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MAJOR ARTICLE

Transitioning to Dolutegravir in a Programmatic Setting: Virological Outcomes and Associated Factors Among Treatment-Naive Patients With HIV-1 in the Kilombero and Ulanga Antiretroviral Cohort in Rural Tanzania

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Background. Virological outcome data after programmatic transition from non-nucleoside reverse transcriptase inhibitor (NNRTI)-based to dolutegravir (DTG)-based antiretroviral therapy (ART) regimens in sub-Saharan Africa (SSA) outside of clinical trials are scarce. We compared viral suppression and associated factors in treatment-naïve people living with HIV (PLHIV) starting DTG- based versus NNRTI-based ART.

Methods. We compared virological suppression at 12 months, after treatment initiation in the two cohorts of participants aged ≥15 years, initiating DTG- and NNRTI-based ART. Drug resistance was assessed among participants with viremia ≥50 copies/mL on DTG.

Results. Viral suppression was achieved for 165/195 (85%) and 154/211 (73%) participants in the DTG- and NNRTI- cohorts, respectively ($P = 0.003$). DTG-based ART was associated with >2 times the odds of viral suppression versus NNRTI-based ART (adjusted odds ratio, 2.10 [95% confidence interval {CI}, 1.12–3.94]; adjusted risk ratio, 1.11 [95% CI, 1.00–1.24]). HIV-1 genotypic resistance testing (GRT) before ART initiation was done in 14 of 30 viremic participants on DTG, among whom nucleoside reverse transcriptase inhibitor (NRTI), NNRTI, and protease inhibitors resistance was detected in 0 (0%), 2 (14%) and 1 (7%), respectively. No resistance was found in the 2 of 30 participants with available GRT at the time of viremia ≥50 copies/mL.

Conclusions. Virological suppression at 1 year was higher in participants initiating DTG- versus NNRTI-based ART. In those with viremia ≥50 copies/mL on DTG-based ART, there was no pretreatment or acquired resistance to the DTG co-administered NRTIs, although the number of samples tested was small.

Keywords. HIV-1; ART-naive; dolutegravir; drug resistance; sub-Saharan Africa.

Globally, almost 38 million people are living with human immunodeficiency virus (HIV) and two-thirds of these reside in sub-Saharan Africa (SSA) [1]. To end the HIV epidemic with the global 95-95-95 targets set by the Joint United Nations Programme on HIV/AIDS for 2025, 1 key element is access to antiretroviral therapy (ART) for all people with HIV (PWH) [2, 3]. Until recently, in most low- and middle-income countries (LMICs), first-line ART consisted of a nonnucleoside reverse transcriptase inhibitor (NNRTI)–based regimen containing either nevirapine or efavirenz. However, in the last years a substantial increase of pretreatment drug resistance (PDR) for NNRTIs has been observed in SSA [4], in some countries exceeding the World Health Organization (WHO)–recommended threshold of 10% [5], thus compromising the ambitious target to end the HIV epidemic by 2030 [6]. PDR resulting in virologic failure might go undetected for long timespans in LMICs due to limited resources for viral load (VL) and resistance testing, leading to increased morbidity, mortality, and onward transmission of virus [7]. Therefore, transition to integrase inhibitors (INSTIs), characterized by a faster viral suppression, a higher barrier to

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resistance, and fewer side effects compared to NNRTIs within randomized controlled trials (RCTs) [8], has been advocated by many national HIV programs.

By the end of 2017, dolutegravir (DTG)–based therapy became available to LMICs as the generic fixed-dose combination of tenofovir disoproxil fumarate, lamivudine, and dolutegravir at the favorable price of 75 US dollars per person per year [9]. Since then, many LMICs have rolled out DTG-based ART. Initially, the WHO advised women of childbearing age to avoid DTG-based ART when planning a pregnancy or not being on consistent contraception, due to a signal for an increased risk of neural tube defects in the offspring of women on DTG-based ART at conception in the Tsepamo study in Botswana [10]. After more data became available showing a considerably lowered risk of neural tube defects, the WHO recommended DTG-based ART for all adolescents and adults in July 2019.

So far, limited data outside of clinical trials are available on the clinical and virologic outcome after the transit from NNRTI-based to DTG-based regimens in SSA [11–13]. Evaluation of the rollout of DTG-based ART under programmatic conditions in resource-limited regions is important given the challenges outlined above. With this study, we aimed to compare viral suppression in treatment-naive patients at 12 months after initiating DGT-based versus NNRTI-based ART. Additionally, we assessed predictors associated with viral suppression and analyzed PDR mutations and acquired resistance, side effects, and pregnancy outcomes in patients initiated on a DTG-based regimen.

METHODS

Study Design and Setting

This is a retrospective, observational study nested within the Kilombero and Ulanga antiretroviral cohort (KIULARCO), a prospective cohort of PWH. The cohort includes patients seen at the Chronic Diseases Clinic of Ifakara, the care and treatment center for PWH of the Saint Francis Referral Hospital, located in rural southeastern Tanzania. The cohort was established in 2005 and captures comprehensive demographic and clinical data, including ART use and monitoring, comorbidities, and treatment outcomes, with details described previously [14, 15].

Study Population

Two groups of PWH aged ≥15 years attending KIULARCO were included in the analysis: (1) treatment-naive patients initiating NNRTI-based ART between 16 December 2016 and 15 December 2017 (referred to as the NNRTI cohort) and (2) treatment-naive patients initiating DTG-based ART between 16 March 2019 and 15 September 2020 (referred to as the DTG cohort). The separation of periods ensured that no patient in the NNRTI cohort would have been switched to a DTG-based regimen by the time of outcome assessment, which could have had an impact on VL results.

We excluded patients initiating protease inhibitor (PI)–based therapy in both periods, patients starting NNRTI-based ART between 16 March 2019 and 15 September 2020, treatment-experienced patients (assessed in the baseline questionnaire by asking if they had ever received ART before), those not starting ART during the given time periods, and those without written informed consent to KIULARCO (Figure 1). Reasons for excluding patients starting PI-based ART was that this is not the usual first-line therapy in Tanzania. Similarly, those initiating NNRTI-based ART during DTG rollout were excluded as they were only few and would have only started on this therapy due to specific criteria.

Data Collection

Data for patient demographics, routine clinical information, and laboratory data as well as information on ART were extracted from OpenMRS, the KIULARCO electronic medical record system. As per routine care and according to the Tanzania National Guidelines for the Management of HIV and AIDS, patients receive a VL measurement at 6 and 12 months after treatment start, and once yearly thereafter for those with a VL <1000 copies/mL. At the same time point as VL measurements, blood samples are stored in a biobank at −80°C for research purposes.

Laboratory Measurements

VL measurement was done using the Abbott Real-time m2000 HIV-1 Assay (Abbott Laboratories, Chicago, Illinois), with a reportable range of 40–10 000 000 copies/mL for blood plasma. For this study, we performed HIV-1 genotypic resistance testing (GRT) from biobanked samples for those with an HIV VL ≥50 copies/mL. In addition, HIV-1 GRT was performed on samples available prior to treatment initiation for cases with a VL ≥50 copies/mL at 12 months using cryopreserved samples, to determine PDR before ART initiation in the DTG cohort.

GRT was performed using a validated in-house polymerase chain reaction (PCR) protocol to determine the HIV-1 drug resistance–associated mutations for reverse transcriptase, protease, and INSTI [16, 17]. In brief, RNA was extracted from 150 µL of plasma using the PureLink Viral RNA/DNA Mini Kit (Invitrogen, Thermo Fisher Scientific), according to the manufacturer's protocol. RNA extracts were retrotranscribed and amplified using the HIV-1 Genotyping Kit Amplification Module (Applied Biosystems, Thermo Fisher Scientific). A direct sequencing reaction was done using 6 overlapping primers, and assembly program (BioEdit 7.2) was used for sequence analysis. Mutations were interpreted according to the Stanford University's HIV Drug Resistance Database Program version 9.2 (http://hivdb.stanford.edu). Drug resistance mutations conferring low, intermediate, or high-level resistance were considered. The reported protease and reverse transcriptase sequences are available in GenBank (accession number OQ627458-OQ627474).

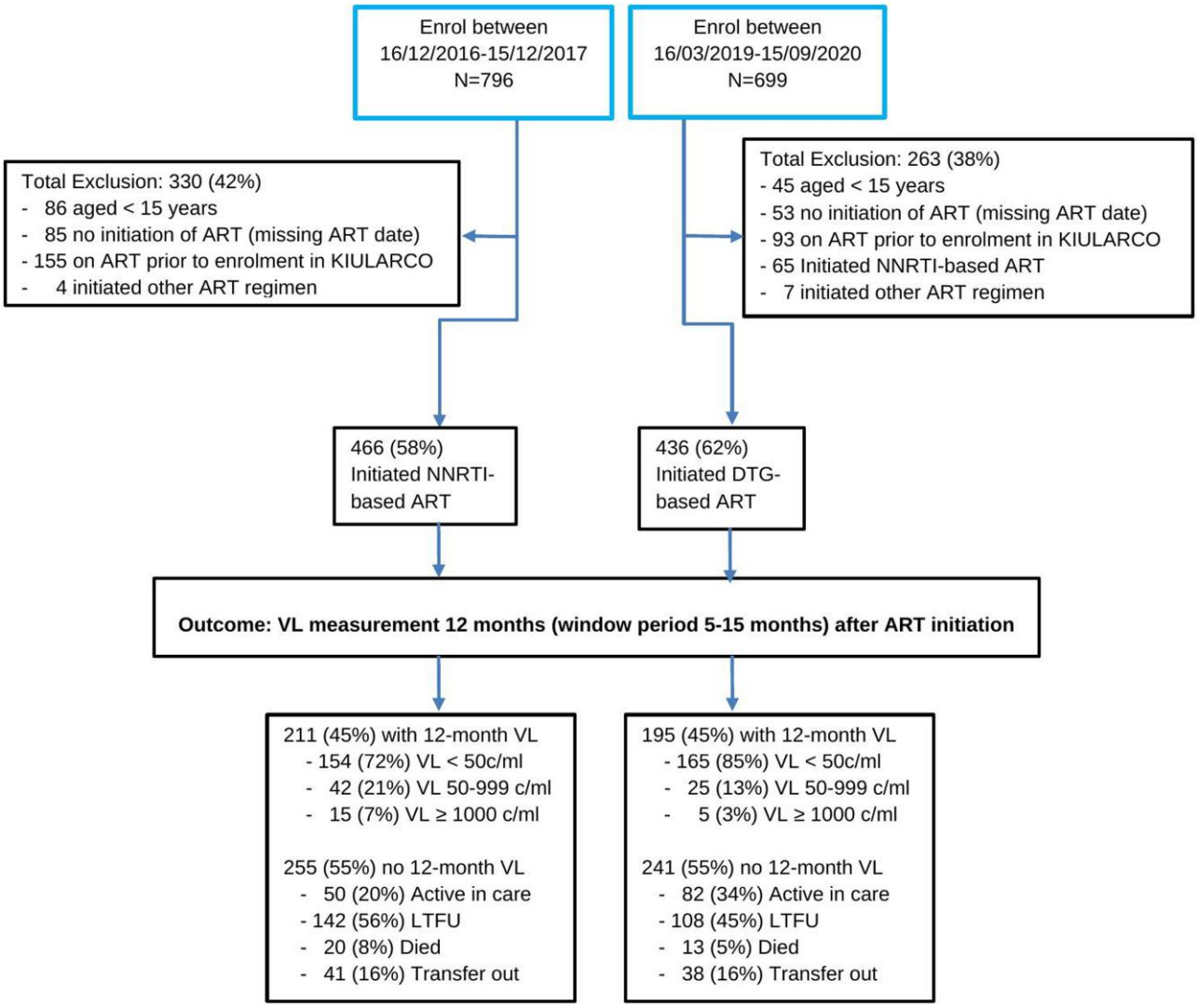

Figure 1. Participant flowchart. Abbreviations: ART, antiretroviral therapy; c/mL, copies per milliliter; DTG, dolutegravir; KIULARCO, Kilombero and Ulanga Antiretroviral Cohort; LTFU, lost to follow-up; NNRTI, nonnucleoside reverse transcriptase inhibitor; VL, viral load.

Definitions

Viral suppression was defined as <50 copies/mL and viremia as defined as ≥50 copies/mL, at 1 time-point measurement, and virological failure was defined as ≥1000 copies/mL after a minimum of 6 months on ART, based on 2 consecutive VL measurements in 3 months (with adherence support following the first VL test), in line with the most recent WHO guidelines [18]. Loss to follow-up (LTFU) was defined as being >60 days late for a scheduled visit.

Tuberculosis was recorded if, within 3 months from enrollment, acid-fast bacilli or a positive Xpert MTB/RIF assay (Cepheid, Sunnyvale, California) from sputum or an extrapulmonary site was documented, or if antituberculosis drugs with an *International Classification of Diseases, Tenth Revision* (*ICD-10*) code or clinical signs suggestive of tuberculosis were present. Unlikely tuberculosis was defined as no prescription of antituberculosis drugs and no diagnosis of tuberculosis by *ICD-10*. For other cases, an indeterminate tuberculosis status was stated and treated as missing data.

Study Outcomes

The primary outcome was viral suppression at 12 months, allowing for a time window of 5–15 months with a preference for the measurement closest to 12 months after treatment start. The secondary outcomes of this study were prevalence of PDR and acquired resistance among patients presenting with viremia on DTG-based ART (defined as the presence of resistance-associated mutations), plus, side effects and pregnancy outcomes in the DTG cohort.

Table 1. Patient Characteristics at Initiation of Nonnucleoside Reverse Transcriptase Inhibitor– or Dolutegravir-Based Antiretroviral Therapy Regimens

Patient Characteristics	Initiated NNRTI-Based ART 2016–2017 (n = 466)	Initiated DTG-Based ART 2019–2021 (n = 436)
Sociodemographics		
Age, y		
15–24	52 (11)	53 (12)
25–34	136 (29)	120 (28)
35–44	164 (35)	138 (32)
≥45	111 (24)	125 (29)
Sex, female	300 (65)	280 (64)
Marital status		
Married/cohabiting	263 (57)	292 (67)
Never married	63 (14)	28 (6)
Separated/divorced/widowed	137 (30)	116 (27)
Disclosed HIV status		
No	85 (21)	113 (28)
Yes	318 (79)	290 (72)
Missing	60 (13)	33 (8)
Education		
None	64 (14)	28 (6)
Primary	347 (75)	368 (84)
Secondary and above	52 (11)	40 (9)
Distance of residence to clinic		
<1 km	182 (42)	240 (56)
2 to <50 km	141 (33)	135 (32)
≥50 km	106 (25)	51 (12)
Missing	34 (7)	10 (2)
Clinical		
ART regimen		
DTG-based	0 (0)	436 (100)
EFV-based	456 (98)	0 (0)
NVP-based	9 (2)	0 (0)
Other	1 (0)	0 (0)
Tuberculosis status[a]		
Unlikely	405 (89)	395 (92)
Yes	52 (11)	33 (8)
Missing	6 (1)	8 (2)
BMI[a], kg/m^2		
Underweight (<18.5)	66 (16)	52 (13)
Normal (18.5–24.9)	259 (62)	230 (57)
Overweight (≥25)	63 (15)	123 (30)
Missing	43 (9)	31 (7)
HIV WHO stage[a]		
I/II	260 (61)	316 (75)
III/IV	166 (39)	107 (25)
Missing	37 (8)	13 (3)
CD4 count, cells/μL[a]		
<100	92 (24)	62 (16)
100–350	166 (42)	184 (47)
≥350	134 (34)	142 (37)
Missing	71 (15)	48 (11)

Data are presented as No. (column %) of those with nonmissing data; missing data rows are No. (column %).

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; DTG, dolutegravir; EFV, efavirenz; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; WHO, World Health Organization.

[a]Tuberculosis, BMI, HIV WHO stage, and CD4 measurements closest to ART initiation within 6 months before and 3 months after.

Statistical Methods

Demographic characteristics were summarized using frequencies and percentages. We descriptively compared baseline characteristics between participants with and without a VL result at 12 months. The proportion of participants with viral suppression in the DTG and NNRTI cohorts was compared

using a χ^2 test. Factors associated with 12-month viral suppression were determined using logistic regression models, reporting odds ratios and 95% confidence intervals (CIs). We also calculated adjusted risk ratios (aRRs) after fitting the multivariable model with standard errors estimated using the delta method [19]. The multivariable model incorporated the following covariates, which were selected a priori: age, sex, marital status, disclosure of HIV status, education level, distance in kilometers of residence from the clinic, body mass index (BMI), HIV WHO stage, CD4 cell count, tuberculosis status, and cohort (DTG-based or NNRTI-based ART). No model selection was done. We performed a sensitivity analysis restricting VL measurement to a time window of 9–15 months from treatment start. The analysis was repeated under the assumption that those LTFU were not virally suppressed, as such participants are likely to be off treatment and therefore not suppressed.

The prevalence of HIV-1 drug resistance, the proportion of patients who discontinued DTG-based ART, and the proportion of women who conceived while on DTG-based ART and their pregnancy outcomes were described descriptively. All analyses were performed using Stata version 15 (StataCorp LP, College Station, Texas).

Ethical Considerations

Written informed consent of patients willing to participate in KIULARCO are obtained at registration. This study received ethical approval from the University of the Witwatersrand Human Research Ethics Committee (Medical) Clearance Certificate No. M210714. Yearly ethical approval for data and sample collection as well as analysis is sought from the Ifakara Health Institute institutional review board (IHI/IRB/No16-2006) and the Health Review Committee of the National Institute for Medical Research of Tanzania (NIMR/HQ/R.8c/Vol.I/378).

RESULTS

Study Population and Baseline Characteristics

There were 436 and 466 patients in the DTG and NNRTI cohorts, respectively (Figure 1). The combined median age in both cohorts was 38 years (interquartile range [IQR], 30–45 years). In the DTG and NNRTI cohorts, 280 (64%) and 300 (65%) patients were female, 292 (67%) and 263 (57%) were married/cohabiting, 290 (72%) and 318 (79%) had disclosed their HIV status, and 51 (12%) and 106 (25%) were resident ≥50 km from clinic, respectively. The clinical parameters were broadly comparable within the 2 groups, with a normal BMI (18.5–25 kg/m^2) in 230 (57%) and 259 (62%), a WHO stage III/IV in 107 (25%) and 166 (39%), a CD4 count of ≥350 cells/mL in 142 (37%) and 134 (34%), and tuberculosis coinfection in 33 (8%) and 52 (11%) participants, respectively (Table 1).

We compared patients with and those without VL tests at 12 months and found them to be broadly comparable with the exception of those with 12-month VL more likely to have disclosed their HIV status (309 [81%] vs 301 [70%]) and to be resident <1 km from clinic (210 [54%] vs 213 [45%]), and less likely to be HIV WHO stage III/IV (115 [29%] vs 159 [35%]) and to have a CD4 count ≥350 cells/μL (118 [31%] vs 151 [38%]). Those without 12-month VL were more likely to have missed baseline characteristic measurements compared to those with VL (Supplementary Table 1).

Virological Outcome

VL data at 12 months after ART initiation were available for 195 of 436 (45%) and 211 of 466 (45%) participants in the DTG and NNRTI cohorts, respectively (Figure 2). Among those with VL results available, viral suppression was achieved for 165 of 195 (85%) and 154 of 211 (73%) participants in the DTG and NNRTI cohorts, respectively ($P = .003$). For those with viremia in the DTG and NNRTI cohorts, 25 of 30 (83%) and 42 of 57 (74%) had a VL 50–999 copies/mL and 5 of 30 (17%) and 15 of 57 (26%) had VL ≥1000 copies/mL, respectively. At 1 year following ART initiation, 108 of 436 (25%) patients in the DTG cohort and 143 of 466 (31%) in the NNRTI cohort were LTFU (Figure 1). Assuming those LTFU were not virally suppressed, 165 of 303 (55%) and 154 of 353 (44%) achieved viral suppression in the DTG and NNRTI cohorts, respectively ($P < .001$).

Factors Associated With Virological Suppression

Results of the univariable and multivariable analyses are shown in Table 2. DTG-based versus NNRTI-based ART was independently associated with improved viral suppression (adjusted odds ratio, 2.10 [95% CI, 1.12–3.94]; aRR, 1.11 [95% CI, 1.00–1.24]). In addition, the following factors were independently associated with viral suppression (Table 2): being separated/divorced/widowed (and to some extent married/cohabiting) versus never married, higher education level, and higher (worse) HIV WHO stage.

In sensitivity analysis restricting VL measurements to a time window of 9–15 months including 59 of 436 (14%) and 133 of 466 (29%) patients in the DTG and NNRTI cohorts, ART regimen was not associated with viral suppression (aRR, 2.12 [95% CI, .82–5.49]), compared to using the 5- to 15-month VL window above (Supplementary Table 2).

HIV-1 Drug Resistance–Associated Mutations

For patients with viremia at 12 months after starting DTG-based ART, blood plasma samples prior to treatment initiation were available for 25 of 30 (83%) patients. Of those, 14 of 25 (56%) samples were successfully PCR amplified and

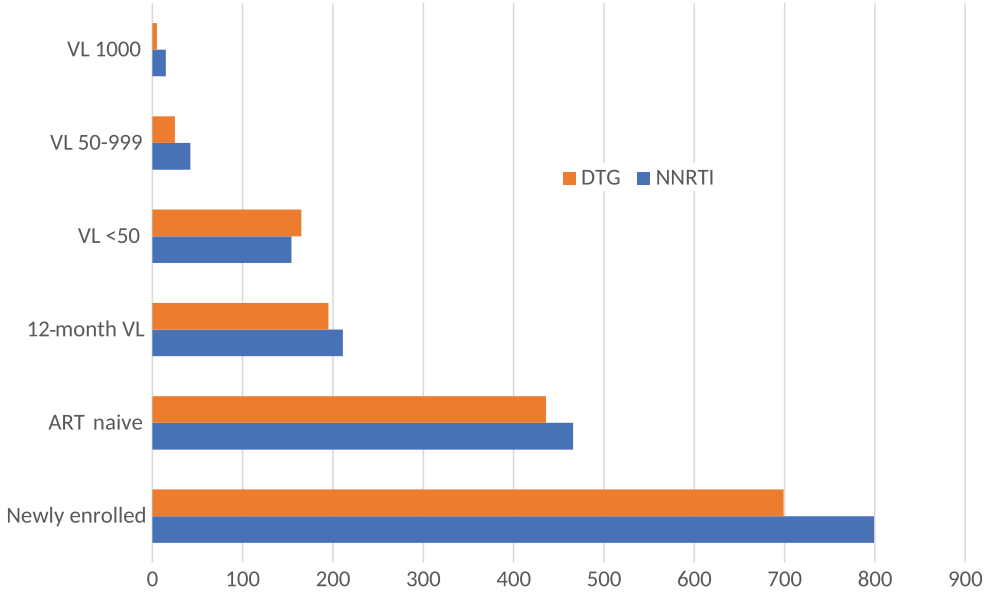

Figure 2. Virologic outcome at 12 mo after initiation of reverse transcriptase inhibitor– and dolutegravir-based antiretroviral therapy in treatment-naive participants. Abbreviations: ART, antiretroviral therapy; DTG, dolutegravir; NNRTI, nonnucleoside reverse transcriptase inhibitor; VL, viral load (copies/mL).

sequenced for PDR determination. In 2 of 14 (14%) samples we detected 1 mutation each, which were V108I and K103N mutations, known to be associated with NNRTI resistance. Additionally, 1 of 14 (7%) patients harbored the Q58E mutation, which is a PI-associated resistance mutation. No mutations associated with NRTI were detected (Table 3).

Blood plasma samples at VL ≥50 copies/mL were available for 13 of 30 (43%) patients. PCR amplification and sequencing for determination of acquired and/or persisting HIV-1 drug resistance–associated mutations was successful for only 2 of 13 (15%) patients. No mutations associated with HIV-1 drug resistance were detected (Table 3).

Side Effects and Pregnancy Outcomes

Seven of 436 (2%) patients discontinued DTG-based ART due to side effects. Of the women initiating DTG-based ART, 33 (12%) women had a documented pregnancy either at treatment initiation or during the follow-up period; 25 (76%) of those delivered a live-born infant with no obvious birth defect, 3 (9%) had a reported abortion, 1 (3%) mother had a stillbirth, and 4 (12%) were LTFU before giving birth.

DISCUSSION

In this prospective real-world study from a rural setting in eastern Africa, we compared the virological outcome of DTG- and NNRTI-based ART in treatment-naive PWH. We found higher virological suppression rates on DTG-based ART compared to NNRTI-based ART at 12 months after initiation. The documented difference in viral suppression in our cohort was even higher than in the first trials evaluating DTG-containing first-line regimens in African settings [20, 21]. The cohorts are comparable as there were no major changes regarding the clinical practice guidelines during the time frames; specifically, ART initiation was recommended for all, regardless of CD4 count, since October 2016 in Tanzania, and VL testing was recommended to monitor treatment success.

Furthermore, we assessed for the presence of PDR among patients with viremia ≥50 copies/mL at months after ART initiation in the DTG cohort. No PDR to NRTI was detected; PDR to NNRTI and PIs was rare, albeit the subgroup for available sequencing data was small. Thus, the observed elevated VL might be due to delayed suppression after treatment start or poor adherence with treatment interruption [22]. Analyses from RCTs and real-life data have shown good virological suppression of DTG-based ART among patients with PDR to NNRTIs [23–25]. In our study we did not systematically screen for PDR to DTG, as resistances to INSTIs would not be expected during the beginning of DTG-based ART rollout, as reported in recent studies in similar settings [26–28]. Moreover, of 30 patients with detectable VL in the DTG-based cohort, 25 (83%) had low viremia (ie, 50–999 copies/mL), which may be a result of momentarily subtherapeutic drug levels due to suboptimal adherence [22].

The fact that we found no HIV-1–associated drug resistance mutations in PWH with a detectable VL on a DTG-based ART is reassuring. However, these results are mitigated by the fact that genotypic results were only available for a small subgroup of participants. While the high proportion of patients with low viremia at 12 months in the DTG-based cohort might be due to

Table 2. Factors Associated With Viral Suppression (HIV-1 RNA <50 Copies/mL) at 12 Months (Window Period 5–15 Months) Among Treatment-Naive Patients Initiating Nonnucleoside Reverse Transcriptase Inhibitor– or Dolutegravir-Based Antiretroviral Therapy

Characteristics	Unadjusted OR (95% CI)[a]	Adjusted OR (95% CI)[a,b]	Adjusted RR (95% CI)[c]
ART regimen			
NNRTI-based	Reference	Reference	Reference
DTG-based	2.16 (1.29–3.62)	2.10 (1.12–3.94)	1.11 (1.00–1.24)
Age, y			
15–24	Reference	Reference	Reference
25–34	1.56 (.62–3.89)	1.81 (.57–5.69)	1.09 (.87–1.37)
35–44	1.05 (.45–2.45)	1.55 (.51–4.73)	1.03 (.82–1.29)
≥45	1.23 (.51–3.00)	1.36 (.43–4.31)	0.99 (.78–1.26)
Sex			
Male	Reference	Reference	Reference
Female	0.65 (.38–1.12)	0.62 (.32–1.21)	0.96 (.85–1.07)
Marital status			
Never	Reference	Reference	Reference
Married/cohabiting	3.19 (1.51–6.74)	2.03 (.70–5.86)	0.80 (.58–1.10)
Separated/divorced/widowed	2.94 (1.29–6.71)	3.32 (1.03–10.7)	1.04 (.93–1.17)
Disclosed HIV status			
No	Reference	Reference	Reference
Yes	1.49 (.81–2.71)	1.58 (.74–3.36)	1.12 (.95–1.32)
Education			
None	Reference	Reference	Reference
Primary	1.42 (.65–3.09)	1.79 (.72–4.49)	1.14 (.90–1.45)
Secondary and above	1.65 (.57–4.79)	4.72 (1.09–20.4)	1.31 (1.02–1.70)
Distance of residence to clinic			
≤1 km	Reference	Reference	Reference
2 to <50 km	1.07 (.60–1.89)	1.27 (.64–2.54)	1.02 (.91–1.15)
≥50 km	0.66 (.33–1.31)	0.66 (.30–1.46)	0.93 (.78–1.11)
Tuberculosis status			
Unlikely	Reference	Reference	Reference
Yes	0.73 (.32–1.64)	1.21 (.44–3.33)	.98 (.81–1.19)
BMI, kg/m^2			
Underweight (<18.5)	0.70 (.35–1.41)	0.86 (.37–2.01)	0.96 (.81–1.15)
Normal (18.5–24.9)	Reference	Reference	Reference
Overweight (≥25)	1.10 (.62–1.95)	1.46 (.68–3.10)	1.06 (.93–1.20)
HIV WHO stage			
I/II	Reference	Reference	Reference
III/IV	2.06 (1.24–3.41)	2.33 (1.17–4.65)	1.14 (1.00–1.34)
CD4 count, cells/μL			
<100	Reference	Reference	Reference
100–349	1.03 (.54–1.96)	0.70 (.32–1.54)	0.93 (.81–1.06)
350	2.13 (.99–4.56)	0.98 (.39–2.45)	1.00 (.87–1.16)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; DTG, dolutegravir; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio.

[a]ORs and 95% CIs obtained from logistic regression.

[b]Adjusted for all variables shown in the table; patients with missing data excluded (n = 330).

[c]aRRs estimated from the multivariable logistic regression model with standard errors estimated using the delta method, adjusted for all variables shown in the table; patients with missing data excluded (n = 330).

early measurement with an expected further decrease, it remains worrisome, as most patients are expected to suppress VL within 3 months and low viremia due to poor adherence may subsequently lead to viral failure and emergence of resistance [29]. Even though resistance to DTG is still uncommon in this setting, evidence from other studies now shows that resistance to DTG may emerge over time, particularly following accumulation of resistance to the NRTI backbone [30–33]. Hence, vigilance and monitoring of low viremia among PWH on DTG-based therapy remain important.

Of note, more than half of the patients in both cohorts had no VL results in the given time span. One reason is the high rate of LTFU, which accounted for 56% and 44% of those without VL results in the NNRTI and the DTG-based cohorts,

Table 3. Patterns of Mutations Detected in the Reverse Transcriptase and Protease Regions of HIV-1 pol Sequences in Participants on Dolutegravir-Based Antiretroviral Therapy With Viral Load ≥50 at 12 Months

Description	At Baseline (n = 14)[a]	At 12 mo (n = 2)[b]
Major NRTI resistance mutations	0 (0)	0 (0)
Major NNRTI resistance mutations	V108I: 1 (7) K103N: 1 (7)	0 (0)
Major PI resistance mutations	Q58E 1: (7)	0 (0)

Data are presented as No. (%).

Abbreviations: NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Fourteen of 25 (56%) samples were tested for pretreatment HIV-1 drug resistance–associated mutations.

[b]Acquired HIV-1 drug resistance–associated mutations were tested for only 2 of 13 (15%) patients at viremia viral load ≥50 copies/mL.

respectively. This rate is comparable to a previous report from the period 2005–2016 from the same clinic with LTFU rates of 41% in the first year after enrollment [34]. Though some of these patients may have silently transferred and collected medication from another clinic, and therefore have a suppressed VL, others are likely to have suboptimal adherence or stopped medication altogether. Importantly, viral suppression rate in the sensitivity analysis was still higher in the DTG-based cohort compared to the NNRTI-based cohort. Regardless, the high rate of LTFU in this rural setting in SSA remains a major concern of the treatment cascade and urgently needs a better understanding of patients' needs and adequate interventions [35].

Being on DTG-based ART was an important factor associated with improved viral suppression, which is in line with existing data from RCTs that showed excellent pharmacokinetic profile and tolerability of DTG, rapid viral suppression, and fewer side effects compared to NNRTIs in treatment-naive and -experienced patients [36–38]. Similarly, in this study, we observed very few patients who discontinued DTG due to side effects. However more data on an extended time span is required and is the aim of future studies. Other factors associated with viral suppression were a higher education level and being separated/divorced/widowed. While other studies have indicated high odds of viral failure in clients who did not disclose their HIV status [39], we found no evidence of such an association. The association of virological suppression with advanced WHO clinical stages in our study might be due to patients feeling worse and therefore more likely to adhere to medication and also receiving closer care and monitoring (and therefore better adherence) [11]. However, this outcome might also be affected by a reporting bias, as these patients are attending the clinic and are tested more frequently.

As in other settings, in the first year of DTG rollout in Tanzania, women of childbearing potential were given the choice to start either DTG-based or NNRTI-based ART, based on informed consent according to the WHO guidelines [40]. Nevertheless, a number of women became pregnant while on DTG. Reassuringly, we did not document obvious birth defects in the 33 women with live births during the study period. One stillbirth and 3 abortions of unknown reasons were reported. While the numbers of this study are too low to draw firm conclusions, it is important to observe uptake among women and pregnancy outcomes as a large observational study from 11 LMICs has shown substantial disparities in the uptake of DTG affecting females of childbearing age [41]. The benefit of rapid viral suppression in pregnant women is of utmost importance to avoid viral transmission to their newborns.

To our knowledge, this is the first study addressing virological outcomes among treatment-naive patients initiating DTG-based ART in Tanzania under programmatic conditions. Our study has several limitations. Most importantly, a large proportion of patients in both cohorts had no VL result in the given time span due to a high rate of LTFU. Another major limitation is unmeasured confounding as these are observational data. Furthermore, many patients who were in active care also had no VL result. Most likely reasons were stockout of reagents or procedural challenges during VL testing implementation. In both timespans, national guidelines recommended VL testing to monitor treatment success. The lack of available VL results might have led to overestimating the rates of viral suppression. Another limitation is that that many blood samples were not available for drug resistance testing. Furthermore, there was significant PCR amplification failure, especially in those with a low VL, which might be due to poor sample storage quality. Finally, all genotypic data were obtained through standard Sanger sequencing; rates of HIV-associated drug resistance mutations would possibly be higher if ultra-sensitive HIV-1 drug resistance testing by next-generation sequencing had been used.

CONCLUSIONS

Our results underline the benefit of programmatic uptake of DTG-based ART in LMICs. We did not find pretreatment resistance to the DTG co-administered NRTIs nor acquired resistance among viremic patients on DTG-based ART, although the number of samples tested was small. Continuous monitoring of pretreatment and acquired resistance under programmatic condition during the rollout of DTG-based first-line is of utmost importance. LTFU remains high and needs further attention as it jeopardizes control of the HIV epidemic.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. J. N., A. E., J. F., J. K., and M. W. conceptualized the study, designed the experiments; A. J. N. wrote the manuscript; A. N., N. K. performed the viral load and resistance testing; A. J. N., A. E., J. O., and F. V. analysed the data; A. J. N., A. E., J. O., F. V., R. N., N. K., J. F., J. K., and M. W. participated in the interpretation of the data, writing, reviewing, and approving the final manuscript. The corresponding author A. J. N. is the guarantor of the paper.

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Data availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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