SHORT COMMUNICATION

Viral suppression after transition from nonnucleoside reverse transcriptase inhibitor-to dolutegravir-based antiretroviral therapy: A prospective cohort study in Lesotho (DO-REAL study)

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Abstract

Objectives: Since 2018, the World Health Organization has recommended dolutegravir (DTG)-containing antiretroviral therapy (ART) for most people living with HIV. Country programmes across Africa have subsequently transitioned from other, mostly nonnucleoside reverse transcriptase inhibitor (NNRTI)-based ART to DTG-based ART. This study aims to assess the virological impact of programmatic transitioning to DTG-based ART in Lesotho.

Methods: The prospective Dolutegravir in Real-Life in Lesotho (DO-REAL) cohort enrols people living with HIV initiating or transitioning to DTG-based ART in Lesotho. Here, we present data from participants who transitioned from NNRTI- to DTG-based ART between February and December 2020. Blood samples collected at transition and at 16 weeks’ follow-up (window 8–32 weeks) were used for viral load (VL) and resistance testing.

Results: Among 1347 participants, follow-up data was available for 1225. The majority (60%) were female, median age at transition was 47 years [interquartile range (IQR): 38–56], and median (IQR) time since ART initiation was 5.9 (3.5–9.0) years. Among those with complete VL data, the rate of viral suppression to < 100 copies/mL was 1093/1116 (98%) before, 1073/1116 (96%) at, and 1098/1116 (98%) after transition. Even among those with a VL ≥ 100 copies/mL at transition, 42/44 (95%) achieved suppression to < 100 copies/mL at follow-up. Seven participants had a VL ≥ 1000 copies/mL at follow-up and did not harbour any integrase mutations associated with resistance to DTG.

Conclusions: The high levels of viral suppression observed are encouraging regarding virological outcomes upon programmatic transitioning from NNRTI- to DTG-based ART.
INTRODUCTION

Antiretroviral therapy (ART) containing dolutegravir (DTG) is recommended as the preferred regimen type of most people living with HIV [1,2]. DTG-based ART leads to superior [3–5] or non-inferior [6–9] virological outcomes and faster viral suppression [3,4,7] compared with commonly available NNRTI-based regimens, has a high barrier to development of drug resistance [3,10], and a favourable tolerability profile [3]. For these reasons, countries including Lesotho are recommending DTG-containing regimens not only for people newly diagnosed with HIV, but also for people transitioning from other, mostly nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens to DTG-containing ART [11].

While DTG-containing ART has good virological outcomes when used in triple and dual drug regimens [3–10,12,13], DTG monotherapy is associated with the development of drug resistance and treatment failure [10], and should therefore be restricted to special circumstances [14]. This has caused concerns that DTG functional monotherapy among ART-experienced people – which could occur through just substituting the NNRTI for DTG in the case of viral resistance to the other two drugs in a three-drug regimen – might likewise adversely impact treatment outcomes [10,15]. Moreover, instances of mutations associated with resistance to DTG have been described in randomized trials even in the context of triple therapy in people with and without prior exposure to first-generation integrase strand transfer inhibitors (INSTIs) [10,16].

Consequently, there is uncertainty regarding the optimal modality for the roll-out of DTG, with open questions including the requirement for previous viral suppression, the viral load (VL) threshold allowing for transition, and the timing of VL measurement before transition. This study aims to assess virological outcomes upon programmatic transitioning from NNRTI- to DTG-based ART in a routine care setting in Lesotho, southern Africa.

MATERIALS AND METHODS

The prospective, registered Dolutegravir in Real Life in Lesotho (DO-REAL) cohort study enrolled people living with HIV initiating or transitioning to a DTG-containing ART regimen at two hospitals in Butha-Buthe district, Lesotho; for logistical reasons, one hospital was dropped after enrolling only seven participants. According to the Lesotho guidelines, patients with a routine VL < 1000 copies/mL were to be transitioned to a first-line DTG-containing regimen typically maintaining the same nucleoside reverse transcriptase inhibitor (NRTI) backbone, whereas patients with two consecutive VLs ≥ 1000 copies/mL with enhanced adherence counseling before the follow-up measurement were to be transitioned to a second-line DTG-containing regimen with an altered NRTI backbone. With regard to the safety signal indicating an increased risk of neural tube defects in the context of DTG taken around the time of conception [17], which has since been corrected downwards [18], Lesotho guidelines recommend an approach based on informed choice for female adolescents and women of childbearing potential [11].

In this analysis, we only include participants who transitioned from NNRTI- to DTG-containing first- or second-line ART in the ART clinic at Butha-Buthe Government Hospital in Lesotho between 10 February 2020 and 31 December 2020. Data were closed for analysis on 5 May 2021. Participants were enrolled into the study on the day of transition and had a follow-up study visit 16 weeks (window: 8–32 weeks) thereafter. Study participants received routine services, with the exception of participant interviews and the collection of a non-routine blood sample at both time points. Samples were transferred to the hospital laboratory for VL testing with a detection limit of 20 copies/mL (cobas® 4800 system; F. Hoffman-La Roche AG, Basel, Switzerland) and stored at −80°C. Resistance testing was performed at the Molecular Virology laboratory, Department of Biomedicine, University of Basel in Basel, Switzerland (RNA extraction, cDNA conversion and amplification) and at SEQ-IT GmbH & Co. KG in Kaiserslautern, Germany (deep sequencing with Illumina MiSeq platform; Illumina Inc., San Diego, CA, USA). Variants occurring with a nucleotide frequency ≥ 10% were considered during analysis. Sequences were uploaded to the Stanford HIV Drug Resistance Database (v.9.0) to assess the presence of resistance-associated mutations. Patient data were retrieved from medical records and participant interviews, and collected in the established secured database of an ongoing open cohort study in Lesotho [19], which also contains participants’ prior routine VL results.

The pill count was calculated as a measure of adherence, and was calculated as follows:

\[
\text{Pill count} = \frac{\text{number of pills dispensed} - \text{number of pills returned}}{\text{number of pills to be taken per day} \times \text{number of days since dispensing}} \times 100\%.
\]

A pill count of 95–100% is considered as good adherence.

KEYWORDS

HIV, integrase inhibitors, observational study, Southern Africa, viraemia
Results are summarized as frequencies and percentages for categorical variables, and medians and interquartile ranges (IQRs) for continuous variables. All analyses were done using Stata/MP v.16.1.

All participants received study information in Sesotho and gave written informed consent. In the case of illiteracy, consent was given by thumbprint and a witness signature was required. DO-REAL, as well as the open cohort study in which it is nested [19], were approved by the National Health Research Ethics Committee of Lesotho (ID134-2016). The prospective DO-REAL cohort was registered with ClinicalTrials.gov on 23 January 2020 (NCT04238767).

RESULTS

Among 1347 individuals transitioning from NNRTI- to DTG-containing ART who were enrolled to the cohort and meet the criteria for this analysis, 16-week follow-up data were available for 1225 (91%) by data closure. Of the remaining 122, 99 remained in care (68 at the same hospital but with no follow-up data collected within the window, 20 at the same hospital but withdrew from the study, 11 transferred out); 22 were recorded as lost to follow-up; and one died (this participant had a VL < 20 copies/mL both before and at transition). According to routine data, the 1225 enrolled and with follow-up data represent > 70% of eligible patients at the clinic.

Table 1 shows characteristics of participants who attended a 16-week follow-up visit (we did not observe any differences in baseline characteristics between participants with vs. those without a follow-up visit within the window period; data not shown). The majority were female, median (IQR) age at transition to DTG was 47 (38–56) years, and median time since ART initiation was 5.9 (3.5–9.0) years. The median time between receiving a previous VL and transitioning to DTG was 16 (12–24) weeks. The vast majority (98%) transitioned from efavirenz (EFV)-containing ART, with only 2% transitioning from nevirapine (NVP)-containing ART. Nine participants (1%) transitioned to second-line ART as a consequence of treatment failure, whereas all others were considered to have transitioned within first-line ART. Both before and after transition, the backbone consisted of lamivudine (3TC)/tenofovir disoproxil fumarate (TDF) for > 93% of participants. Adherence was higher in women than men, especially at transition (Table 1).

A routine VL result from before transition, a VL at transition, and a VL at follow-up were available for 1217/1225 (99%), 1174/1225 (96%) and 1166/1225 (95%) participants, respectively. Data on VL were available at all three time points for 1116/1225 (91%) participants. Figure 1 shows

| TABLE 1 | Participant characteristics and adherence among participants who attended a follow-up visit |
|-----------------------------------------------|-----------------------------------------------|
|                                | At transition to DTG | At follow-up |
| N = 1225                                      |                                |                                |
| **Baseline characteristics**                  |                                |                                |
| Female                                       | 731 (60%)                     |                                |
| Age (years)                                  | 47 (38–56)                     |                                |
| Time taking ART (years)                      | 5.9 (3.5–9.0)                  |                                |
| Time since HIV diagnosis (years)              | 7.1 (3.9–10.6)                 |                                |
| Time since last viral loada (weeks)           | 16 (12–24)                     |                                |
| **ART immediately before transition**         |                                |                                |
| ABC/3TC/EFV                                   | 28 (2%)                        |                                |
| AZT/3TC/EFV                                   | 37 (3%)                        |                                |
| TDF/3TC/EFV                                   | 1135 (93%)                     |                                |
| ABC/3TC/NVP                                   | 1 (0.1%)                       |                                |
| AZT/3TC/NVP                                   | 13 (1%)                        |                                |
| TDF/3TC/NVP                                   | 11 (1%)                        |                                |
| **ART immediately after transition**          |                                |                                |
| ABC/3TC/DTG                                   | 41 (3%)                        |                                |
| AZT/3TC/DTG                                   | 10 (1%)                        |                                |
| TDF/3TC/DTG                                   | 1174 (96%)                     |                                |
| **Transition type**                           |                                |                                |
| Programmatic transition within first-line ART | 1216 (99%)                     |                                |
| Switch to second-line ART due to treatment failure | 9 (1%)                         |                                |
| Backbone changed at transition                | 71 (6%)                        |                                |
| **Adherence**                                 |                                |                                |
| Good adherence defined as pill count 95–100%b | 967 (82%) 882 (90%)            |                                |
| Among women (N = 731)                         | 607 (85%) 527 (91%)            |                                |
| Among men (N = 494)                           | 360 (76%) 355 (89%)            |                                |
| ART missed on two or more consecutive days in past monthc | 98 (8%) 80 (7%)            |                                |
| Among women (N = 731)                         | 44 (6%) 41 (6%)                |                                |
| Among men (N = 494)                           | 54 (11%) 39 (8%)               |                                |
| **Viral load category**                       |                                |                                |
| Overalld | N = 1174 | N = 1166 |
| < 20 copies/mL                                | 1029 (88%) 1053 (90%)          |                                |
| 20–99 copies/mL                               | 98 (8%) 94 (8%)                |                                |
| 100–999 copies/mL                             | 25 (2%) 12 (1%)                |                                |
| ≥ 1000 copies/mL                              | 22 (2%) 7 (1%)                 |                                |
| Overall, among womene                        | N = 696 | N = 698 |
Table 1 (Continued)

| N = 1225 | At transition to DTG | At follow-up |
|----------|----------------------|--------------|
| < 20 copies/mL | 620 (89%) | 640 (92%) |
| 20–99 copies/mL | 52 (7%) | 48 (7%) |
| 100–999 copies/mL | 14 (2%) | 5 (1%) |
| ≥ 1000 copies/mL | 10 (1%) | 5 (1%) |
| Overall, among men | N = 478 | N = 468 |
| < 20 copies/mL | 409 (86%) | 413 (88%) |
| 20–99 copies/mL | 46 (10%) | 46 (10%) |
| 100–999 copies/mL | 11 (2%) | 7 (2%) |
| ≥ 1000 copies/mL | 12 (3%) | 2 (0.4%) |
| If VL at transition < 20 copies/mL | N = 987 | |
| < 20 copies/mL | 912 (92%) | |
| 20–99 copies/mL | 62 (6%) | |
| 100–999 copies/mL | 8 (1%) | |
| ≥ 1000 copies/mL | 5 (1%) | |
| If VL at transition 20–99 copies/mL | N = 93 | |
| < 20 copies/mL | 70 (75%) | |
| 20–99 copies/mL | 20 (22%) | |
| 100–999 copies/mL | 3 (3%) | |
| ≥ 1000 copies/mL | 0 | |
| If VL at transition 100–999 copies/mL | N = 24 | |
| < 20 copies/mL | 20 (83%) | |
| 20–99 copies/mL | 3 (13%) | |
| 100–999 copies/mL | 1 (4%) | |
| ≥ 1000 copies/mL | 0 | |
| If VL at transition ≥ 1000 copies/mL | N = 20 | |
| < 20 copies/mL | 14 (70%) | |
| 20–99 copies/mL | 5 (25%) | |
| 100–999 copies/mL | 0 | |
| ≥ 1000 copies/mL | 1 (5%) | |

Note: For continuous variables, brackets indicate the interquartile range.
Abbreviations: 3TC, lamivudine; ABC, abacavir; AZT, azidothymidine; DTG, dolutegravir; EFV, efavirenz; NVP, nevirapine; TDF, tenofovir disoproxil fumarate.

Among all participants with VL data at follow-up, 19/1166 (2%) had a follow-up VL ≥ 100 copies/mL including 7/1166 (1%) with a follow-up VL ≥ 1000 copies/mL. Among those with a follow-up VL ≥ 100 copies/mL, 17/19 had a VL < 100 copies/mL at or before transition and remained on an unchanged NRTI backbone, and 2/19 had a VL ≥ 100 copies/mL at transition (544 and 22 000 copies/mL) and had an NRTI backbone change at transition to DTG. Sequencing of the sample taken at transition (544 copies/mL: not sequenced; 22 000 copies/mL: reverse transcriptase sequenced) and/or follow-up sample (271 and 17 900 copies/mL; reverse transcriptase and integrase regions sequenced for both) identified a K103N mutation conferring resistance to EFV and NVP for one participant, and no mutations associated with NRTI or INSTI resistance were detected. Of the seven with a follow-up VL ≥ 100 copies/mL, none harboured any mutations associated with DTG resistance in the integrase region; sequencing of the reverse transcriptase region was successful for four samples and no resistance-associated mutations were detected.

**DISCUSSION**

In order to assess virological outcomes within programmatic transitioning to DTG-based ART, this prospective cohort study assessed virological outcomes among people routinely changing from NNRTI- to DTG-based ART in a government hospital setting in Lesotho.

The vast majority of participants, including those with viraemia at transition, achieved viral suppression by follow-up. Furthermore, viraemia detected at follow-up was unlikely to be caused by drug resistance: among 19 participants with viraemia ≥ 100 copies/mL at follow-up, only two had viraemia ≥ 100 copies/mL at transition and neither harboured NRTI resistance (assessed at transition and/or follow-up); furthermore, among seven with viraemia ≥ 1000 copies/mL at follow-up, none harboured any resistance-associated mutations in the integrase region, suggesting suboptimal adherence as the cause of viraemia. These results support the virological effectiveness of pragmatic transitioning taking into account the patient’s most recent available data.
This study has several limitations. First, 122 participants had no follow-up data and a further 59 had no follow-up VL. While the majority of these remained in care, their 16-week virological status is unknown. Second, it is not yet certain whether the viral suppression observed during this short-term follow-up will remain stable over time. Third, the median time between the most recent VL before transition and the transition to DTG was only 16 weeks in this cohort. A longer time-frame between the previous VL test and transition would probably increase the proportion of participants with viraemia and, subsequently, NRTI resistance at transition, with unclear implications on viral suppression after transition to DTG. Fourth, the high rate of viral suppression at transition in this study limits its capacity to assess the impact of NRTI backbone resistance on viral suppression after transition to DTG-based ART. Given the high rate of viral suppression at transition in this cohort – with >96% having a VL < 100 copies/mL – caution is advised in extrapolating these results to populations with higher rates of viraemia or with a greater time differential between the last available VL and the time of transition to DTG. Further studies as well as longer-term follow-up are needed to assess the short- and long-term efficacy of DTG in the context of NRTI resistance and functional monotherapy. The major strength of this study is that it included >70% of patients transitioned in this cohort and was conducted in a routine healthcare setting with minimal intervention of the study on clinical procedures and clinical decision-making. Its representativeness is supported by the fact that the rates of viral suppression observed among people in care are in line with the national average of 97% [20].

Overall, these results are encouraging regarding the short-term virological effectiveness of programmatic transitioning from NNRTI- to DTG-based ART.

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CONFLICTS OF INTEREST
TK reports advisory board membership fees from ViiV and Gilead for work outside of this study. NDL reports having received travel grants to attend IAS, AIDS and CROI conferences from Gilead Sciences Sarl. All other authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS
NDL conceptualized this study. JAB and NDL designed the study with key input from BLN, AA, NT, JM and TK. BLN managed the study on site and oversaw all on-site procedures including consenting, data collection and on-site data cleaning. KM and IR conducted consenting procedures (together with Reitumetse Pea and Kelebone Moqethei, mentioned above) and collected data from medical records; KM, BLN and Reitumetse Pea collected blood samples. JAB conducted off-site data cleaning and analysed the data. LU performed resistance testing. JAB and NDL wrote the first version of the manuscript. All authors provided feedback on the manuscript and approved the final version.

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