

Superior Outcomes With Continuing Tenofovir Versus Switching to Zidovudine in Second-Line Antiretroviral Therapy in Haiti

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We compared viral suppression rates between patients who continued tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) vs switched to zidovudine (ZDV)/3TC in combination with a boosted protease inhibitor after failure of first-line efavirenz/TDF/3TC. We found higher rates of viral suppression with continued TDF/3TC compared with switching to ZDV/3TC.

Keywords. genotypic resistance; HIV; second-line therapy; tenofovir disoproxil fumarate; zidovudine.

World Health Organization (WHO) guidelines recommend an optimized nucleoside reverse transcriptase inhibitor (NRTI) backbone for second-line antiretroviral therapy (ART), meaning that patients who fail tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) are switched to zidovudine (ZDV)/3TC plus a third agent [1]. This approach follows a longstanding tenet of infectious disease management, the avoidance of changing only 1 drug in a failing regimen, and is supported by data suggesting that this population is more likely to have genotypic resistance to TDF than ZDV [2].

However, ZDV is rarely prescribed in high-income settings due to toxicity and twice-daily administration. Moreover, several studies have documented high rates of viral suppression among patients with no predicted-active NRTIs, indicating that

NRTIs may retain substantial efficacy in spite of predicted genotypic resistance [3–5]. This may be due to reduced viral fitness or enhanced drug susceptibility associated with certain mutations or retained partial efficacy of NRTIs in combination with a third agent with a high barrier to resistance.

We conducted a retrospective analysis to compare outcomes for patients at the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO) who continued TDF vs switched to ZDV for second-line ART.

METHODS

Study Setting, Participants, and Design

GHESKIO, a Haitian nongovernmental organization located in Port-au-Prince, has been providing ART for nearly 20 years. Initially, first-line ART included a nonnucleoside reverse transcriptase inhibitor (NNRTI) + 2 NRTIs; efavirenz (EFV)/TDF/3TC was the preferred regimen from 2010 until the end of 2018, when dolutegravir (DTG) became available. Treatment failure was defined by clinical and immunologic criteria until 2016, when viral load testing became available; a threshold of 1000 copies/mL is used to define virologic failure, in accordance with WHO guidelines. In a sample of 235 adults who failed first-line ART at GHESKIO, rates of intermediate or high-level resistance were 82.6%, 21.7%, 3.4%, and 49.4%, to EFV, TDF, ZDV, and 3TC, respectively, according to the Stanford HIV Drug Resistance Database version 9.0 [6, 7]. Prevalent NRTI resistance-associated mutations included M184V/I in 39.1%, K65R/N in 15.7%, and both mutations in 10.2%.

The current study included data for all adult (≥ 18 years) patients at GHESKIO who failed EFV/TDF/3TC and switched to a second-line regimen that included either TDF/3TC or ZDV/3TC in combination with lopinavir/ritonavir (LPV/r) or atazanavir/ritonavir (ATV/r) from 2012 to 2018. Patients who had been prescribed any additional ART medications were excluded.

Statistical Analysis

Data from the electronic medical record included age, education, marital status, duration of first-line ART, and year of second-line ART initiation. Data were de-identified and analyzed using SAS version 9.4 software (SAS Institute, Cary, North Carolina). One-year and 2-year retention were defined as having at least 1 visit >365 and >730 days, respectively, after initiating second-line ART. Adherence was measured by calculating the medication possession ratio, which is the proportion of medications dispensed during a defined period. The window period for 1-year and 2-year viral load tests was 6 to 18 months, and 18 months to 30 months after initiation of second-line ART,

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with the latest result utilized if repeat testing was conducted. Viral suppression was defined as human immunodeficiency virus type 1 (HIV-1) RNA <200 copies/mL in the main analyses; in a sensitivity analysis, we defined viral suppression as HIV-1 RNA <1000 copies/mL.

Baseline characteristics are presented using descriptive statistics. We compared baseline characteristics and retention, adherence, and virologic suppression rates between patients taking TDF vs ZDV using χ^2 tests for categorical and Wilcoxon rank-sum tests for continuous variables. We assessed predictors of 1-year and 2-year viral suppression using multivariable logistic regression, adjusting for available baseline characteristics.

RESULTS

From 2012 to 2018, a total of 1017 patients failed EFV/TDF/3TC and switched to LPV/r or ATV/r in combination with TDF/3TC or ZDV/3TC. The median duration of first-line ART was 2.5 years (interquartile range [IQR], 1.6–3.5). Second-line ART regimens included ZDV/3TC/ATV/r in 56 (6%), ZDV/3TC/LPV/r in 228 (22%), TDF/3TC/ATV/r in 315 (31%), and TDF/3TC/LPV/r in 418 (41%). Patients taking TDF were more likely to be female, with later year of second-line ART initiation (Table 1).

One year after initiation of second-line ART, 857 (84%) patients were retained on second-line treatment, 96 (9%) were lost to follow-up, 42 (4%) died, 18 (2%) transferred to a different clinic, and 4 (<1%) initiated third-line ART, with no significant differences based on NRTI backbone. Median adherence was 85% (IQR, 63%–97%) in the TDF group and 81% (IQR, 56%–94%) in the ZDV group ($P = .010$). One-year viral load tests were conducted for 434 (70%) patients taking TDF and 144 (60%) taking ZDV ($P = .005$); among those who were tested, 244 (56%) taking TDF and 54 (38%) taking ZDV had HIV-1 RNA <200 copies/mL ($P < .001$).

Two years after initiation of second-line ART, 726 (71%) patients were retained on second-line treatment, 157 (15%) were lost to follow-up, 67 (7%) died, 30 (3%) transferred, and 37 (4%) initiated third-line ART, with no significant difference based on NRTI backbone. Median adherence was 80% (IQR, 63%–92%)

Table 1. Baseline Characteristics

Characteristic	TDF (n = 733)	ZDV (n = 284)	P Value
Age at second-line ART initiation, y, median (IQR)	41.1 (33.9–50.2)	40.4 (34.5–49.4)	.727
Female sex	381 (52)	128 (45)	.048
No school or primary school only	431 (59)	165 (58)	.839
Living with spouse or partner	360 (49)	158 (56)	.062
Duration of first-line EFV/TDF/3TC, y, median (IQR)	2.6 (1.6–3.5)	2.4 (1.6–3.5)	.850
Year of second-line ART initiation			<.001
2012–2015	180 (25)	120 (42)	
2016–2018	553 (75)	164 (58)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; EFV, efavirenz; IQR, interquartile range; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

in the TDF group and 78% (IQR, 56%–92%) in the ZDV group ($P = .432$). Two-year viral load tests were conducted for 372 (72%) patients taking TDF and 160 (77%) taking ZDV/3TC ($P = .122$); among those who were tested, 218 (59%) taking TDF and 70 (44%) taking ZDV had HIV-1 RNA <200 copies/mL ($P = .002$).

In multivariable analysis, predictors of HIV-1 RNA <200 copies/mL after 1 year of second-line ART included taking TDF vs ZDV (odds ratio [OR], 2.12 [95% confidence interval {CI}, 1.43–3.15]) and attending at least some secondary school (OR, 1.49 [95% CI, 1.04–2.13]) (Table 2). Predictors of HIV-1 RNA <200 copies/mL after 2 years of second-line ART included taking TDF vs ZDV (OR, 1.85 [95% CI, 1.26–2.71]) and older age (OR, 1.02 per decade [95% CI, 1.00–1.04]). Results were similar when viral suppression was defined as HIV-1 RNA <1000 copies/mL (Supplementary Table 1).

DISCUSSION

We found that switching TDF/3TC to ZDV/3TC in second-line ART, in accordance with WHO guidelines, was associated with lower rates of viral suppression than continuing TDF/3TC [1]. We attribute the poor outcomes with ZDV/3TC to medication-related side effects and twice-daily dosing of a multi-tablet

Table 2. Predictors of HIV-1 RNA <200 Copies/mL at 1 and 2 Years After Switch to Second-Line Treatment

Variable (Reference Category)	1 Year (n = 578)		2 Years (n = 532)	
	OR (95% CI)	P Value	OR (95% CI)	P Value
TDF (vs ZDV)	2.12 (1.43–3.15)	<.001	1.85 (1.26–2.71)	.002
Age at second-line ART initiation (per decade)	1.00 (.99–1.02)	.593	1.02 (1.00–1.04)	.015
Female sex (vs male sex)	1.06 (.75–1.49)	.750	1.15 (.80–1.64)	.445
Secondary school and above (vs primary or no school)	1.49 (1.04–2.13)	.031	1.34 (.93–1.93)	.117
Living with spouse or partner (vs single)	1.34 (.96–1.88)	.086	0.95 (.67–1.35)	.776
Time on first-line EFV/TDF/3TC (years)	1.03 (.90–1.17)	.662	0.98 (.86–1.12)	.759
Initiation of second-line ART from 2016 to 2018 (vs 2012–2015)	1.33 (.82–2.15)	.245	0.95 (.63–1.46)	.827

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; CI, confidence interval; EFV, efavirenz; OR, odds ratio; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

regimen, as we have reported low rates of ZDV resistance in this population [6]. Our study was conducted in a routine clinical setting, without access to ART resistance testing to guide treatment decisions in patients with virologic failure. These findings are relevant for HIV programs globally, because TDF/3TC/DTG (TLD) is a once-daily, well-tolerated, single-tablet regimen.

DTG was not yet available for second-line therapy in Haiti at the time these study data were collected, and the patients received LPV/r or ATV/r as their third agent. The Nucleosides and Darunavir/Dolutegravir in Africa (NADIA) trial, which compared DTG vs ritonavir-boosted darunavir (DRV/r) and TDF/3TC vs ZDV/3TC in patients failing first-line NNRTI-based ART, reported high rates of viral suppression with both DTG and DRV/r, even in the subgroup with high-level resistance to the NRTIs prescribed [8]. Moreover, a prospective study among patients failing first-line ART in South Africa reported high rates of viral suppression with TLD, though 65% had at least low-level resistance to TDF and 3TC [9]. These findings indicate that TDF can be continued in second-line ART without compromising efficacy.

Other studies have also called the significance of NRTI mutations into question. The Resistance Testing to Improve Management of Virologic Failure in Sub-Saharan Africa (REVAMP) trial found that genotypic resistance testing after first-line failure did not improve viral suppression rates in Uganda and South Africa, and the Europe-Africa Research Network for Evaluation of Second-Line Therapy (EARNEST) and Study of Options for Second-Line Effective Combination Therapy (SELECT) studies found that viral suppression rates were high even among patients with no predicted-active NRTIs [3–5, 10]. The efficacy of compromised NRTIs may be attributable to partial retained activity, or by maintaining selective pressure for viruses with reduced fitness or increased susceptibility to tenofovir, as described with the M184V/I mutant. The Comparative Efficacy and Safety Study of Dolutegravir and Lopinavir/Ritonavir in Second-line Treatment (DAWNING) study, which compared DTG vs LPV/r + 2 NRTIs in patients failing NNRTI-based regimens with at least 1 fully active NRTI, found higher response rates for those receiving WHO-recommended vs other second-line NRTIs; however, the alternative regimens included combinations other than TDF/3TC, and high viral suppression rates were reported in those who received TDF in the presence of K65R [11, 12].

We do not attribute the low rate of viral suppression in our cohort to drug resistance, as we have reported low rates of resistance to protease inhibitors in this population [6]. Many studies have reported poor outcomes for second-line ART, particularly with LPV/r-based regimens [13]. The REVAMP trial found that about 60% of patients achieved HIV-1 RNA <200 copies/mL, and DAWNING and EARNEST reported HIV-1 RNA <50 copies/mL in 70% and 74% of participants receiving LPV/r + 2 NRTIs, although outcomes are often better in clinical trials than in routine practice [5, 10, 12]. The tolerability and ease of dosing

of TLD may facilitate adherence, particularly when combined with patient-centered approaches to care.

Our study is limited by retrospective design and low rate of viral suppression. Despite these limitations, our results indicate that in routine clinical practice, continuing TDF in second-line ART is associated with higher rates of viral suppression than switching to ZDV. These findings highlight the need to update the WHO guidelines to recommend both the removal of ZDV from the optimized NRTI backbone, and the continuation of TDF in the preferred second-line regimen.

Notes

Patient consent. Due to the retrospective nature of the research, it was not feasible to obtain informed consent. All data abstraction activities were conducted in accordance with ethical standards of the Helsinki Declaration. This study used retrospective data that had been routinely collected in the electronic medical record for patients receiving care at Le Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) since 2003. This study was reviewed and approved by the institutional review boards of GHESKIO, Weill Cornell Medical College, and Brigham and Women's Hospital.

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