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MAJOR ARTICLE

Transitioning Women With Human Immunodeficiency Virus to First-Line Preferred Regimen of Tenofovir Disoproxil Fumarate, Lamivudine, and Dolutegravir in Sub-Saharan Africa

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Background. In 2019, the World Health Organization (WHO) recommended combined tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD) as the preferred first-line regimen for adults and adolescents with human immunodeficiency virus (HIV), regardless of childbearing status. Nevertheless, final eligibility is determined by local policies, which may vary from WHO recommendations. We examined TLD transition by sex across 5 HIV care programs in sub-Saharan Africa supported by the United States President's Emergency Plan for AIDS Relief (PEPFAR)

Methods. The African Cohort Study (AFRICOS) enrolls people with HIV engaged in care in Uganda, Kenya (South Rift Valley and Kisumu West), Tanzania, and Nigeria. People with HIV with ≥1 study visit after the country introduced TLD were included. We generated Kaplan-Meier curves to compare TLD transition by sex from (1) the time countries introduced TLD and (2) the time of TLD eligibility according to local policies.

Results. Among 2476 participants enrolled through September 2021 at 4 sites in sub-Saharan Africa and eligible to transition to TLD, fewer women (68%) than men (80%; $P < .001$) were taking TLD. Kaplan-Meier analysis showed that time to transition varied by site, with women in Tanzania transitioning at the same rate as men. In Nigeria, women initially had a slower transition but caught up to men. After adjustment for local policies, women in Kisumu West transitioned at the same rate as men. In South Rift Valley and Uganda, women were less likely to be transitioned.

Conclusions. Although TLD has been the WHO's preferred regimen since 2019, transition of women to potentially lifesaving TLD has been slower than for men at certain clinical sites, even after accounting for local eligibility criteria.

Keywords. HIV; gender disparities; TLD.

Attaining and maintaining virologic suppression is key to achieving human immunodeficiency virus (HIV) epidemic control and reaching the UNAIDS 95-95-95 goals in 2030 [1]. The adoption of optimized antiretroviral therapy (ART) harmonizes treatment options, simplifies drug procurement, lowers costs, and enhances access to treatment for people with HIV (PWH) across different population groups, and improves program outcomes at national and subnational levels [2–6]. In addition, the use of new and improved ART regimens offers promise of increased treatment efficiency, adherence, tolerability, safety, convenience, and improved quality of life for PWH [7, 8]. In 2016, consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection released by the World Health Organization (WHO) included dolutegravir (DTG), an integrase strand transfer inhibitor, as a new alternative option in first-line ART regimens [9].

Current data suggests that DTG-based regimens are better at achieving and maintaining viral suppression than efavirenz-based regimens [10–13]. The use of DTG-based regimens has also been associated with reduced need for regimen switch, as well as lower risk of major HIV drug resistance mutations, compared with efavirenz-based regimens [14, 15]. There is evidence that DTG-based therapy also has superior outcomes compared with boosted protease inhibitor–based regimens in PWH who commence second-line therapy with ≥ 1 active nucleoside reverse-transcriptase inhibitor [16].

Early safety data suggested an increased risk of neural tube defects in infants of women with HIV receiving DTG at conception [17, 18]. Based on initial available evidence, the WHO made a conditional recommendation for the use of DTG as a

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preferred drug in treatment-naive PWH initiating ART in 2018 but added a note of caution when DTG was given to women of childbearing potential [19]. However, additional data in 2019 from more clinical trials showed that the risk of exposed infants developing neural tube defects were lower than initially suggested. Coupled with an assessment of benefits and risks through modelling studies [20–22], WHO expanded the recommendation to use DTG-based regimens as the preferred first- and second-line treatment for all populations, including pregnant women and those of childbearing potential in 2019 [23].

Currently, the preferred first-line ART is a fixed-dose combination of tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD). Even among individuals with extensive nucleoside reverse-transcriptase inhibitors resistance, DTG in combination with nucleoside reverse-transcriptase inhibitors was effective in obtaining viral suppression in the NADIA trial [24]. Thus, DTG-based regimens, is also recommended as a preferred second-line ART regimen for patients in whom non–DTG-based regimens fail. Countries were encouraged to start the transition to DTG-based regimens for all patients with newly diagnosed HIV, and for those who are stable on nonnucleoside reverse-transcriptase inhibitor–based ART as well as those who need to switch to second-line treatment.

Following this updated guidance by WHO, many national health systems have modified their HIV treatment policies and guidelines to include eligibility for DTG-based regimens for women of childbearing potential. Local policies also detail who is eligible for receiving TLD. A recent multicountry observational cohort study revealed disparities in uptake of DTG-based regimens among women of childbearing potential, with countries that began implementing the implementation of DTG before the issuance of the safety signal experiencing slower uptake [25]. The objective of this study was to assess sex differences in time to TLD transition in HIV clinics in sub-Saharan Africa supported by the United States President's Emergency Plan for AIDS Relief (PEPFAR).

METHODS

The African Cohort Study (AFRICOS), started in 2013, is a longitudinal prospective cohort study that enrolls people without HIV and PWH who are engaged in care in PEPFAR-supported programs at 12 clinical care sites in 4 countries: Kayunga, Uganda; South Rift Valley and Kisumu West, Kenya; Abuja and Lagos, Nigeria; and Mbeya, Tanzania. Participants are aged ≥15 years and complete study visits every 6 months. At each visit, participants complete sociodemographic and behavioral questionnaires; clinicians complete a medical history and perform a physical examination, and laboratory assessments are conducted. ART regimens are extracted from medical record review at each visit. For this analysis, we included all PWH with ≥1 clinic visits after the country switched to TLD as of 1 September 2021. Viral suppression was defined by a viral load <1000 copies/mL.

All participants in AFRICOS provide written informed consent. The study was approved by institutional review boards of the Makerere University School of Public Health, the Tanzania National Institute of Medical Research, the Kenya Medical Research Institute, the Nigerian Ministry of Defense, and the Walter Reed Army Institute of Research.

TLD Eligibility Requirements by Site

In Nigeria, TLD transition started in October 2018 (Figure 1). Initially, only individuals who were virally suppressed and were unlikely to conceive were eligible for TLD. Eligibility was expanded to all women in August 2020. In Kenya, transition to TLD began in December 2018 and was initially available to those who were virally suppressed and women aged ≥50 years who were virally suppressed. In March 2019, viral load suppression was no longer required, and in January 2020, all women were eligible. Uganda started transitioning to TLD in December 2018 for those who had a viral load test showing suppression within the last 6 months. Women needed to be taking precautions against becoming pregnant. In October 2020, all women became eligible and in February 2021, the window period for showing documentation of viral load suppression requirement was expanded to 12 months. Tanzania transitioned to TLD in March 2019 and required women to be taking pregnancy prevention measures. This requirement was removed in January 2020. There was no requirement for viral load suppression. For all sites, prevention measures against pregnancy included reporting using a family planning method or not being sexually active since the last visit.

Statistical Analysis

We used χ^2 and Kruskal-Wallis tests to compare characteristics at the most recent visit between those who did and did not transition to TLD. We then generated Kaplan-Meier curves to determine whether the transition to TLD differed by sex and by (1) country and (2) country but adjusted entry into the analytic population based on local eligibility requirements, as outlined above. Multivariable Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for the association of (1) sex and site with time to TLD transition, controlling for age and viral suppression; and (2) sex and age with TLD transition, controlling for viral suppression. As a small subset of women were transitioned to TLD before meeting eligibility criteria, we ran a sensitivity analysis including the women at their actual TLD initiation date rather than the eligibility date.

RESULTS

As of 1 September 2021, there were 3108 participants enrolled in AFRICOS. Of these, 2476 (80%) were eligible to be transitioned to TLD based on the country eligibility criteria listed above. Looking specifically at viral load suppression, 844 of 916 men

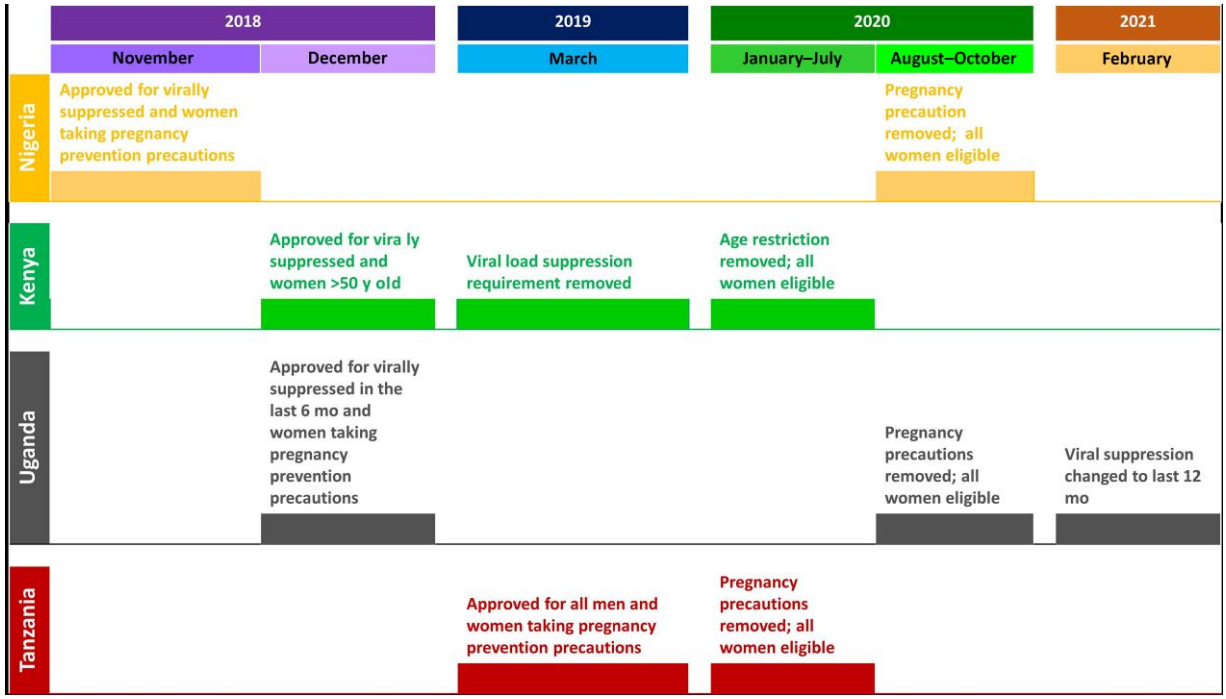

Figure 1. Country-level eligibility criteria for tenofovir disoproxil fumarate, lamivudine, and dolutegravir regimen.

(92%) and 1236 of 1309 women (94%) were virally suppressed (<1000 copies/mL; $P = .03$). Of those eligible, 1799 participants (73%) had ≥1 visit while receiving TLD (Table 1). A higher percentage of participants from the Nigeria (79.8%) and Kisumu West sites were transitioned to TLD compared with the South Rift Valley site (79.3% vs 64.0%, respectively; $P < .001$). Participants who transitioned to TLD had a median age (interquartile range) of 44.7 (36.4–52.6) years, compared with 40.9 (35.5–51.3) years ($P < .001$) for those who did not transition to TLD. Among those who were virally suppressed, the majority were on TLD (75.7%) while the majority who were not suppressed were those who were not on TLD (72%).

Examining Kaplan-Meier curves without accounting for local policies (Figure 2), women in Tanzania transitioned at the same rate as men, while in Nigeria women initially had a slower transition but eventually caught up to men (Figure 2*E* and 2*F*). In Kisumu West, women initially transitioned at the same rate, followed by slowing, and then their rate equalized with that for male transition (Figure 2*D*). In Uganda and the South Rift Valley, women did not transition as quickly as men and still lag (Figure 2*B* and 2*C*). After accounting for local eligibility criteria, the transitions were similar for men and women in Kisumu West (Figure 2*D*). However, women in Uganda and the South Rift Valley still were less likely to have transitioned to TLD (Figure 2*B* and 2*C*).

After controlling for viral suppression and age, women in Uganda (aHR, 0.40 [95% CI, .31–.51]) and Kenya (South Rift Valley, 0.42 [.34–.51]; Kisumu West, 0.63 [49–.82]) had a lower rate of transitioning to TLD than men (Table 2). Findings were similar but slightly attenuated after adjusting study entry for country-level eligibility (aHR [95% CI] 0.46 [.36–.60] for Uganda, 0.47 [.38–.58] for South Rift Valley; and 0.70 [.52–.96] for Kisumu West) (Table 2). In the sensitivity analysis allowing inclusion of women whose TLD initiation preceded the country-specific TLD eligibility date, findings were similar, with only women in Uganda and Kenya having slower rates of transitioning to TLD than men.

Examining the interaction between age and sex and adjusting for viral suppression, for all age categories, women had a slower rate of transitioning to TLD compared with men in the same age category (Table 3). Women in the 30–39-year age group had the slowest rate of transition compared with men in the same age range (aHR [95% CI], 0.37 [.28–.48]).

DISCUSSION

This study found that, even after accounting for local policies, women who were eligible for TLD were less likely to transition to it in Uganda and in South Rift Valley, Kenya. Uganda and Kenya began TLD implementation in December 2018, before the 2019 WHO updated recommendations, when counseling and consent were required for women of childbearing age to be on TLD. According to one study, staff shortages to provide counseling, obtaining consent, and community education were likely barriers to transitioning women in Uganda and South Africa [26]. The change in 2019 would have required local

Table 1. Participant Characteristics at the Most Recent Visit by Treatment Status as of 1 September 2021

Characteristic	Participants, No. (%)			
	Not on TLD (n = 677)	On TLD (n = 1799)	Total (N = 2476)	*P* Value
Study site				
Kayunga, Uganda	121 (27.9)	312 (72.1)	433 (100.0)	<.001[a]
South Rift Valley, Kenya	301 (36.0)	536 (64.0)	837 (100.0)	
Kisumu West, Kenya	102 (20.7)	391 (79.3)	493 (100.0)	
Mbeya, Tanzania	95 (22.1)	335 (77.9)	430 (100.0)	
Abuja and Lagos, Nigeria	57 (20.2)	225 (79.8)	282 (100.0)	
Sex				
Male	209 (20.4)	814 (79.6)	1023 (100.0)	<.001[a]
Female	467 (32.2)	985 (67.8)	1452 (100.0)	
Age at visit, y				
15–29	107 (30.1)	249 (69.9)	356 (100.0)	<.001[a]
30–39	189 (35.7)	340 (64.3)	529 (100.0)	
40–49	241 (27.4)	640 (72.6)	881 (100.0)	
≥50	139 (19.6)	570 (80.4)	709 (100.0)	
Education				
None or some primary	215 (27.3)	572 (72.7)	787 (100.0)	.56
Primary or some secondary	276 (28.3)	699 (71.7)	975 (100.0)	
Secondary and above	185 (25.9)	528 (74.1)	713 (100.0)	
Marital status				
Not married	303 (47.9)	787 (44.5)	1090 (45.4)	.14
Married	329 (52.1)	980 (55.5)	1309 (54.6)	
Using some form of pregnancy prevention				
No	67 (10.7)	144 (8.1)	211 (8.8)	<.001[a]
Yes	222 (35.3)	393 (22.2)	615 (25.6)	
NA (male)	209 (33.2)	814 (46.0)	1023 (42.6)	
NA (not sexually active)	131 (20.8)	420 (23.7)	551 (23.0)	
Viral suppression				
≥1000 copies/mL	67 (72.0)	26 (28.0)	93 (100.0)	<.001[a]
<1000 copies/mL	446 (24.3)	1392 (75.7)	1838 (100.0)	

Abbreviations: NA, not applicable; TLD, tenofovir disoproxil fumarate, lamivudine, and dolutegravir.

[a]Significant at $P < .05$.

policy changes, retraining, and community education which likely slowed scaling up of women on TLD. In addition, Uganda and Kenya had more restrictive local policies initially, which may have contributed to the delay. In contrast, Tanzania began implementing TLD in March 2019 after the updated guidelines and more global experience had been gained.

Our study also found that, regardless of age, women were still less likely than their male counterparts to be on TLD. We initially thought women outside their reproductive ages would transition at the same time as men in the same age category, especially in Kenya, where the initial policy allowed for women ≥50 years old to be transitioned. The slower transition, regardless of age, may reflect providers' hesitation initiating TLD in women generally, underscoring a need for provider retraining and community education. With specific regard to women of childbearing age, there may have been issues with access to contraceptives in some countries, a requirement for most initial policies. In Uganda and Kenya, studies suggest there are unmet contraceptive needs and concerns for stockouts [26–28]. In addition, contraceptive use among adolescents and young adults and in some rural communities can be inconsistent [28–30]. These concerns may have contributed to limited use of TLD in younger women. Identifying and addressing barriers to optimal care should be programmatic priorities, and women with HIV should be a central part of policy changes and outreach to their communities. Focus groups or surveys with healthcare providers should also be considered and could provide more insight into barriers for transitioning women, especially those ≥50 years old.

Interestingly, though the same country policies applied to both Kisumu West and South Rift Valley, Kenya, women in Kisumu West did not experience a delay in TLD transition, while those in South Rift Valley did. Such a difference between sites suggests local differences in healthcare treatment and management. Regional variation in healthcare practice may be the result of differences in regional spending, clinician education, availability of commodities, and community awareness and expectations [31]. South Rift Valley is home to a mostly rural, mobile population who may access care at different health centers or may have challenges accessing healthcare routinely. Given the mobility, there may be a data recording and tracking component that will need further investigation. Differences in uptake between sites may also be due to differences in provider knowledge and comfort with possible inability to monitor women being transitioned to TLD.

Allowing community-based organizations to provide ARTs and contraception may allow for more continuity of treatment care and improve access to treatment regimens. However, at the time of this analysis, the proportion of eligible women who had transitioned to TLD in Kenya had plateaued below the proportion of men, with considerably fewer women than men in South Rift Valley transitioned to TLD. This is not inconsequential, TLD has improved efficacy and tolerability over other regimens [10, 15, 16, 32], and when women are not given access to this regimen, they are essentially relegated to second-tier care, with consequent compromises in health outcomes and quality of life. Furthermore, any diminution of viral suppression can have further downstream effects, including potential increases in transmission.

Strengths of the current study include the multicountry analysis as well as nearly 3 years of follow-up after TLD policy adoption. However, the study is not without a few limitations. In order to run analyses across countries, we used the WHO definition for viral suppression of 1000 copies/mL. However, some of the countries required stricter definitions of suppression. In addition, other countries permitted use of TLD by women of childbearing age if they signed consent forms, which we were unable to track in our data. While we used dates that policies

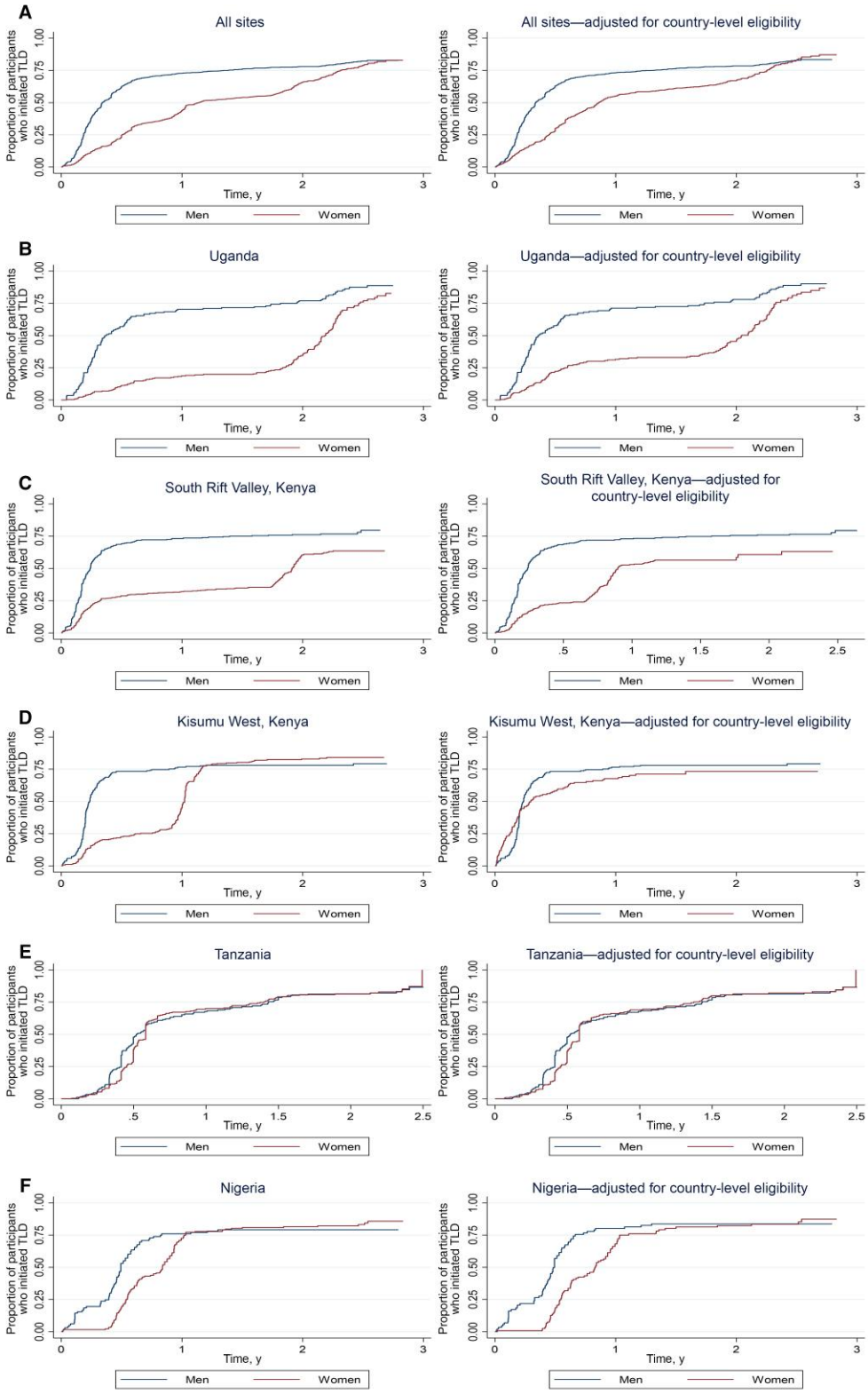

Figure 2. Kaplan-Meier curve for transition to tenofovir disoproxil fumarate, lamivudine, and dolutegravir regimen by site, with and without country eligibility criteria as of 1 September 2021.

Table 2. Hazard Ratios and 95% Confidence Intervals for Time to Uptake of Tenofovir Disoproxil Fumarate, Lamivudine, and Dolutegravir Regimen as of 1 September 2021

Country, Age Group, and Viral Suppression	Main Analysis		Adjusted for Country-Level Policies	
	HR	95% CI	HR	95% CI
Uganda				
Men	Reference	…	…	…
Women	0.40	.31–.51	0.47	.36–.60
South Rift Valley, Kenya				
Men	Reference	…	…	…
Women	0.42	.34–.51	0.47	.38–.58
Kisumu West, Kenya				
Men	Reference	…	…	…
Women	0.63	.49–.82	0.70	.52–.96
Tanzania				
Men	Reference	…	…	…
Women	0.96	.73–1.26	0.94	.71–1.24
Nigeria				
Men	Reference		…	
Women	0.90	.68–1.20	0.74	.55–1.02
Age at visit, y				
15–29	Reference		…	
30–39	1.02	.84–1.23	1.02	.82–1.27
40–49	1.31	1.10–1.55	1.14	.94–1.37
≥50	1.68	1.41–2.01	1.46	1.22–1.76
Viral suppression				
≥1000 copies/mL	Reference	…	…	…
<1000 copies/mL	3.89	2.63–5.76	3.71	2.29–6.01

Abbreviations: CI, confidence interval; HR, hazard ratio; TLD, tenofovir disoproxil fumarate, lamivudine, and dolutegravir.

Table 3. Unadjusted and Adjusted Hazard Ratios for Time to Uptake of Tenofovir Disoproxil Fumarate, Lamivudine, and Dolutegravir as of 1 September 2021

Age Group and Viral Load	Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI
Age 15–29 y				
Men	Reference	…	…	…
Women	0.78	.60–1.01	0.69	.51–.94
Age 30–39 y				
Men	Reference	…	…	…
Women	0.41	.33–.51	0.37	.28–.48
Age 40–49 y				
Men	Reference	…	…	…
Women	0.51	.43–.59	0.50	.42–.60
Age ≥50 y				
Men	Reference	…	…	…
Women	0.80	.68–.95	0.73	.60–.88
Viral load				
<1000 copies/mL	Reference	…	…	…
≥1000 copies/mL	3.62	2.45–5.34	4.06	2.75–6.00

Abbreviations: CI, confidence interval; HR, hazard ratio.

were enacted, in reality, implementation of those policy changes may have occurred at a different date and could have been delayed, especially in more rural clinical sites. Finally, we did not account for challenges with commodities and the availability of TLD in each country. However, limited supplies should have affected each sex equally.

In conclusion, our data found significant sex disparities with women less likely to be started on lifesaving TLD. Denying women the benefit of improved likelihood of viral suppression unnecessarily puts them at higher risk for poor health outcomes and may increase mother-to-child and partner transmission. Two years after policies restricting use among women were reversed and local eligibility has been expanded to all PWH, uptake is still lagging in some geographic areas. Work is needed to educate providers and engage women with HIV in demanding equitable care. Policy makers should ensure that they have access to robust data before drafting recommendations, because changes to guidelines may have lasting effects, as our data demonstrate. As new treatments become available, equitable access to optimized ART requires a flexible and robust pharmacovigilant surveillance system and a comprehensive public health communication strategy engaging PWH, healthcare providers, and communities.

Notes

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