Virologic Impact of the Dolutegravir Transition: Prospective Results From the Multinational African Cohort Study

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Background: The real-world impact on viral suppression of switching from non-dolutegravir-based therapy to tenofovir/lamivudine/dolutegravir (TLD) is not thoroughly characterized in Africa. We described the virologic consequences of switching regimens in the African Cohort Study (AFRICOS), an observational cohort in Nigeria, Kenya, Uganda, and Tanzania.

Methods: Among antiretroviral-experienced people living with HIV (PLWH) in AFRICOS, we compared viral load (VL) non-suppression (VL $\geq 1000$ copies/mL) among those who switched with those who never switched to TLD, restricting to participants who had at least 1 visit with a recorded VL after the countrywide rollout of TLD. We calculated Kaplan–Meier curves and conducted Cox proportional hazards modeling to estimate adjusted hazard ratios and 95% confidence intervals for factors potentially associated with nonsuppression.

Results: As of September 1, 2021, there were 3108 PLWH enrolled. Among 1576 participants who switched to TLD, 1486 (94.3%) remained suppressed after transition, 12 (0.8%) remained unsuppressed, and 38 (2.4%) lost suppression, compared with 652 (82.1%), 75 (9.4%), and 46 (5.8%), respectively, of 797 participants who did not switch ($P < 0.001$). After adjustment for sex, age, study site, and self-reported antiretroviral therapy adherence, virally suppressed participants who did not switch to TLD had significantly higher rates of losing viral suppression compared with those who switched (adjusted hazard ratio: 4.26; 95% confidence interval: 2.72 to 6.68).

Conclusions: PLWH transitioning to TLD had higher rates of viral suppression compared with those who remained on other regimens. Even within a highly suppressed population, TLD transition provided significant benefits for achieving or maintaining viral suppression.

Key Words: dolutegravir, virologic response, HIV integrase inhibitors

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INTRODUCTION

Dolutegravir (DTG)-based antiretroviral therapy (ART) has a high genetic barrier to resistance and causes fewer adverse events, resulting in higher rates of viral suppression.1–7 Consequently, in 2018, tenofovir disoproxil fumarate–lamivudine–DTG (TLD) was recommended as a preferred first-line treatment by the World Health Organization (WHO)8 and rolled out as the preferred regimen in programs supported by the President’s Emergency Plan for AIDS Relief (PEPFAR).

However, there are limited data on the real-world effectiveness of TLD among ART-experienced people living...
with HIV (PLWH), particularly in African settings, where treatment may be less individualized than in more resource-rich settings. Questions remain about the comparable effectiveness of TLD in people transitioning from other regimens. We examined viral nonsuppression [viral load (VL) ≥ 1000 copies/mL], as well as time to viral nonsuppression across 12 PEPFAR-supported clinical sites in Africa.

METHODS

Study Design and Setting

The African Cohort Study (AFRICOS) is an ongoing observational study that began enrolling PLWH in January 2013 from 12 clinics in Kayunga, Uganda; South Rift Valley and Kisumu West, Kenya; Mbeya, Tanzania; and Lagos and Abuja, Nigeria. Nonpregnant PLWH aged 18 years and older have been eligible for enrollment since 2013; participation was expanded to include clinic clients as young as 15 years in 2020. Every 6 months, participants answer a behavioral questionnaire, extensive medical record reviews are conducted, and laboratory testing including VL quantification is performed.

Analytic Population

For these analyses, we compared outcomes of interest among participants who switched to TLD at any time with participants who never switched to TLD over the course of follow-up. Only participants who had at least 2 VLs and at least 1 visit with available VL data after the country rollout of TLD through September 1, 2021, were included. Nigeria began TLD rollout in October 2018 and Kenya and Uganda began rollout in December 2018. All 3 required a VL < 1000 copies/mL to start TLD; that requirement was removed by Kenya in March 2019. Tanzania began rollout in March 2019 without the requirement for VL suppression. To assess the effects of TLD, participants who switched to TLD were excluded if they had been on TLD for less than 3 months. To compare time to viral nonsuppression, survival analyses were further restricted to participants with a VL < 1000 copies/mL at the visit before TLD switch or the first visit during the analysis period among nonswitchers. All participants had 2 VLs included in this analysis. For those who switched to TLD, the first VL was the VL performed at the visit before transitioning to TLD. For those who did not switch to TLD, the first VL was their first available VL after the country rollout of TLD through September 1, 2021. The second VL for both groups was either the VL from the most recent visit (through September 1, 2021) or first visit with virologic nonsuppression and was at least 3 months after a switch.

Measures

The main outcome was viral nonsuppression, defined as a VL ≥ 1000 copies/mL to be consistent with PEPFAR programming and WHO guidelines. Standard polymerase chain reaction (PCR)-based clinical tests were used at each site. The main exposure was TLD use, which was abstracted from medication record review. Available data from documented visits were used; visit adherence was not determined. ART adherence was based on the self-reported number of doses missed and dichotomized as missing zero or any doses in the 30 days before the study visit.

Analytic Methods

Descriptive statistics were performed using the Fisher exact test for categorical variables and the Kruskal–Wallis test for continuous variables, comparing participants who did and did not transition to TLD. Among all participants with available VL data, we descriptively examined change in VL after TLD transition. For participants who did not switch, we compared their first eligible VL to the most recent VL. We used Cox proportional hazards modeling to estimate hazard ratios and 95% confidence intervals (CIs) to estimate time to viral nonsuppression by regimens. Only visits occurring after the respective country began transitioning to TLD were included. Confounders were selected a priori based on the literature. Models were adjusted for study site, age, sex, and self-reported ART adherence.

Ethical Considerations

The study was approved by institutional review boards of the Walter Reed Army Institute of Research and all collaborating institutions. All participants provided written informed consent before enrollment.

RESULTS

Of the 3108 PLWH enrolled in AFRICOS, 2382 completed a visit after their respective country adopted TLD as first-line ART, and 2342 had VL data available. Of participants with VL data, 797 remained on their current regimen while 1868 switched to a DTG-based regimen, including 1782 who switched to TLD, of whom 1576 had been on TLD for at least 3 months and were included in these analyses. TLD switch was more common among men than women (77.1% vs. 59.0%; P < 0.001), and the median age was higher for PLWH who had switched to TLD compared with PLWH who had not [45.6 years (interquartile range: 37.5–53.5) vs. 40.1 years (33.5–47.2)]. TLD transition varied by site with a higher percentage of participants switching to TLD in Nigeria (78.4%); Kisumu West, Kenya (73.9%); and Tanzania (70.4%) compared with Uganda (39.8%) and South Rift Valley, Kenya (40.8%, P < 0.001). Among those who remained on their regimen, 107 (13.6%) reporting missing one or more doses, compared with 187 (11.9%) of those who did switch (P = 0.25). Most participants transitioned from tenofovir-lamivudine-efavirenz (TLE) (64.4%), while 15.2% transitioned from azidothymidine–lamivudine–nevirapine. Only 12 (<1%) participants transitioned to TLD from a protease inhibitor-based regimen.

Change in Viral Load

Among the 1576 participants who switched to TLD, 1486 (94.3%) had VLs < 1000 copies/mL at the visit before
switch and remained suppressed after transition, compared with only 652 of 797 (81.8%) participants who did not switch to TLD (Fig. 1). Among the participants who switched to TLD, 12 (0.8%) had and maintained VLs $\geq 1000$ copies/mL and 38 (2.4%) participants with VLs $< 1000$ copies/mL had VLs rise above 1000 copies/mL. Comparatively, among those who did not switch, 75 (9.4%) had and maintained VLs $\geq 1000$ copies/mL and 46 (5.8%) participants with VLs $< 1000$ copies/mL had VLs rise above 1000 copies/mL ($P < 0.001$). Examining finer changes in VLs by including a category for low-level viremia (VL 50–999 copies/mL), 84.0% of participants who switched to TLD maintained a VL $\leq 50$ copies/mL compared with 69.8% of participants who did not switch to TLD ($P < 0.001$).

There were 37 participants with a VL $\geq 1000$ copies/mL on TLE at the time of TLD transition and who had a VL measured at least 3 months after switching; 33 (89.2%) had a VL $< 1000$ copies/mL after switching, whereas 4 remained with VLs $\geq 1000$ copies/mL. Of the 12 participants previously on a protease inhibitor-based regimen, 8 remained virally suppressed after switching to TLD (66.7%), 1 became suppressed (8.3%), and 3 were unsuppressed at transition and remained unsuppressed (25.0%).

**Time to Viral Nonsuppression (Viral Loads $\geq$1000 Copies/mL)**

Among the 2085 participants with a VL $< 1000$ copies/mL at the time of TLD switch or the first eligible study visit, there was a combined total of 83 (4.0%) participants who developed viral nonsuppression. The mean time between the 2 VLs was 1.55 years for the 1505 participants who switched to TLD (median = 1.73 years; IQR = 1.03–2.05 years) and 1.41 years for the 580 participants who did not switch to TLD (median = 1.51 years; IQR = 0.66–2.00 years).

Thirty-seven (2.5%) of those who switched to TLD developed viral nonsuppression, compared with 46 (7.9%) of those who did not switch to TLD ($P < 0.001$).

In the unadjusted proportional hazards model, participants who did not switch to TLD had 3.59 times the hazard of developing viral nonsuppression compared with those who transitioned to TLD (95% CI: 2.33 to 5.55; Table 1). After adjustment for sex, age, study site, and self-reported ART adherence, virally suppressed participants who did not switch to TLD had significantly higher rates of losing viral suppression compared with those who switched (adjusted hazard ratio: 4.26; 95% CI: 2.72 to 6.68).

**DISCUSSION**

We found that among ART-experienced, virally suppressed PLWH, those who switched to TLD maintained viral suppression better than those individuals who continued on other regimens. These findings support the programmatic intention to switch all PLWH to TLD to maximize viral suppression and reduce individual and community VLs.

Our findings are similar, and additive, to what has been reported in the literature. A study among key populations in Nigeria demonstrated that a greater proportion of participants who switched to TLD had a VL $< 200$ copies/mL after 3 months compared with a similar group of patients maintained on TLE for another 6 months before switching (88% vs. 76.3%). Similarly, a study in Lesotho showed that after switching to TLD, the proportion of participants with a VL $< 100$ copies/mL increased from 96% to 98%, and the percentage with pill count-based adherence $>95$% improved from 82% to 90%.

**FIGURE 1. VL category by antiretroviral therapy switch status.** VL suppression defined as a VL $< 1000$ copies/mL, and nonsuppressed defined as a VL $\geq 1000$ copies/mL. For participants who did not transition to TLD, the preswitch VL was the first available VL after the country began rollout of TLD.
Current WHO guidelines recommend changing nucleoside reverse transcriptase inhibitors (NRTIs) at the time of transition from a failing first-line regimen to minimize the risk of developing resistance. However, we found that nearly 90% of participants unsuppressed on TLE were able to suppress on TLD despite not changing the NRTI backbone. Previously, we found among a subset of ART-experienced AFRICOS participants that 68% had an NRTI mutation suggesting high levels of resistance in this cohort. These data add to a growing body of literature documenting that even when PLWH have viral nonsuppression on tenofovir or other NRTIs, TLD is an effective regimen. Similar results were observed in the NADIA trial and the DO-REAL study, with high levels of viral suppression after switching to TLD among those with a K65R viral mutation or intermediate- to high-level tenofovir resistance. Similarly, the DO-REAL study showed high levels of viral suppression, defined as a VL < 400 copies/mL, after switching to TLD among those with a K65R viral mutation or intermediate- to high-level tenofovir resistance. Similarly, the DO-REAL study in Lesotho showed that among 44 participants with a VL above 100 copies/mL at transition, 42 (95%) dropped their VLs to below 100 copies/mL at follow-up. These findings suggest that maintaining a tenofovir backbone rather than switching to zidovudine may be an appropriate option when switching to DTG-based therapy, allowing for continued 1 pill, once-a-day dosing and sparing the substantial adverse events associated with prolonged zidovudine therapy.

This study is not without a few limitations. Most countries required viral suppression as a requirement to initiate TLD; therefore, we were unable to perform formal modeling with this group given the small sample size. We focused this analysis on 2 VLs and used a VL cutoff of 1000 copies/mL; although a single VL above that threshold is notable, the design of this study prohibits us from commenting on persistent nonsuppression and low-level viremia, both of which are more established clinical considerations. Participants enrolled in the study received additional attention and diagnostic services beyond the standard of care, which may limit generalizability to individuals not enrolled in AFRICOS. In addition, VL testing as part of the study visit was scheduled independently from routine HIV care visits when ART regimen changes were made, so there were varying durations between regimen changes and VL measurements across participants. Some countries required viral suppression in the 6 or 12 months before TLD initiation, so the populations who did and did not switch may not be equivalent in viral suppression and ART adherence, which could bias the results. However, given that we restricted our survival analysis to only participants who were suppressed below 1000 copies/mL we believe this bias to be minimal. Finally, there may be other confounders which were not measured or included in this analysis, which could further limit comparability of the groups. If, for example, providers used some unrecorded judgment to decide who was and was not switched to TLD (eg, a perceived adherence issue), that could have biased these results.

These data provide insights into the real-world impact of the TLD transition in Africa, demonstrating that even among PLWH with high rates of viral suppression, TLD provides an additional benefit and can further reduce rates of viral nonsuppression and community VLs.

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**TABLE 1. Unadjusted and Adjusted Hazard Ratios for Time to Viral Non-suppression (Viral Load ≥ 1000 Copies/mL)**

| On TLD | N (%) | Unadjusted Hazard Ratio | Unadjusted 95% CI | Adjusted Hazard Ratio | Adjusted 95% CI |
|--------|-------|-------------------------|-------------------|-----------------------|-----------------|
| Yes    | 1576 (66.4%) | Ref | — | — | — |
| No     | 797 (33.6%) | 3.59 | 2.33 to 5.55 | 4.26 | 2.72 to 6.68 |
| Sex    |       |       |       |       |       |
| Male   | 970 (40.9%) | Ref | — | — | — |
| Female | 1403 (59.1%) | 0.80 | 0.51 to 1.23 | 0.55 | 0.35 to 0.88 |
| Age    |       |       |       |       |       |
| 18–29  | 301 (12.7%) | Ref | — | — | — |
| 30–39  | 514 (21.7%) | 0.93 | 0.41 to 2.08 | 1.08 | 0.46 to 2.51 |
| 40–49  | 872 (36.7%) | 1.10 | 0.48 to 2.10 | 1.22 | 0.57 to 2.60 |
| 50+    | 686 (28.9%) | 0.69 | 0.32 to 1.50 | 1.00 | 0.44 to 2.24 |
| Study site |       |       |       |       |       |
| Kayunga, Uganda | 397 (16.7%) | Ref | — | — | — |
| South Rift Valley, Kenya | 823 (34.7%) | 1.44 | 0.72 to 2.88 | 1.52 | 0.76 to 3.06 |
| Kisumu West, Kenya | 463 (19.5%) | 1.06 | 0.48 to 2.37 | 1.18 | 0.53 to 2.66 |
| Mbeya, Tanzania | 412 (17.4%) | 1.84 | 0.82 to 4.13 | 1.98 | 0.87 to 4.53 |
| Abuja and Lagos, Nigeria | 278 (11.7%) | 1.72 | 0.80 to 3.71 | 1.59 | 0.71 to 3.56 |
| Missed ART |       |       |       |       |       |
| None   | 2062 (87.5%) | Ref | — | — | — |
| Missed ≥1 | 294 (12.5%) | 2.80 | 1.73 to 4.53 | 2.68 | 1.58 to 4.56 |

Missed ART was based on participant self-reported number of doses in the last 30 days.
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