Viral Load Status Before Switching to Dolutegravir-Containing Antiretroviral Therapy and Associations With Human Immunodeficiency Virus Treatment Outcomes in Sub-Saharan Africa

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Background. Dolutegravir is being rolled out globally as part of preferred antiretroviral therapy (ART) regimens, including among treatment-experienced patients. The role of viral load (VL) testing before switching patients already on ART to a dolutegravir-containing regimen is less clear in real-world settings.

Methods. We included patients from the International epidemiology Databases to Evaluate AIDS consortium who switched from a nevirapine- or efavirenz-containing regimen to one with dolutegravir. We used multivariable cause-specific hazards regression to estimate the association of the most recent VL test in the 12 months before switching with subsequent outcomes.

Results. We included 36 393 patients at 37 sites in 5 countries (Democratic Republic of the Congo, Kenya, Rwanda, Tanzania, Uganda) who switched to dolutegravir from July 2017 through February 2020, with a median follow-up of approximately 11 months. Compared with those who switched with a VL <200 copies/mL, patients without a recent VL test or with a preswitch VL ≥1000 copies/mL had significantly increased hazards of an incident VL ≥1000 copies/mL (adjusted hazard ratio [aHR], 2.89; 95% confidence interval [CI], 1.99–4.19 and aHR, 6.60; 95% CI, 4.36–9.99, respectively) and pulmonary tuberculosis or a World Health Organization clinical stage 4 event (aHR, 4.78; 95% CI, 2.77–8.24 and aHR, 13.97; 95% CI, 6.62–29.50, respectively).

Conclusions. A VL test before switching to dolutegravir may help identify patients who need additional clinical monitoring and/or adherence support. Further surveillance of patients who switched to dolutegravir with an unknown or unsuppressed VL is needed.

Keywords. antiretroviral agents; clinical decision-making; HIV integrase inhibitors; viral load; prognosis.

Dolutegravir, an integrase strand transfer inhibitor, with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), is now the preferred antiretroviral therapy (ART) regimen globally for people living with human immunodeficiency virus (HIV) [1, 2]. In low- and middle-income countries (LMICs), dolutegravir is being scaled up most commonly as a first-line regimen of a once-daily fixed-dose combination tablet that also contains tenofovir disoproxil fumarate and lamivudine [3]. In addition to starting patients newly initiating ART on dolutegravir, patients already on regimens that contain non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as nevirapine and efavirenz, are being switched to dolutegravir [4, 5] because of its superior efficacy and tolerability and high barrier to HIV drug resistance [6]. By 2025, dolutegravir-containing regimens are expected to be the most widely used ART among people living with HIV in LMICs [7].

The World Health Organization (WHO) guidelines recommend at least yearly testing of viral load (VL) for patients established on ART and encourage assessing VL before switching from an NNRTI to dolutegravir [1, 2]. A VL <1000 copies/mL is the recommended cutoff to switch to a first-line regimen of dolutegravir with a tenofovir NRTI backbone. For patients with a VL ≥1000 copies/mL that remains elevated despite adherence support, the WHO currently recommends a second-line dolutegravir regimen that substitutes tenofovir with zidovudine.

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a Members of the contributing IeDEA regions are listed in the Supplementary Materials.

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Resource-constrained settings often have limited access to genotypic resistance testing [8], so a persistently unsuppressed VL may indicate underlying resistance mutations [9]. Because resistance to both tenofovir and lamivudine/emtricitabine is prevalent [10, 11], some ART-experienced patients with an unknown or unsuppressed VL might be switched to regimens in which dolutegravir is the only fully active antiretroviral drug [12, 13]. Exposure to dolutegravir monotherapy may potentially increase the risk for treatment failure and integrase strand transfer inhibitor resistance mutations [14–16]. Despite the WHO guidance, some patients may not have a VL test before switching to dolutegravir. Use of routine VL monitoring remains limited in some resource-constrained settings [8, 17], and national ART guidelines differ in their recommendation for VL testing before regimen changes [18, 19]. In addition, VL testing coverage is sensitive to disruptions of public health systems, whereby VL testing may only be done or available at irregular time intervals, as evidenced during the coronavirus disease 2019 pandemic [20].

Routine clinical care data from the initial stages of the global dolutegravir rollout may provide evidence for how VL monitoring can inform clinical care for patients in HIV treatment programs transitioning to dolutegravir and ultimately preserve it as a treatment option. In this study, we sought to describe VL testing status among patients who switched to dolutegravir in sub-Saharan Africa and then examine associations with subsequent HIV treatment outcomes while on dolutegravir.

METHODS

Data Sources

Data came from the International epidemiology Databases to Evaluate AIDS research consortium, which collects and harmonizes HIV treatment and care data across 7 geographical regions. This analysis included data from the Central Africa (CA) and East Africa (EA) regions. Sites contributing to CA and EA are mostly public facilities with diverse levels of care and comprehensiveness of clinical services offered. Patient data are collected at clinical encounters and are deidentified at the site level before being transmitted to a regional data management center. Site-level data are collected through site surveys that ascertain level of care, availability of services, and other service-related and contextual information [21]. Research ethics committees at sites and regional data management centers provided ethical oversight and approved the use of deidentified data for this analysis.

Inclusion and Exclusion Criteria

We included patients who were aged ≥16 years at the time of HIV care enrollment who switched to a dolutegravir-containing regimen from a nevirapine- or efavirenz-containing regimen from July 2017 through February 2020, started ART ≥6 months before switching, and had ≥6 months of possible follow-up after switching. We excluded patients who had a conflicting dolutegravir start date.

Measures

We examined the following 5 outcomes: an incident VL ≥1000 copies/mL, with a subsequent VL test ≥1000 copies/mL or no subsequent VL test during follow-up; new or recurrent pulmonary tuberculosis or WHO clinical stage 4 event, based on documentation of a clinical diagnosis, with pulmonary tuberculosis additionally imputed based on documentation of initiating a tuberculosis treatment regimen; switch to a protease inhibitor (PI)–containing regimen; switch back to an NNRTI-containing regimen; and death from any cause or loss to program. Death was based on a site's standard practices for ascertainment (ie, active or passive), including estimation of date of death if unknown. Loss to program was defined as either lost to follow-up (ie, no record for ≥7 months immediately preceding the date of site database closure) or known to leave care. The last recorded date of contact was used to determine when patients were lost to program. Death or lost to program was a competing event for the first 4 outcomes. Switching to a non-dolutegravir–containing regimen (other than that related to the outcome, if applicable) was a competing event for all outcomes. Patients were followed from the date of switching to dolutegravir until the outcome of interest, a competing event, date of site database closure, or administrative censoring 18 months after switching. As some clinical events (eg, incident VL ≥1000 copies/mL) were documented on the same day as switching regimens, the clinical event always took precedence.

The main exposure variable was preswitch VL status, that is, a VL measured in the 12 months before switching to dolutegravir (inclusive of the day of switching) and VL result among those with a test (ie, <200 copies/mL, 200–399 copies/mL, 400–999 copies/mL, and ≥1000 copies/mL). VL testing was conducted in accordance with sites' local clinical protocols and was reported as a numeric variable or as undetectable, using the lower limit for detection of the assay used. For patients who had multiple VL tests prior to switching to dolutegravir, we used the VL test closest to the date of switching.

Other variables examined were age group, sex, initial NRTI backbone when starting dolutegravir, year of starting ART, preswitch NNRTI, prior AIDS diagnosis (ie, CD4 count <200 cells/mm^3 or CD4+ percentage <14%, WHO clinical stage 4 event for EA, or documentation of AIDS diagnosis for CA), history of disengagement from care (ie, gap with no record for ≥7 months in up to 5 years before switching), site urbanicity, site level of care, and country. The time interval used to define a history of disengagement from care and lost to follow-up extended the previously validated 6-month interval [22] by 1 month to reduce scheduling-related misclassification among patients with differentiated service delivery with visits every 6 months.

Statistical Analyses

We computed frequencies and proportions of the sample characteristics, medians and interquartile ranges (IQRs) for time from most recent VL test until switching to dolutegravir and time from switching until an event (among those with the outcome of interest), and incidence rates for outcomes, overall and stratified by preswitch VL status. We used cause-specific hazards regression to determine the association between preswitch VL status and each outcome, with a random effect for site. We first ran crude models and then multivariable models adjusted for age group, sex, history of disengagement from care, and prior AIDS diagnosis as potential confounders. Patients with a history of disengagement from care may be less likely to have a VL test because of missing visits and be at higher risk for worse HIV treatment outcomes [23–26]. Prior AIDS diagnosis was included because patients with advanced HIV disease are at higher risk for poor outcomes [27] and may be subject to more intensive monitoring [28], inclusive of VL testing, but may also have more difficulty in achieving viral suppression [26]. Analyses for the VL outcome were limited to patients who had VL testing after switching to dolutegravir (Supplementary Table 1). Analyses for the pulmonary tuberculosis and WHO clinical stage 4 event outcome were limited to EA, as these data were not available for CA. We conducted sensitivity analyses of the multivariable models by limiting to countries outside of Kenya, as most data were from Kenya, and stratifying by median time from preswitch VL until initiating dolutegravir. Analyses were conducted using SAS 9.4 (SAS Institute).

RESULTS

Sample Disposition and Characteristics

From July 2017 through February 2020, 37 765 patients who switched to dolutegravir were assessed for eligibility, and 36 393 individuals were included (Supplementary Figure 1) from 37 sites in 5 countries: Kenya (82%), Uganda (9%), Rwanda (5%), Tanzania (3%), and Democratic Republic of the Congo (0.5%). Less than half (42%) of patients received care at rural sites, and 33% received care at sites with a primary level of care. Overall, 84% of patients were aged 30–59 years, and 52% were female. The majority (82%) started ART before 2016, 54% had a prior AIDS diagnosis, and 12% had a history of disengagement from care. Over half (55%) of patients switched from efavirenz, and 96% had an initial NRTI backbone that contained tenofovir after switching to dolutegravir (Table 1).

Viral Load Testing Before Switching to Dolutegravir and Differences by Sample Characteristics

In the 12 months before switching to dolutegravir, 96% of patients had a VL test and 4% did not. Of those with a VL test, 91% had a VL <200 copies/mL, 5% had a VL 200–399 copies/mL, 3% had a VL 400–999 copies/mL, and 1% had a VL ≥1000 copies/mL (Table 1). Median time from VL test to switch was 1.8 months (IQR, 0.9–4.6). Compared with patients with a preswitch VL <200 copies/mL, patients without a preswitch VL test or with a preswitch VL ≥1000 copies/mL had a younger age distribution, started ART later, more often switched from efavirenz, more often had a history of disengagement from care, and more often received care at sites that were outside of Kenya, rural sites, and sites with a primary level of care.

HIV Treatment Outcomes After Switching to Dolutegravir

For the incident VL ≥1000 copies/mL outcome (N = 30 459), the median follow-up time was 11.5 months (IQR, 9.8–13.9) since switching to dolutegravir until the outcome (n = 444), switching to a PI- or NNRTI-containing regimen (n = 2183), death or loss to program (n = 544), or database closure or administrative censoring (n = 27 288). For the pulmonary tuberculosis and WHO clinical stage 4 event outcome (N = 34 559), the median follow-up time was 11.0 months (IQR, 9.0–12.9) since switching to dolutegravir until the outcome (n = 109), switching to a PI- or NNRTI-containing regimen (n = 2886), death or loss to program (n = 1296), or database closure or administrative censoring (n = 30 268). For switch to a PI- or NNRTI-containing regimen and death or lost to program outcomes (N = 36 393), the median follow-up time was 11.1 months (IQR, 9.0–13.3) since switching to dolutegravir until death or loss to program (n = 1392), switching to a PI-containing regimen (n = 115) or NNRTI-containing regimen (n = 2790), or database closure or administrative censoring (n = 32 096). Among patients who switched to an NNRTI-containing regimen, 69% were female (Supplementary Table 2). The descending incidence of HIV treatment outcomes was as follows: switch to an NNRTI-containing regimen (8.3 per 100 person-years), death or loss to program (4.1 per 100 person-years), incident VL ≥1000 copies/mL (1.5 per 100 person-years), pulmonary tuberculosis or WHO clinical stage 4 event (0.3 per 100 person-years), and switch to a PI-containing regimen (0.3 per 100 person-years; Table 2). Among patients with each outcome of interest, median time until event varied by preswitch VL status.

Association Between Preswitch Viral Load and HIV Treatment Outcomes

Patients with a preswitch VL ≥1000 copies/mL had significantly greater hazards of an incident VL ≥1000 copies/mL (adjusted hazard ratio [aHR], 6.60; 95% confidence interval [CI], 4.36–9.99), pulmonary tuberculosis or a WHO clinical stage 4 event (aHR, 13.97; 95% CI, 6.62–29.50), switch to a PI-containing regimen (aHR, 30.53; 95% CI, 17.87–52.18), switch to an NNRTI-containing regimen (aHR, 2.83; 95% CI, 2.22–3.61), and death or loss to program (aHR, 2.56; 95% CI, 1.81–3.63) compared with those who switched with a VL <200 copies/mL (Table 2). Patients without a preswitch VL load test had significantly greater hazards of an incident VL ≥1000 copies/mL (aHR, 2.89; 95% CI, 1.99–4.19, pulmonary tuberculosis or a WHO clinical stage 4 event (aHR, 4.78; 95% CI, 2.77–8.24), switch to an

Table 1. Viral Load Status in the 12 Months Before Switching to Dolutegravir and Characteristics of Patients and Sites

		Most Recent VL in the 12 Months Before Switching to Dolutegravir				
Variables	Overall Sample	<200 Copies/mL	200–399 Copies/mL	400–999 Copies/mL	≥1000 Copies/mL	No VL Test
Preswitch VL status, N (row %)	36 393 (100)	31 848 (87.5)	1720 (4.7)	993 (2.7)	400 (1.1)	1432 (3.9)
Preswitch VL test to dolutegravir switch, median (interquartile range), months	1.8 (0.9–4.6)	1.8 (0.9–4.6)	1.8 (0.9–4.6)	2.4 (0.9–5.5)	2.1 (0.7–4.6)	Not applicable
Patient characteristics	N = 36 393	N = 31 848	N = 1720	N = 993	N = 400	N = 1432
Age group, N (column %), y						
17–30	1172 (3.2)	945 (3.0)	42 (2.4)	19 (1.9)	39 (9.8)	127 (8.9)
30–39	5817 (16.0)	4981 (15.6)	239 (13.9)	135 (13.6)	109 (27.3)	353 (24.7)
40–49	13 169 (36.2)	11 551 (36.3)	624 (36.3)	381 (38.4)	135 (33.8)	478 (33.4)
50–59	11 514 (31.6)	10 195 (32.0)	604 (35.1)	300 (30.2)	78 (19.5)	337(23.5)
≥60 y	4721 (13.0)	4176 (13.1)	211 (12.3)	158 (15.9)	39 (9.8)	137 (9.6)
Sex, N (column %)						
Female	18 907 (52.0)	16 626 (52.2)	877 (51.0)	530 (53.4)	199 (49.8)	675 (47.1)
Male	17 486 (48.1)	15 222 (47.8)	843 (49.0)	463 (46.6)	201 (50.3)	757 (52.9)
Year of starting antiretroviral therapy, N (column %)						
≤2005	2647 (7.3)	2354 (7.4)	138 (8.0)	83 (8.4)	18 (4.5)	54 (3.8)
2006–2010	13 419 (36.9)	11 901 (37.4)	680 (39.5)	395 (39.8)	92 (23.0)	351 (24.5)
2011–2015	13 719 (37.7)	12 009 (37.7)	625 (36.3)	369 (37.2)	155 (38.8)	561 (39.2)
≥2016	6608 (18.2)	5584 (17.5)	277 (16.1)	146 (14.7)	135 (33.8)	466 (32.5)
Preswitch non-nucleoside reverse transcriptase inhibitor, N (column %)						
Efavirenz	20 118 (55.3)	17 597 (55.3)	854 (49.7)	380 (38.3)	251 (62.8)	1036 (72.4)
Nevirapine	16 275 (44.7)	14 251 (44.8)	866 (50.4)	613 (61.7)	149 (37.3)	396 (27.7)
Nucleoside/nucleotide reverse transcriptase inhibitor backbone when starting dolutegravir, N (column %)						
Tenofovir + lamivudine/emtricitabine	34 683 (95.5)	30 407 (95.7)	1643 (95.6)	916 (92.7)	352 (88.2)	1365 (95.5)
Zidovudine + lamivudine/emtricitabine	1193 (3.3)	998 (3.1)	70 (4.1)	64 (6.5)	28 (7.0)	33 (2.3)
Other[a]	439 (1.2)	374 (1.2)	6 (0.4)	8 (0.8)	19 (4.8)	32 (2.2)
Missing	78	69	1	5	1	2
Prior AIDS diagnosis, N (column %)	19 740 (54.2)	17 187 (54.0)	1034 (60.1)	649 (65.4)	210 (52.5)	660 (46.1)
History of disengagement from care, N (column %)	4399 (12.1)	3357 (10.5)	208 (12.1)	133 (13.4)	97 (24.3)	604 (42.2)
Country, N (column %)						
Democratic Republic of the Congo	165 (0.5)	10 (0.03)	3 (0.2)	1 (0.1)	9 (2.3)	142 (9.9)
Kenya	29 923 (82.2)	26 360 (82.8)	1645 (95.6)	923 (93.0)	243 (60.8)	752 (52.5)
Rwanda	1669 (4.6)	1341 (4.2)	27 (1.6)	14 (1.4)	61 (15.3)	226 (15.8)
Tanzania	1221 (3.4)	1034 (3.3)	11 (0.6)	11 (1.1)	54 (13.5)	111 (7.8)
Uganda	3415 (9.4)	3103 (9.7)	34 (2.0)	44 (4.4)	33 (8.3)	201 (14.0)
Site urbanicity, N (column %)						
Rural	15 379 (42.3)	13 425 (42.2)	613 (35.6)	398 (40.1)	185 (46.3)	758 (52.9)
Urban	21 014 (57.7)	18 423 (57.9)	1107 (64.4)	595 (59.9)	215 (53.8)	674(47.1)
Site level of care, N (column %)						
Primary	12 122 (33.3)	10 532 (33.1)	532 (30.9)	263 (26.5)	180 (45.0)	615 (43.0)
Secondary	13 602 (37.4)	11 886 (37.3)	778 (45.2)	450 (45.3)	123 (30.8)	365 (25.5)
Tertiary	10 669 (29.3)	9430 (29.6)	410 (23.8)	280 (28.2)	97 (24.3)	452 (31.6)

Abbreviation: VL, viral load.

[a]Other primarily consisted of abacavir-containing backbones (91%; 399 of 439).

Table 2. Description of Human Immunodeficiency Virus Treatment Outcomes During Follow-up and Associations With Viral Load Status Before Switching to Dolutegravir

Outcomes,Total and By Preswitch VL Status	Number of Events	Number of Person-Years	Crude Incidence Rate per 100 Person-Years (95% CI)	Median (Interquartile Range) Months Until Event	Unadjusted Hazard Ratio[a] (95% CI); *P* Value	Adjusted Hazard Ratio[b] (95% CI); *P* Value
Incident VL ≥1000 copies/mL					N = 30 459	N = 30 459
Total	444[c]	29 739	1.5 (1.4–1.6)	5.3 (3.2–9.2)		
Preswitch VL, copies/mL						
<200	322	26 297	1.2 (1.1–1.4)	5.5 (3.3–9.2)	Reference	Reference
200–399	34	1547	2.2 (1.6–3.1)	5.6 (3.3–11.2)	1.63 (1.14–2.33); *P* = .007	1.61 (1.13–2.30); *P* = .008
400–999	28	1036	2.7 (1.9–3.9)	6.9 (3.5–14.9)	1.79 (1.21–2.65); *P* = .004	1.75 (1.18–2.59); *P* = .005
≥1000	26	245	10.6 (7.2–15.6)	4.0 (2.8–6.6)	7.23 (4.79–10.91); *P* < .001	6.60 (4.36–9.99); *P* < .001
No VL test	34	614	5.5 (4.0–7.8)	2.5 (1.0–7.0)	3.57 (2.48–5.15); *P* < .001	2.89 (1.99–4.19); *P* < .001
Pulmonary tuberculosis or World Health Organization clinical stage 4 event					N = 34 559	N = 34 559
Total	109[d]	31 760	0.3 (0.3–0.4)	3.2 (1.2–7.1)		
Preswitch VL, copies/mL						
<200	78	28 066	0.3 (0.2–0.3)	3.8 (2.0–7.4)	Reference	Reference
200–399	4	1637	0.2 (0.1–0.7)	7.7 (4.1–11.1)	1.49 (0.54–4.12); *P* = .441	1.46 (0.53–4.04); *P* = .465
400–999	2	1077	0.2 (0.05–0.7)	4.8 (4.1–5.6)	1.06 (0.26–4.35); *P* = .933	1.00 (0.25–4.11); *P* = .996
≥1000	8	250	3.2 (1.6–6.4)	2.9 (1.0–5.8)	15.98 (7.65–33.42); *P* < .001	13.97 (6.62–29.50); *P* < .001
No VL test	17	732	2.3 (1.4–3.7)	0.9 (0.5–1.8)	5.49 (3.22–9.36); *P* < .001	4.78 (2.77–8.24); *P* < .001
Switch to a protease inhibitor–containing regimen					N = 36 393	N = 36 393
Total	115[e]	33 799	0.3 (0.3–0.4)	3.3 (1.8–7.6)		
Preswitch VL, copies/mL						
<200	79	29 647	0.3 (0.2–0.3)	3.7 (1.8–7.0)	Reference	Reference
200–399	5	1671	0.3 (0.1–0.7)	7.6 (2.8–9.9)	1.35 (0.54–3.35); *P* = .519	1.35 (0.54–3.36); *P* = .516
400–999	6	1094	0.5 (0.2–1.2)	9.5 (7.6–10.2)	2.80 (1.20–6.52); *P* = .017	2.72 (1.17–6.35); *P* = .020
≥1000	19	323	5.9 (3.7–9.2)	1.8 (1.0–5.3)	31.14 (18.36–52.80); *P* < .001	30.53 (17.87–52.18); *P* < .001
No VL test	6	1064	0.6 (0.3–1.3)	2.8 (2.1–12.5)	2.14 (0.91–5.00); *P* = .080	2.13 (0.90–5.04); *P* = .086
Switch to a non-nucleoside reverse transcriptase inhibitor–containing regimen					N = 36 393	N = 36 393
Total	2790[f]	33 799	8.3 (8.0–8.6)	3.1 (1.9–6.4)		
Preswitch VL, copies/mL						
<200	2352	29 647	7.9 (7.6–8.3)	3.2 (2.0–6.4)	Reference	Reference
200–399	116	1671	6.9 (5.8–8.3)	3.7 (2.5–7.3)	0.98 (0.81–1.18); *P* = .798	0.99 (0.82–1.20); *P* = .940
400–999	90	1094	8.2 (6.7–10.1)	3.6 (1.7–7.4)	1.24 (1.00–1.53); *P* = .048	1.20 (0.97–1.49); *P* = .092
≥1000	69	323	21.3 (16.8–27.0)	1.4 (0.9–2.8)	3.51 (2.75–4.48); *P* < .001	2.83 (2.22–3.61); *P* < .001
No VL test	163	1064	15.3 (13.1–17.9)	2.3 (1.0–4.6)	1.80 (1.53–2.12); *P* < .001	1.55 (1.31–1.83); *P* < .001
Death or loss to program					N = 36 393	N = 36 393
Total	1392[g]	33 799	4.1 (3.9–4.3)	4.0 (1.0–8.1)		
Preswitch VL, copies/mL						
<200	1050	29 647	3.5 (3.3–3.8)	4.4 (1.4–8.4)	Reference	Reference
200–399	69	1671	4.1 (3.3–5.2)	4.9 (1.8–8.8)	1.14 (0.89–1.46); *P* = .286	1.14 (0.90–1.46); *P* = .283

Table 2. Continued

Outcomes, Total and By Preswitch VL Status	Number of Events	Number of Person-Years	Crude Incidence Rate per 100 Person-Years (95% CI)	Median (Interquartile Range) Months Until Event	Unadjusted Hazard Ratio[a] (95% CI); *P* Value	Adjusted Hazard Ratio[b] (95% CI); *P* Value
400–999	43	1094	3.9 (2.9–5.3)	7.2 (3.1–11.1)	1.12 (0.82–1.52); *P* = .478	1.12 (0.82–1.52); *P* = .486
≥1000	34	323	10.5 (7.5–14.7)	4.4 (1.0–7.2)	3.03 (2.15–4.28); *P* < .001	2.56 (1.81–3.63); *P* < .001
No VL test	196	1064	18.4 (16.0–21.2)	1.4 (0.03–3.9)	5.38 (4.57–6.33); *P* < .001	3.77 (3.19–4.46); *P* < .001

Abbreviations: CI, confidence interval; VL, viral load.

[a]Models included a random effect for site but were not adjusted for covariables.

[b]Models included a random effect for site and were adjusted for age group, sex, prior AIDS diagnosis, and history of disengagement from care.

[c]18% (79 of 444) had a subsequent VL test ≥1000 copies/mL, and 82% (365 of 444) had a single VL ≥1000 copies/mL with no subsequent VL test. Patients who had a single VL ≥1000 copies/mL and later resuppressed on a subsequent VL test were not included.

[d]In nonmutually exclusive categories, 83% (90 of 109) had pulmonary and/or extrapulmonary tuberculosis, 9% (10 of 109) had extrapulmonary cryptococcosis, 6% (6 of 109) had Kaposi sarcoma, and 5% (5/109) had documentation of another World Health Organization clinical stage 4 event.

[e]72% (83 of 115) switched to a ritonavir-boosted atazanavir-containing regimen, and 28% (32 of 115) switched to a ritonavir-boosted lopinavir-containing regimen.

[f]86% (2403 of 2790) switched to an efavirenz-containing regimen, and 14% (387 of 2790) switched to a nevirapine-containing regimen.

[g]15% (213 of 1392) died, 36% (508 of 1392) were lost to follow-up, and 48% (671 of 1392) were known to leave care.

NNRTI-containing regimen (aHR, 1.55; 95% CI, 1.31–1.83), and death or loss to program (aHR, 3.77; 95% CI, 3.19–4.46) compared with those who switched with a VL <200 copies/mL.

In sensitivity analyses (Supplementary Table 3), substantial power was lost when the sample was limited to patients outside of Kenya, but similar patterns in associations were observed despite wide confidence intervals. When stratifying preswitch VL by the median time until initiating dolutegravir (ie, 56 days), associations between a preswitch VL ≥1000 copies/mL and outcomes were generally similar regardless of timing.

DISCUSSION

Patients who switched to dolutegravir with a VL ≥1000 copies/mL or without a recent VL test had worse HIV treatment outcomes, which emerged shortly after switching, compared with patients who switched with a suppressed VL. Although they represented only 5% of patients in the sample, globally, in LMICs, there were several million people living with HIV with an unknown or unsuppressed VL on NNRTI-containing ART before the widespread implementation of dolutegravir [4]. Therefore, the public health implications of interventions to improve outcomes among these patients could be substantial.

Patients with a preswitch VL ≥1000 copies/mL generally had the most adverse HIV treatment outcomes, but we do not know how their outcomes compared with what their outcomes would have been had they not switched to dolutegravir, that is, the counterfactual. The cohorts included in this analysis do not have ready access to genotypic resistance testing for patients with viral nonsuppression on a first-line regimen, so we were unable to determine if resistance mutations explained the associations with more adverse outcomes. Previous research in this setting indicates that mutations relevant to NRTIs (eg, K65R, M184V/I) are common among patients unsuppressed on nevirapine- or efavirenz-containing regimens [29, 30]. Nevertheless, most patients, even with partial or extensive NRTI resistance, can achieve viral suppression on a dolutegravir-containing regimen [31–33]. Most patients with a preswitch VL ≥1000 copies/mL did not have tenofovir substituted with zidovudine; however, recent data support that this would unlikely compromise at least 48-week viral suppression [32–34]. We think it is plausible that patients with preswitch VL ≥1000 copies/mL had adherence issues that went unresolved after switching to dolutegravir; however, we did not have data on whether additional adherence support was provided. It may be possible that clinicians anticipated that switching to a more potent dolutegravir-containing regimen with a higher genetic barrier to resistance would reverse the risk for adverse treatment outcomes, and adherence issues went unaddressed.

For patients without a preswitch VL test, we would hypothesize that the underlying distribution of actual VL levels included a sizable proportion with an elevated VL based on

the associations with HIV treatment outcomes. This group of patients appeared to be at especially high risk of poor adherence because of the high prevalence of prior disengagement from care and increased hazards of death or loss to program. In settings with access to routine VL testing, HIV treatment programs should train providers to use preswitch VL to inform treatment decisions before a planned regimen change to dolutegravir and consider additional clinical monitoring and/or adherence support for patients with an unsuppressed VL. At a population level, ongoing surveillance of patients who switched to dolutegravir without a recent VL test or with an unsuppressed VL may help to identify ways to prevent differentially adverse outcomes among these 2 patient groups. Although this study provides some insight from the initial rollout, examination of the long-term effectiveness of dolutegravir use at scale in real-world settings is essential.

This study provides additional evidence into the use of a threshold of <1000 copies/mL on a VL test in the previous 12 months to recommend switching. Ongoing low-level viral replication is associated with increased risk of HIV drug resistance and virologic failure [35–37]; therefore, this threshold has been questioned as possibly being too high [5]. Our findings support this threshold, as switching above it was associated with the highest hazard ratios for outcomes. However, switching with any unsuppressed VL (≥200 copies/mL) was associated with significantly increased hazards of some outcomes, albeit at a lower magnitude.

Some limitations should be considered in the interpretation of this study. The proportion of patients with a preswitch VL that was ≥1000 copies/mL or unknown is likely larger outside of our sample. Our sample included patients established on ART, most for several years, before switching to dolutegravir who might have had better adherence and viral suppression than patients more recently initiating ART. Furthermore, sites in rural locations and those with a primary level of care, with potentially less access to routine VL testing, were underrepresented [8]. Nevertheless, we would not expect smaller proportions of these exposures to bias associations with HIV treatment outcomes. Females were also underrepresented, and most patients who switched back to an NNRTI-containing regimen were female, both of which were due to now resolved concerns about infant neural tube defects [38]. We anticipate more female patients initiating and continuing dolutegravir with consequentially lower overall discontinuation rates. Although we had a large overall sample size, some exposure categories had small sample sizes; with short-term follow-up, the incidence of outcomes was low. Consequentially, confidence intervals were wide for some associations. Longer-term follow-up would allow for more precise estimates and, importantly, would allow for determination of associations with long-term outcomes. In addition to patients with a persistently elevated VL ≥1000 copies/mL, the VL outcome included patients with a single VL ≥1000 copies/mL and no subsequent testing. As the lack of confirmatory testing does not necessarily mean that resuppression on dolutegravir did not occur, this variable may not be fully prognostic of future virologic failure. Confirmatory testing may not always be done, especially in resource-constrained settings [39]; however, because resuppression with dolutegravir is more common than with NNRTIs [40], this approach may need to be reconsidered.

In conclusion, our study supports that a preswitch VL may be useful in identifying patients at elevated risk for adverse HIV treatment outcomes after switching to dolutegravir who may benefit from additional clinical monitoring and/or adherence support. Surveillance of patients who switched without a recent VL test or with an unsuppressed VL may help identify ways to preserve dolutegravir-containing ART as a long-term treatment option.

Supplementary Data

Supplementary materials are available at *Clinical 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

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