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Longitudinal Viral Load Outcomes of Adults with HIV after Detectable Viremia on Tenofovir, Lamivudine, and Dolutegravir

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Abstract

Background: To inform optimal management of HIV viremia on TLD, we examined viral load (VL) outcomes of a large cohort of adult PLHIV on TLD in Nigeria.

Methods: We conducted a retrospective study of adult PLHIV who had ≥1 VL after initiating TLD during January 2017–February 2023. VLs were categorized as undetectable (≤50 copies/mL), low low-level viremia (LLV, 51-199 copies/mL), high LLV (200-999 copies/mL), virologic non-suppression (VLNS, ≥1000 copies/mL), and virologic failure (VF, ≥2 consecutive VLNS results). Among patients with ≥2 VLs on TLD, we described how viremia changed over time and examined virologic outcomes after VF. We identified predictors of subsequent VLNS using mixed-effects logistic regression and conducted planned contrasts between levels of VL result and regimen types.

Results: Analysis of 82,984 VL pairs from 47,531 patients demonstrated viral resuppression to ≤50 copies/mL at follow-up VL in 66.7% of those with initial low LLV, 59.1% of those with initial high LLV, and 48.9% of those with initial VLNS. Of 662 patients with a follow-up VL after VF, 94.6% stayed on TLD; of which 57.8% (359/621) were undetectable at next VL without

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Authors' contributions

OS and SV conceptualized the study. IJ, AO, AE, OO, SD, and DO, collected the data. KM curated the data. OS, SV, HC, and KM developed the methodology. OS, SV, KM, and HC conducted the formal analysis, with supervision from AA, AB, and AMB. KM and AO accessed and verified the data. OS, KM, SV, and HC drafted the manuscript. All authors critically reviewed and revised the final manuscript.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies. Applicable federal law for ethical review include: 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

regimen change. Previous low LLV (aOR 1.74, 1.56–1.93), high LLV (aOR 2.35, 2.08–2.65), and VLNS (aOR 6.45, 5.81–7.16) were associated with increasingly higher odds of subsequent VLNS, whereas a previously undetectable VL (aOR 1.08, 0.99–1.71) on TLD was not.

Conclusions: Despite increased odds of subsequent VLNS, most PLHIV with detectable viremia on TLD, including those with VF, will resuppress to an undetectable VL without a regimen change.

Keywords

dolutegravir; TLD; Nigeria; viral load; virologic suppression; HIV

Introduction

In 2018, the World Health Organization recommended tenofovir, lamivudine, and dolutegravir (TLD) as the preferred first-line regimen[1] for people living with HIV (PLHIV) because of its high efficacy in achieving viral suppression[2-4] and its higher barrier to developing HIV drug resistance when compared to non-nucleoside reverse transcriptase inhibitors (NNRTIs).[5] Since then, most sub-Saharan countries have transitioned a vast majority of PLHIV to TLD, and routinely report viral suppression for over 95% of those on treatment.[6] However, most assessments of viral suppression are conducted cross-sectionally, and outcomes after non-suppression for those on TLD and other dolutegravir (DTG)-based regimens have not been widely studied. For the small proportion of PLHIV who do not suppress on TLD, understanding likelihood of future suppression can help inform program planning, treatment course, and regimen changes.[7] To inform optimal management of HIV viremia, we examined longitudinal virologic outcomes among a large cohort of adult PLHIV on TLD in Nigeria.

Methods

We used longitudinal patient data to assess virologic outcomes, categorized as undetectable viral load (VL ≤50 copies/mL), low low-level viremia (LLV, 51–199 copies/mL), high LLV (200–999 copies/mL), virologic non-suppression (VLNS, ≥1000 copies/mL), and virologic failure (VF, two or more consecutive VLNS results) in patients aged ≥15 years on TLD in the Federal Capital Territory of Nigeria during January 2017—February 2023 and with at least one documented VL result on TLD, irrespective of receipt of other regimens. Key available demographic and clinical variables and VL data were extracted from the National Data Repository (NDR), an electronic medical record database of patient services provided to PLHIV in public facilities developed by the Federal Ministry of Health of Nigeria for monitoring, reporting, and evaluation of patient services provided to PLHIV. We described the demographic and clinical characteristics of patients with at least one VL result on TLD. For VLNS outcomes, we included patients with at least one VL on TLD and at least one subsequent VL on any regimen. We further evaluated patients with two consecutive VLs on TLD to assess how viremia changed over time and described follow-up VLs as undetectable, low LLV, high LLV, or VLNS. For analysis of outcomes following VF on TLD, we included patients with at least two consecutive VLNS results on TLD and at least one subsequent VL immediately after VF, irrespective of change in regimen.

Predictors of VLNS at the subsequent VL were identified for each pair of consecutive VLs using mixed-effects logistic regression, with patient and facility incorporated as random intercepts. Models were adjusted for clinically relevant variables (e.g., sex, age at ART initiation, ART duration, time between VLs, regimen type, pregnant or breastfeeding status, key population status, VL result). Interactions between age and sex, and VL result and regimen type were also assessed. A purposeful selection procedure[8] was used to determine variables to include in the adjusted model: variables with $p<0.25$ in univariable models were included in the multivariable model; variables with $p>0.05$ in the multivariable model were excluded if coefficients in the resulting smaller model changed by less than 20%. Final model fits were assessed using area under receiver operating characteristic curve. Unadjusted odds ratios (ORs) and adjusted odds ratios (aORs) were calculated for univariable and multivariable models, respectively. Planned contrasts between levels of VL result and regimen types were conducted. Descriptive analyses were conducted in Python version 3.7.6 and outcomes analyses in R version 4.0.2, using the lme4 package.[9]

The study was approved by the Nigerian National Health Research Ethics Committee (NHREC/01/01/2007-13/11/2020), who waived the requirement of obtaining informed consent given the retrospective study design. The U.S. Centers for Disease Control and Prevention human research protection procedures determined the study to be non-research.

Results

Between 2017–2023, 101,728 patients ever received HIV treatment, of whom, 85,533 patients had a documented ART regimen prior to their first VL, of which 72,011 received TLD at least once. Among those who received TLD at least once, 63,521 had at least one VL result on TLD and were included in the descriptive cohort. We included 47,979 patients with at least one VL result following a VL on TLD in an outcomes cohort. Individuals without a follow-up VL could not be analyzed longitudinally and were thus, excluded. (Supplementary Section A). Overall, of patients who received TLD at least once, 11.6% (8,373/72,011) were potentially lost to follow-up (Supplementary Section B).

Median age of the descriptive cohort was 35 years [IQR: 30–42] and 29.3% (18,595) were male (Table 1). Female sex workers and men who have sex with men accounted for 30.9% (19,640) and 10.7% (6,799) of the population, respectively. Most patients initiated ART in 2020 or later (56.3%, 35,767), and 61.1% (38,814) had only ever been exposed to DTG-based regimens, of which 98.8% (38,331) were exclusively exposed to TLD. Remaining patients were started on other regimens, most commonly NNRTIs, and transitioned to TLD. Of the total, 36.6% (23,264) of patients had at least one detectable VL (≥51 copies/mL) on TLD at some point during the study period: 20.3% (12,918) had low LLV, 10.4% (6,637) had high LLV, and 13.5% (8,607) had VLNS. Of these, 88.2% (20,547) had a follow-up VL after detectable VL, for which median time between VL results was 336 [IQR: 247–373] and 196 [IQR: 124–315] days for the LLV and VLNS groups, respectively.

For outcomes, data from 47,531 patients on TLD contributed 82,984 pairs of consecutive VLs. We observed viral suppression to an undetectable VL at subsequent VL in 66.7% of those with preceding low LLV, 59.1% of those with preceding high LLV, and 48.9% of

those with preceding VLNS (Figure 1). We observed viral suppression to <1000 copies/mL at the subsequent VL in 93.3% (8,739/9,369) of preceding low LLV, 90.7% (4,395/4,845) of preceding high LLV, and 71.3% (4,398/6,166) of preceding VLNS. Of all pairs of consecutive VLs on TLD, 3.4% (2,848/82,984) consisted of a detectable (>50 copies/mL) VL result followed by VLNS; these pairs belonged to 4.7% (2,242/47,531) of patients with two or more consecutive VLs on TLD.

VF occurred in 2.4% (1,151/47,531) of patients with at least two consecutive VLs on TLD and 21.0% (1,151/5,489) of patients with preceding VLNS on TLD. Of 662 patients with a subsequent VL after VF on TLD, 94.6% stayed on TLD; of which 57.8% (359/621) suppressed to an undetectable VL and 92.1% (571/621) suppressed to <1000 copies/mL at the subsequent VL. The remaining 6.2% of patients were switched to an alternate regimen after VF on TLD; of which 31.7% (13/41) suppressed to an undetectable VL and 48.0% (32/41) suppressed to <1000 copies/mL at the subsequent VL on the alternate regimen. Of the patients who were switched to alternate regimens, 32 were switched to protease inhibitors (PIs), 2 were switched to NNRTIs, and 5 were switched to non-standard regimens.

Age 15–24 years at ART initiation was associated with subsequent VLNS for both males (aOR [95% CI]: 2.879, 2.361-3.511) and females (aOR 2.115, 1.759-2.544), when compared with females aged ≥55 years. Status as a member of a key population (aOR 0.637, 0.517–0.786) was associated with lower odds of subsequent VLNS. Compared with previous undetectable VL on an NNRTI, previous low LLV (aOR 1.715, 1.540–1.911), high LLV (aOR 2.281, 2.020–2.576), or VLNS (aOR 7.534, 6.850–8.288) on DTG was associated with increased odds of subsequent VLNS, whereas a previous undetectable VL (aOR 1.079, 0.995–1.170) on DTG was not. However, planned contrasts showed that, compared with NNRTIs, DTG was associated with lower odds of subsequent VLNS within each VL category except ≤50 copies/mL (low LLV aOR 0.797, 0.674–0.944; high LLV 0.565, 0.472–0.676; VLNS 0.416, 0.378–0.457) (Supplementary Section C).

Discussion

Among a cohort of over 63,000 PLHIV on TLD in Nigeria, most patients with detectable viremia, and even VF, subsequently resuppressed to a VL <1000 copies/mL at the next VL without a regimen change. Young adulthood at ART initiation and a previously detectable VL were associated with increased odds of subsequent VLNS. Previous low LLV, high LLV, and VLNS results were associated with increasingly higher odds of subsequent VLNS when compared to a previously undetectable VL, but odds of subsequent VLNS were lower for PLHIV on DTG compared to those on NNRTIs with comparable VL results. Despite increased odds of subsequent VLNS with detectable viremia, VF only occurred in 2.4% of PLHIV on TLD. These results are consistent with recent evidence that shows DTG is more durable than older antiretroviral medications.[10]

Almost half of detectable VLs on TLD in our cohort were due to low LLV, and of those, most resuppressed at next VL. The small proportion of patients with high LLV, VLNS, and VF while on TLD may benefit from further evaluation given the potential to develop drug resistance and/or transmit HIV. While currently available data do not

suggest an increased risk of HIV transmission with LLV,[11] PLHIV with LLV remain at increased risk for subsequent VLNS and VF,[12] further signaling the need for durable virologic suppression. Fortunately, our data suggests this population will be relatively small, so targeted interventions like objective adherence monitoring among PLHIV who cannot achieve or maintain durable virologic suppression may not be cost-prohibitive for lower resourced countries.

Of the patients that did experience VF on TLD, a significant majority were maintained on TLD, and a high proportion resuppressed to undetectable at subsequent VL. These findings are consistent with recent randomized clinical trial data that show that a greater proportion of patients on DTG resuppress to an undetectable VL after VF than patients on NNRTIs.[13] In our cohort, of those who did change regimens after VF, a majority were switched to PIs. While reasons for switching ART regimens are often complex and multifactorial, the risk of treatment-emergent drug resistance is negligible for DTG.[14] Among PLHIV experiencing VF, VL monitoring may point to a need for more intensive adherence interventions instead of a regimen change, and only a small proportion may require cost-intensive genotyping to identify HIV drug resistance.

This study had several limitations. Longitudinal results were limited to participants with follow-up VLs, thereby selecting for individuals who remained in care, potentially overestimating resuppression rates (Supplementary Section D). Objective ART adherence measurements were not available. However, increasing attention and more-detailed records on interruptions in treatment may allow for inclusion in future analyses. Lastly, HIV drug resistance data and deaths are not routinely captured in the NDR. Acknowledging the importance of drug resistance in virologic suppression and outcomes, its prevalence is currently under investigation in Nigeria.

Overall, we observed excellent virologic outcomes, even among those with initial VLNS and VF, among adult PLHIV on TLD in this large cohort of patients in Nigeria. Facilitating medication adherence with monitoring and strategic interventions for the subset with high LLV, VLNS and VF may help achieve VL resuppression, prevent HIV transmission, preserve TLD as a durable HIV treatment option, and limit HIV drug resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest and Source of Funding:

We declare no conflicts of interest. HIV program support was provided by the US President’s Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the funding agencies.

Data Availability Statement

No new primary data were collected for this study. Data is owned by the Federal Ministry of Health and requests for additional use may be directed to the National Coordinator, National AIDS and STD Control Programme (NASCP) (Dr Adebola Bashorun, bashogee@yahoo.com).

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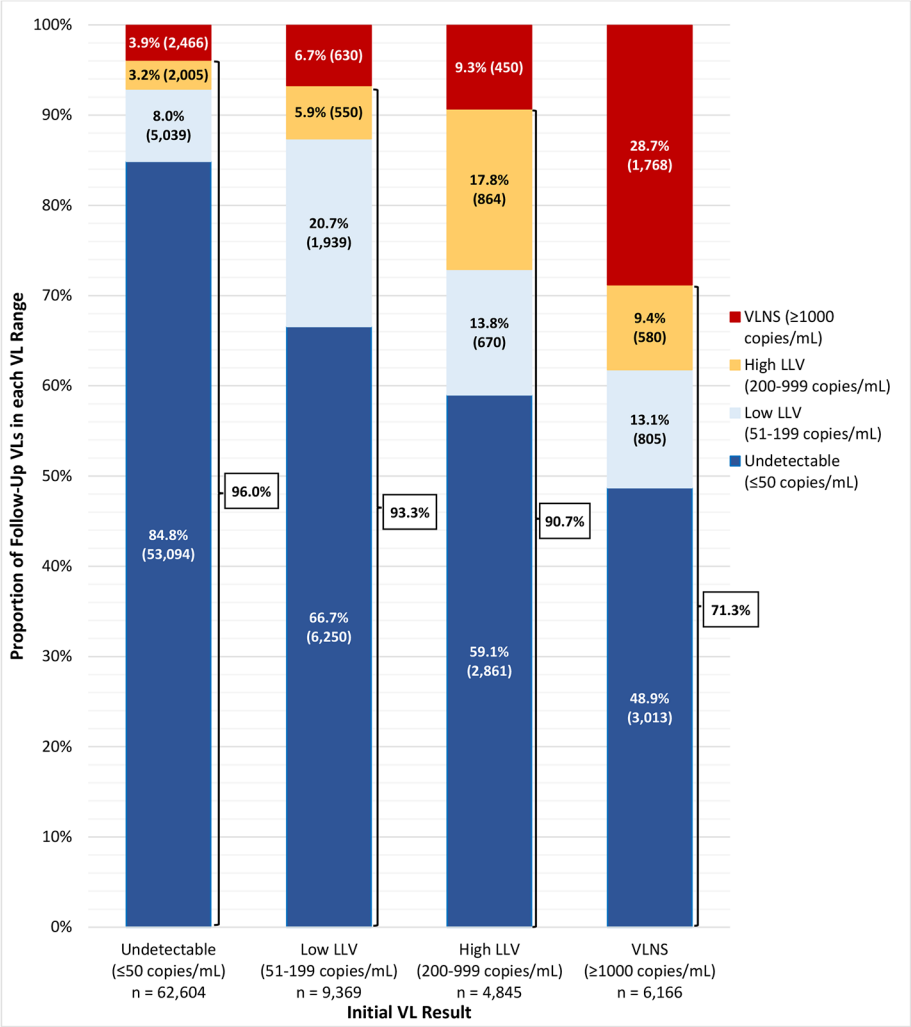

Figure 1.

Proportion of follow-up viral loads (VLs) that are undetectable, low low-level viremia (LLV), high LLV or virologic non-suppression (VLNS) by preceding VL result among patients with consecutive VLs on tenofovir lamivudine dolutegravir (TLD) in Federal Capital Territory, Nigeria, 2017–2023.

VL = viral load. LLV = low-level viremia. VLNS = virologic non-suppression. TLD = tenofovir lamivudine dolutegravir. Due to rounding, percentages may not sum to exactly 100.0.

Table 1.

Demographic and clinical characteristics of adults with HIV on dolutegravir-based regimens in Federal Capital Territory, Nigeria 2017–2023.

Attribute	Value
Total patients, N (%)	63,521 (100.0)
Sex	
Female, N (%)	44,926 (70.7)
Male, N (%)	18,595 (29.3)
Age, median (IQR):	35 (30-42)
15-24, N (%)	4,461 (7.0)
25-34, N (%)	26,765 (42.1)
35-44, N (%)	20,631 (32.5)
45-54, N (%)	8,616 (13.6)
55+, N (%)	3,048 (4.8)
ART start year	
≤2015, N (%)	13,316 (21.0)
2016, N (%)	3,750 (5.9)
2017, N (%)	3,716 (5.9)
2018, N (%)	3,199 (5.0)
2019, N (%)	3,773 (5.9)
2020, N (%)	20,484 (32.2)
2021, N (%)	12,274 (19.3)
2022, N (%)	3,009 (4.7)
Pregnant/breastfeeding status (ever documented)	
Pregnant, N (%)	3,619 (5.7)
Breastfeeding, N (%)	3,148 (5.0)
Key populations	
FSW, N (%)	19,640 (30.9)
MSM, N (%)	6,799 (10.7)
PWID, N (%)	674 (1.1)
TGP, N (%)	156 (0.2)
Regimen exposure (ever documented)	
NNRTI exposure	
Efavirenz, N (%)	21,300 (33.5)
Nevirapine, N (%)	7,210 (11.3)
Dolutegravir exposure	
TLD, N (%)	63,521 (100.0)
Other DTG-based regimens, N (%)	697 (1.1)
Only DTG-based regimens, N (%)	38,814 (61.1)
Only TLD, N (%)	38,331 (60.3)

Attribute	Value
Protease inhibitor exposure	
Ritonavir-boosted lopinavir, N (%)	664 (1.1)
Ritonavir-boosted atazanavir, N (%)	585 (0.9)
Days between VL results, median (IQR)	344 (266-381)
VL <50 copies/mL, median (IQR)	343 (280-380)
VL 51-999 copies/mL, median (IQR)	336 (247-373)
VL ≥1000 copies/mL, median (IQR)	196 (124-315)
Total documented VLs, N (%)	192,820 (100.0)
Total documented VLs per patient	
1, N (%)	12,901 (20.3)
2, N (%)	21,167 (33.3)
3, N (%)	8,628 (13.6)
4, N (%)	6,402 (10.1)
5, N (%)	6,124 (9.6)
6+, N (%)	8,299 (13.1)
Maximum documented VL result	
≤50, N (%)	36,758 (57.9)
51-199, N (%)	9,943 (15.7)
200-999, N (%)	5,506 (8.6)
≥1000, N (%)	11,314 (17.8)
At least 1 documented VL result in range	
≤50, N (%)	58,395 (91.9)
51-199, N (%)	15,315 (24.1)
200-999, N (%)	8,626 (13.6)
≥1000, N (%)	11,314 (17.8)
Total number of documented VLs on TLD, N (%)	150,512 (100.0)
Number of VLs on TLD per patient	
1, N (%)	14,955 (23.5)
2, N (%)	24,209 (38.1)
3, N (%)	14,282 (22.5)
4, N (%)	7,498 (11.8)
5+, N (%)	2,577 (4.1)
Maximum documented VL result on TLD	
≤50, N (%)	40,257 (63.4)
51-199, N (%)	9,674 (15.2)
200-999, N (%)	4,983 (7.8)
≥1000, N (%)	8,607 (13.5)
At least 1 documented VL result in range, while on TLD	
≤50, N (%)	57,772 (90.9)

Attribute	Value
51-199, N (%)	12,918 (20.3)
200-999, N (%)	6,637 (10.4)
≥1000, N (%)	8,607 (13.5)

ART = antiretroviral therapy. FSW = female sex worker. MSM = men who have sex with men. PWID = people who inject drugs. TGP = transgender person. NRTI = nucleoside reverse transcriptase inhibitor. TDF = tenofovir disoproxil fumarate. NNRTI = non-nucleoside reverse transcriptase inhibitor. TLD = tenofovir, lamivudine, dolutegravir. DTG=dolutegravir. VL=viral load.