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# Immunological and Virological Outcomes among Treatment Experienced HIV-Infected Patients on Dolutegravir Regimen in Tanzania

Betty A. Maganda[1], Baraka Kivuraya[1], Ritah F. Mutagonda[2]*, Mary Temu[1]

[1]Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
[2]Department of Clinical Pharmacy and Pharmacology, School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

***Corresponding author:**

Dr. Ritah F. Mutagonda

Muhimbili University of Health and Allied Sciences

P. O. Box 65001

Dar es Salaam, Tanzania

Email: rmutagonda@muhas.ac.tz

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**Abstract**

***Introduction***

The integrase inhibitor dolutegravir (DTG) has recently replaced the non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine) in several Sub-Saharan African countries, including Tanzania. Since this change, there is scarce data on the current treatment outcomes focusing on treatment-experienced HIV-infected patients switched to DTG based regimens in Tanzania.

***Objectives***

This study aimed to investigate immunological and virological outcomes among treatment-experienced HIV-infected patients who were switched to DTG based regimen in Tanzania.

***Results***

We enrolled 397 patients, majority (65%) were female patients with mean age of 42.7 (95% CI; 40.7 – 44.7) years. The mean baseline CD4+ cell count was 457.1 (95% CI; 426.6 – 489.8) cells/mm$^3$ with 8.3% of patients with CD4+ cell count <200 cells/mm$^3$. The mean baseline viral load (VL) was 169.8 (95% CI; 128.8 – 223.9) copies/ml, whereby 20.6% had VL ≥ 1000 copies/ml. After the use of a new fixed dose combination of Tenofovir (TDF) 300 mg + Lamivudine (3TC) 300 mg + DTG 50 mg (TLD) for at least 24 weeks, the overall rate of virological suppression (<50 copies/ml) was 89.9% (95%CI 86.7% - 92.7%). The significant predictors of virological failure were overall duration on ART use (p = 0.004), duration on TDF + 3TC, and Efavirenz (EFV) (TLE) (p = 0.007), and baseline VL (p < 0.001).

***Conclusion***

TLD regimen has provided favorable preliminary results among patients who previously used TLE in HIV/AIDS treatment by showing good virological and immunological outcomes. The long-term treatment outcomes require further investigation.

***Keywords:*** *HIV, Dolutegravir, Virological-outcomes, Immunological-outcomes, Adverse drug reactions.*

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**Introduction**

In Tanzania, about 1.7 million people were living with human immunodeficiency virus (HIV) infection as of 2019 (1). Tanzania continues to be a global priority country in preventing and treating HIV infection. HIV infection in Tanzania is commonly caused by HIV-1 sub-types A, C, D, and their recombinants (2). The percentage of people living with HIV and receive antiretroviral treatment in Tanzania Mainland has increased from 52% in 2005 to 72% in 2018 (2). The introduction of antiretroviral therapy (ART) in the mid-1990s has significantly reduced HIV-associated morbidity and mortality. There has been a reduction in deaths associated with HIV from 52,000 in 2010 to 27,000 in 2019 (1). ART has transformed HIV from a worldwide epidemic to a manageable chronic condition (3).

The current recommended first-line ART regimen in the management of HIV infection is the use of one integrase inhibitor (INSTI) Dolutegravir (DTG) in combination with two nucleoside reverse-transcriptase inhibitors (NRTIs) (lamivudine and tenofovir fumarate) (4). Tanzania is among the 70 low- and middle-income countries that recently adopted DTG regimens use in 2019 (2). The change towards DTG based ART is based on its high tolerability, non-inferior or slightly higher efficacy and few drug-drug interactions than previous non-nucleoside reverse transcriptase (NNRTI) based regimens (5). It was reported that DTG also has a high genetic barrier to developing drug resistance, which is essential given the rising trend of resistance to efavirenz (EFV) and nevirapine (NVP)-based regimens (6). Adopting the new regimen in Tanzania has resulted in treatment-experienced patients switching from a fixed-dose combination of tenofovir, lamivudine, and efavirenz (TLE) to a fixed-dose combination of lamivudine and tenofovir fumarate and DTG (TLD).

Despite effective therapies, treatment failure is inevitable in some HIV-infected patients on ART. If treatment-experienced patients are switched, they may have a previous history of failure on an NRTI or NNRTI previously used, representing a high risk of treatment failure. HIV RNA viral load (VL) and CD4+ T cell count are the two surrogate markers for monitoring HIV-infected patients' treatment outcomes. VL monitoring is a much-preferred approach to monitor early treatment failure (2, 7). VL count above 1000 copies/ml and CD4+ cell count below 100 cells/mm3 from measurements taken six months after initiation of highly active ART are regarded as treatment failure (2). Therefore, this study evaluated immunological and virological outcomes among treatment-experienced HIV-infected patients previously on TLE regimen who switched to TLD regimen.

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## Methodology

### *Study design and setting*

This was a single-center, retrospective cohort study conducted at Muhimbili National Hospital (MNH). MNH is the only national referral hospital located in Dar-es-Salaam, Tanzania. It has a HIV care and treatment clinic (CTC) offering services to more than 5,000 HIV-infected patients and with about 500 patients per week. This retrospective study was conducted between June and September 2020.

### *Study population*

The study population consisted of HIV-infected patients from 15 years and above who were previously on the TLE regimen for six months or more and were switched from April 2019 to TLD regimen. All VL copies/ml and CD4+ cell count records of the study patients were recorded following the hospital routine; hence, not all patients had VL and CD4+ cell count measurements consistently. We considered the VL and CD4 count tests recorded up to 36 weeks after using TLD. Patients with incomplete data or those who died or were lost to follow-up within 24 weeks of switching were excluded.

### *Data collection*

Data was extracted from the HIV Care and Treatment Clinic (CTC2) database at MNH. The CTC2 database is database for HIV/AIDS clinics used to manage data on their HIV/AIDS care and treatment patients. It is one of the national HIV care and treatment monitoring and evaluation tool and is used by more than 300 HIV/AIDS clinics in every region of Tanzania. The CTC2 database contains patients' information such as socio-demographics, clinical data, laboratory results, records on pharmacy refill and the ART regimen used.

The information collected from the database included baseline data such as sex, age, weight, total duration on ART, and duration on TLE. Laboratory data such as VL and CD4+ cell count just before the switch and 24 weeks after switching to TLD were recorded.

### *Data management and statistical analysis*

Extracted data were transferred to the statistical package for social sciences (SPSS software version 23 Chicago Inc., USA) for cleaning and analysis. Tables were used during data summarization accordingly. The primary outcome of this study was virological suppression (<50 copies/ml) after 24 weeks of using the TLD regimen (2). Secondary outcomes were mean change in CD4+ cell count and VL copies/ml 24 weeks after using TLD regimen.

Continuous variables were log-transformed before analyzing the mean and mean difference using paired t-test. Bivariate logistic regression model was used to determine predictors of treatment failure (VL >50 copies/ml) among patients who were switched from TLE to TLD. All values with a p-value < 0.05 were statistically significant.

**Results**

Out of 397 patients who were switched from TLE to TLD regimens 77.8% were aged more than 35 years and 65.2% were female. Majority of them (93.7%) had used ART for more than 5 years whereby 96.2% had used TLE regimen for more than 2 years. More than half of the patients had baseline of VL <50 copies/ml and 8.3% had CD4+ cell count >200cells/mm$^3$ (just before switching to TLD regimen) (Table 1).

**Table 1: Socio-demographic and baseline characteristics of patients (n = 397)**

| Variable | Mean (95%CI) | Frequency | Proportion (%) |
|---|---|---|---|
| **Age (years)** | 42.7 (40.7 – 44.7) | | |
| <18 | | 17 | 4.3 |
| 18 - 35 | | 71 | 17.9 |
| >35 | | 309 | 77.8 |
| **Sex** | | | |
| Male<br>Female | | 138<br>259 | 34.8<br>65.2 |
| **Weight (kg)** | 63.1 (61.7 – 64.6) | | |
| **Duration on ART (months)** | 83.2 (81.3 – 87.1) | | |
| 27 - 60 | | 25 | 6.3 |
| 61 - 120 | | 305 | 76.8 |
| >120 | | 67 | 16.9 |
| **Duration on TLE (months)** | 70.8 (67.6 – 74.1) | | |
| ≤ 12 | | 1 | 0.3 |
| 13 - 24 | | 14 | 3.5 |
| > 24 | | 382 | 96.2 |
| **Baseline VL (copies/ml)** | 169.8 (128.8 – 223.9) | | |
| < 50 | | 211 | 53.1 |
| ≥ 50 - <1000 | | 105 | 26.4 |
| ≥ 1000 | | 81 | 20.4 |
| **Baseline CD4+ cell count (cells/mm$^3$)** | 457.1 (426.6 – 489.8) | | |
| < 200 | | 32 | 8.3 |
| ≥ 200 | | 352 | 91.7 |

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**Virological and immunological outcomes post switch to TLD regimen**

The proportion of patients who attained virological suppression (n=397) was 89.9% (95%CI 86.7% - 92.7%) (Figure 1). Virological failure (VL ≥ 1000 count/ul) was present in 9 (2.3%) patients 24 weeks after switching to TLD regimen (Figure 1). Of the 9 patients with treatment failure 8 (88.9%) had baseline VL ≥ 1000 copies/ml when using TLE. Equally, 24 (6.3%) patients had CD4+ cell count of < 200 cells/mm$^3$ after 24 weeks of using TLD regimen. There was a significant mean virological (7.24 (95% CI; 5.37 – 9.77) copies/ml) ($p < 0.001$) and immunological CD4+ cell count (-1.1 (95% CI; -(1.0 – 1.2) cells/mm$^3$) ($p = 0.022$) changes after using TLD regimen for more than 24 weeks. In the multivariable logistic regression analysis, duration on ART use (odds ratio (OR) 1.14; 95% confidence interval (CI) (1.04 – 1.25), $p = 0.004$), duration on TLE use (OR 0.88; 95% CI (0.80 – 0.97), $p = 0.007$) and baseline VL copies/ml ($p < 0.01$) were associated with virological suppression outcome (Table 2).

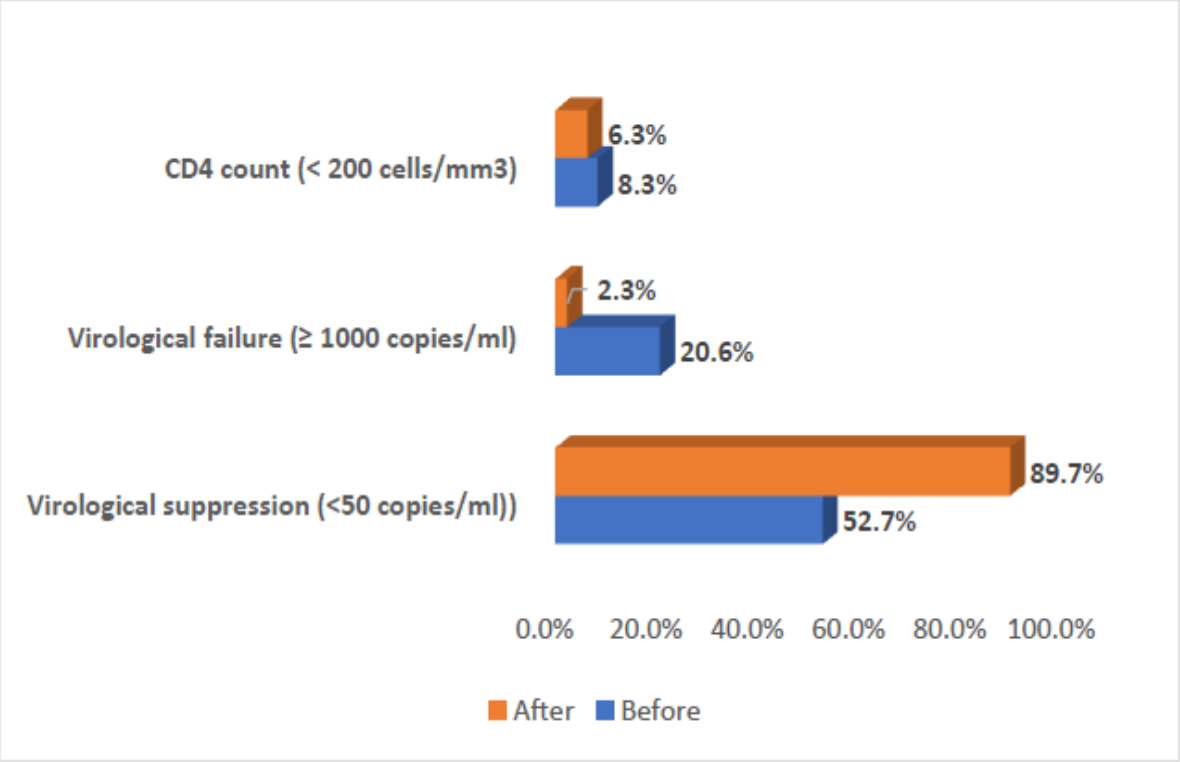


**Figure 1. Immunological and virological outcomes before and after switch to TLD**

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**Table 2: Factors associated with virological suppression after switch to TLD**

| Variable | n (%) | OR (95%CI) | P-value | AOR (95% CI) | P-value |
|---|---|---|---|---|---|
| Age (years) | 40/397 (10.1%) | 1.02 (0.99 – 1.04) | 0.109 | 1.03 (0.99 - 1.05) | 0.050 |
| Weight | 40/397 (10.1%) | 1.01 (0.99 – 1.03) | 0.423 | - | |
| Duration on ART use (months) | 40/397 (10.1%) | 1.01 (1.04 – 1.09) | 0.048 | 1.14 (1.04 - 1.24) | 0.005 |
| Duration on TLE (months) | 40/397 (10.1%) | 1.01 (0.99 – 1.02) | 0.088 | 0.88 (0.81-0.97) | 0.008 |
| Baseline CD4 count (cells/mm$^3$) | 40/397 (10.1%) | 0.99 (0.99 – 1.00) | 0.075 | 0.67 (0.19 - 2.31) | 0.522 |
| Baseline VL (copies/ml) | | | | | |
| < 50<br>≥ 50 - <1000<br>≥ 1000 | 19/211 (9.0%)<br>7/105 (6.7%)<br>14/81 (17.3%) | 0.46 (0.21 – 1.00)<br>0.34 (0.13 – 0.89)<br>Reference | 0.054<br>0.028 | 0.37 (0.17-0.82)<br>0.26 (0.09 0.72) | 0.015<br>0.009 |
| Sex | | | | | |
| Male<br>Female | 27/138 (19.5%)<br>13/259 (5%) | 1.12 (0.56 – 2.25)<br>Reference | 0.752 | - | |

## Discussion

DTG-based regimens are now recommended as the preferred first-line ART in the management of HIV-infected patients. TLD has essentially replaced prior recommendations for EFV-based regimens. With changes in first-line ART regimens and continued expansion in antiretroviral access in resource-limited settings, monitoring response to therapy is becoming an increasingly critical issue. Treatment failure due to drug resistance and poor adherence poses a challenge to the success of the ART program. For this reason, the WHO recommends routine HIV VL testing for monitoring ART effectiveness. Successful ART decreases HIV VL and improves immune recovery by increasing CD4+ cell count. Thus, this study evaluated the immunological and virological outcomes among HIV-infected patients who were switched from TLE to TLD.

Ideally, HIV-infected patients should have undetectable VL from six months of starting ART or after changing from one combination of ART to another for various reasons. In this study, a potent antiretroviral effect in patients who did not have VL<50 copies/ml on TLE was observed after six months of using TLD. There was a tremendous increase in the proportion of patients who attained virological suppression from 52.7% to 89.9% after the switch to TLD. The superiority of the DTG-based regimen has been evidenced when compared to the EFV-based regimen in other studies (8, 9). DTG has been reported to be superior to EFV with respect to viral suppression even during the more extended follow-up periods of up to 96 weeks (10). High efficacy of DTG regimen has been reported even in patients with previous virological failure (11). This indicates the successful adoption of the TLD regimen in African countries, enabling the progress towards achieving the third 95–95–95 target of the Joint United Nations Programme on HIV/AIDS (UNAIDS). The virological success rate observed in this study is comparable to that reported in previous studies assessing VL suppression at 24 weeks of DTG-based regimen from Brazil (89.1%) (12) and India (88.8%) (13). However, lower proportions have been reported in other African countries among treatment naïve patients in Cameroon (74.5%) (14) and in pregnant women in South Africa and Uganda (74%) (9).

In line with previous studies conducted in Tanzania (15, 16), a significant number (20.6%) of patients at baseline had VL ≥ 1000 copies/ml. After the switch to TLD, a low proportion of patients 9 (2.3%) had VL ≥ 1000 copies/ml, of which 8 patients had the baseline VL ≥ 1000 copies/ml before the switch. These groups of patients are classified as suspected virological failure. High VL has been reported as a significant predictor of virological failure in patients using DTG based regimens (14, 16). The virological failure can be contributed by many factors, including poor adherence, duration on ART, high baseline VL, low drug concentration in the body, or the mutation of the HIV. Long duration of ART use could contribute to poor adherence among patients. Poor adherence to ART can lead to the development of resistant HIV strains to ART. Therefore, these findings highlight the importance of close follow-up of patients who had a high VL (≥ 1000 copies/ml) in previous ART regimens after the switch to TLD regimen to be able to optimize treatment outcomes for patients with high VL. Monitoring patients with high VL requires monthly follow-up and repeated VL testing after 3 months of enhanced adherence counseling (2).

The relatively small but significant differences in CD4+ cell count was observed after switching from TLE to TLD. Previous studies have also reported comparable findings

showing an increase in CD4+ cell count after switching to a DTG-based regimen compared to other ART regimens (12, 17, 18). High immunological effectiveness of DTG based regimens have also been reported in HIV-2 patients who are known to have poor CD4 count recovery when using ART (13).

In conclusion, the use of the TLD regimen in the treatment-experienced HIV-infected patients previously on the TLE regimen has shown favorable treatment outcomes virologically and immunologically. Therefore, we recommend continuous monitoring of long term virological and immunological outcomes of DTG based regimen among HIV/AIDs patients in Tanzania.

**Limitations**

The availability of both CD4+cell counts and VL tests before and after the switch to TLD was pertinent for the studied population. However, the CD4 and VL test records after the switch were still missing during the study period. Thus, more patients were further excluded from the study. The study was conducted in the urban settings at the national hospital with satisfactory number of health care providers, adequate supply of ARVs and good monitoring of ART use, therefore the generalization of findings to other lower-level health facilities requires further investigation.

**Declarations**

***Ethical consideration and consent to participate***

This study was approved by the ethics committee and institutional review board at the Muhimbili University of Health and Allied Sciences (MUHAS) Ref. No. DA.25/111/01/. Permission to conduct this study at the study site - MNH was granted, and access to the database was provided to the principal investigator. Based on the retrospective nature of the study where data was collected from the database, the consent to pa rticipate was waived.

***Availability of data and materials***

The datasets used and analyzed during the current study is available from the corresponding author on reasonable request.

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**Patient consent for publication**.

Not required

**Competing interests**

The authors declare that they have no competing interests.

**Authors' Contributions**

BAM participated in the conception of the study and manuscript writing. BK participated in research designing and data collection. RFM participated in research designing, data analysis, and interpretation, and drafting of the manuscript. MT participated in research designing and manuscript revising. All authors read and approved the final manuscript.

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