (11.5)</td>
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<tr>
<td>DRV/r + DTG</td>
<td>15 (2.4)</td>
<td>15 (10.1)</td>
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</tr>
<tr>
<td>LPV/r + DTG</td>
<td>9 (1.4)</td>
<td>9 (6.1)</td>
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</table>

ART = antiretroviral therapy, DTG = Dolutegravir, TDF/FTC = Tenofovir/emtricitabine; ABC/3TC = Abacavir/lamivudine; AZT/3TC = Zidovudine/lamivudine; ATV/r = Atazanavir/ritonavir; DRV/r = Darunavir/ritonavir; LPV/r = Lopinavir/r
Figure 1. Quarterly uptake of dolutegravir-based antiretroviral therapy

Figure 2. Flow-chart of patients eligible for virologic outcome assessment

Figure 3. Viral suppression rates of dolutegravir-based antiretroviral therapy

Of 30 patients with virologic failure, 17 patient had viral load >200 copies/ml, 7 had missing viral load measurement and 6 discontinued treatment.