

Implementing a Tenofovir-Based First-Line Regimen in Rural Lesotho: Clinical Outcomes and Toxicities After Two Years

Helen Bygrave, MBChB,* Nathan Ford, MPH, PhD,†‡ Gilles van Cutsem, MBChB, MPH,†‡
Katherine Hilderbrand, MSc,†‡ Guillaume Jouquet, MBA,* Eric Goemaere, MBChB, PhD,†
Nathalie Vlahakis, MBChB,* Laura Triviño, MBChB,*
Lipontso Makakole, MBChB,§ and Katharina Kranzer MBBS, MSc^{||}

Background: The latest World Health Organization guidelines recommend replacing stavudine with tenofovir or zidovudine in first-line antiretroviral therapy in resource-limited settings. We report on outcomes and toxicities among patients on these different regimens in a routine treatment cohort in Lesotho.

Methods: All adult patients initiating antiretroviral therapy from January 1, 2008, to December 31, 2008, were included in the analysis and followed until December 31, 2009. Choice of regimen was determined by clinical criteria.

Results: Of 1124 patient records analyzed, median age was 39 years, and the majority (67.7%) were women. Five hundred eighty-seven patients were started on tenofovir, 255 on zidovudine, and 282 on stavudine. Patients on zidovudine were more than twice as likely to experience a toxicity-driven regimen substitution compared with tenofovir (adjusted hazard ratio: 2.32, 95% confidence interval: 1.23 to 4.40); for patients on stavudine, the risk of a toxicity-driven regimen switch was almost 6 times higher than tenofovir (adjusted hazard ratio: 5.43, 95% confidence interval: 3.31 to 8.91).

Conclusions: Our findings support the latest World Health Organization Guidelines, in particular the adoption of tenofovir in first line, given the advantages in terms of tolerability and availability as a once-daily formulation.

Key Words: antiretroviral therapy, mortality, regimen substitution, tenofovir, toxicity

(*J Acquir Immune Defic Syndr* 2011;56:e75–e78)

Received for publication August 28, 2010; accepted November 30, 2010.
From the *Médecins Sans Frontières, Morija, Lesotho; †Médecins Sans Frontières, Cape Town, South Africa; ‡Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa; §Scott Hospital, Morija, Lesotho; and ^{||}Department of Epidemiology and Population Health, Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom.

The authors have no funding or conflicts of interest to disclose.
Correspondence to: Helen Bygrave, Médecins Sans Frontières, PO Box 27401, Rhine Road, Sea Point 8050, South Africa (email: helen.bygrave@joburg.msf.org).

Copyright © 2011 by Lippincott Williams & Wilkins

INTRODUCTION

Antiretroviral therapy (ART) has transformed HIV infection into a manageable, lifelong disease. Simple, potent, and tolerable first-line regimens are critical to successful ART outcomes in the long term.¹ Currently, the most commonly used backbone drug in resource-limited settings is stavudine, a drug associated with a high rate of side-effects related to its mitochondrial toxicity, including lactic acidosis, peripheral neuropathy and lipodystrophy.² These side-effects have led to stavudine use being abandoned in developed countries in favour of less toxic alternatives, predominantly tenofovir disoproxil fumarate (tenofovir).³ Tenofovir exhibits lower rates of side-effects,⁴ and its long intracellular half-life allows for formulation as a once-a-day regimen [together with lamivudine or emtricitabine and efavirenz].⁵ In randomized trials, tenofovir has demonstrated comparable or greater efficacy compared with other first-line regimens such as zidovudine, stavudine, or abacavir.^{6–8}

For these reasons, the World Health Organization (WHO) revised its guidelines for ART in late 2009 to recommend phasing out of stavudine in resource-limited settings,⁹ and many countries in southern Africa are currently revising their guidelines to replace stavudine with the WHO-recommended alternatives of tenofovir or zidovudine. Before these recommendations, only a few countries in Africa (Zambia, Namibia, Lesotho, and Botswana) had adopted tenofovir in first line.² Thus there is a scarcity of reporting of outcomes on tenofovir compared with other regimens in low-resource settings.

In this article, we report on outcomes and toxicities among patients on tenofovir, zidovudine, and stavudine-based first-line ART in a routine treatment cohort in Lesotho.

METHODS

Study Setting and Treatment Protocols

In 2006, Médecins Sans Frontières and the Ministry of Health and Social Welfare established a decentralized HIV/AIDS care and treatment program at the primary health care level in Scott Health Service Area, Lesotho, serving a population of approximately 200,000 people.¹⁰ Lesotho opted to implement a tenofovir-based first-line regimen in late

2007.⁹ Tenofovir is prescribed to all nonpregnant adults aged >18 years with adequate renal function (creatinine clearance (CrCl) >50 mL/min). Zidovudine is provided in case of pregnancy or where CrCl is <50 mL/min; and stavudine for those patients who are excluded from receiving zidovudine (hemoglobin <8 g/dL) or tenofovir. All regimens include lamivudine and either nevirapine or efavirenz; those on tenofovir were almost exclusively on efavirenz, whereas there was an equal proportion on both nevirapine and efavirenz for those initiated on zidovudine or stavudine. The 3 regimens were used concurrently during the period of this analysis due to the phased introduction of tenofovir while staff became familiar with the new protocol.

Data Extraction and Analysis

All adult patients (>18 years) initiating ART from January 1, 2008, to December 31, 2008, were included in the analysis and followed until December 31, 2009. All toxicities were noted in the patient files upon receipt of laboratory results by clinical staff. Data were extracted from patient files by a team of 3 clinicians, entered into an Access database, and exported into STATA (version 11) for analysis. Patients with severe renal insufficiency (CrCl <30 mL/min) were removed from analysis to avoid bias by baseline renal function. Descriptive analyses were based on percentages and frequencies for categorical variables and medians and interquartile ranges (IQR) for continuous variables. We described probability of survival and regimen switching among patients initiating ART on tenofovir-based, zidovudine-based, or stavudine-based regimens using Nelson–Aalen cumulative hazards estimates and modelled the risk of mortality, loss to follow-up, and toxicity-driven regimen substitution using Cox regression adjusting for the following confounders identified a priori: age (<40 and >40 years), gender, tuberculosis at initiation, pregnancy at initiation, baseline CD4 (≤ 200 and >200 cells/mm³ and baseline creatinine (30–50 mL/minute, >50 mL/minute, and missing). Endpoints were the time from ART initiation to (1) death, (2) loss to follow-up or (3) first toxicity-driven switch. Time was censored at loss to follow-up (defined as missing an appointment for more than 90 days) and transfer for the mortality analysis, death, and transfer for the loss to follow-up analysis and for all 3 for the regimen substitution analysis. All reported *P* values are exact and 2-tailed; and for each analysis, a *P* value of <0.05 was considered significant.

The analysis was approved by Médecins Sans Frontières's independent Ethics Review Board.

RESULTS

Between January 01, 2008, and December 31, 2008, 1185 adult patients were enrolled into care according to the national guidelines criteria for ART (CD4 <350 or Stage III and IV). Forty-eight patients had no baseline CD4 and 13 patients had a baseline CrCl <30 mL/min and were excluded from further analysis. Of the 1124 patient records carried through for analysis, median age was 39 years, and the majority (761, 67.7%) were women. Five hundred eighty-seven patients were started on a tenofovir-based regimen, 255 on an zidovudine-based regimen, and 282 on a stavudine-

based regimen. Median time on treatment was 483 days for tenofovir (IQR: 392–585), 493 days for zidovudine (IQR: 349–580), and 480 days for stavudine (IQR: 277–610) (Table 1). Fewer women were initiated on tenofovir (53.5%) compared with zidovudine (89%) or stavudine (78%); this was due to initial misconceptions among health providers that tenofovir should not be prescribed to women of childbearing age. Almost all women (98%) who were pregnant at initiation were initiated on a zidovudine-based regimen. Almost all patients initiated on a tenofovir-based regimen (96.8%) received a baseline renal function test; the proportion of patients with a low baseline creatinine clearance (30–50 mL/min) was higher for patients on zidovudine and stavudine, consistent with the fact that low creatinine clearance was an exclusion criteria for tenofovir administration.

The overall mortality rate for the cohort was 6.5 per 100 person-years [confidence interval (CI) 95%: 5.3 to 7.9 per 100 person-years], with a trend toward a higher mortality rate among patients on non-tenofovir regimens: for those started on tenofovir, the mortality rate was 5.1 per 100 person-years (CI 95%: 3.8 to 7.0), compared with 7.5 per 100 person-years for those started on zidovudine (CI 95%: 5.0 to 11.1) and 8.3 per 100 person-years for those started on stavudine (CI 95%: 5.8 to 11.7). In multivariate analysis comparing the risk of mortality, there was a nonsignificant trend toward higher mortality among patients on zidovudine [adjusted hazard ratio (aHR): 1.68, CI 95%: 0.88 to 3.21] or stavudine (aHR 1.40, CI 95%: 0.79 to 2.49) compared with tenofovir. Differences in loss to-follow up were not statistically significant.

The rate of toxicity-driven regimen substitutions overall was 8.0 switches per 100 person-years (CI 95%: 6.7 to 9.6); this rate differed significantly according to drug regimen. Patients on tenofovir switched at a rate of 3.0 switches per 100 patient-years (CI 95%: 2.0 to 4.5) compared with 8.1 switches per 100 patient-years for zidovudine (CI 95%: 5.4 to 12.1) and 18.8 switches per 100 patient-years for stavudine (CI 95%: 14.8 to 24.1) (Fig. 1.) In multivariate analysis, patients on zidovudine were more than twice as likely to experience a toxicity requiring a regimen substitution compared with those on tenofovir (aHR: 2.32, 95% CI: 1.23 to 4.40); for patients on stavudine, the risk of a toxicity-driven regimen switch was almost 6 times higher compared with tenofovir (aHR: 5.43, 95% CI: 3.31 to 8.91). Among patients on tenofovir experiencing a toxicity requiring a regimen change (*n* = 19), the most common reason for switching was renal toxicity (18 patients). For zidovudine (*n* = 15), it was severe anemia (11 patients). For stavudine (*n* = 42), it was severe neuropathy (29 patients) and lipodystrophy (11 patients); 2 patients had severe lactic acidosis.

DISCUSSION

In this nurse-managed community cohort, tenofovir was found to be associated with substantially lower rate of toxicity-driven regimen substitution compared with zidovudine and stavudine, consistent with other published reports.¹¹ There was also a tendency toward improved survival, but this did not reach statistical significance. Tenofovir-associated renal toxicity was low: of the 5% who developed toxicity, the

TABLE 1. Characteristics of Patients According to Treatment Regimen

	Total Patients (n = 1124)	Tenofovir, (n = 587)	Zidovudine, (n = 255)	Stavudine, (n = 282)
CD4, median (IQR)*	211 (119–284)	212 (119–283)	233 (149–303)	185 (95–267)
Time on ART (days), median (IQR)	485 (369–587)	483 (392–585)	493 (349–580)	480 (277–610)
Female, n (%)	761 (67.7%)	314 (53.5%)	227 (89.0%)	220 (78.0%)
Age, median (IQR)	39.0 (30.8–49.2)	39.3 (32.4–48.4)	34.3 (28.4–46.2)	42.3 (32.1–53.5)
Pregnant at initiation†				
No	1044 (93.0%)	313 (99.8%)	149 (65.6%)	219 (99.6%)
Yes	80 (7.0%)	1 (0.2%)	78 (34.4%)	1 (0.4%)
Backbone regimen				
Nevirapine	290 (25.8%)	1 (0.2%)	134 (52.5%)	155 (55.0%)
Efavirenz	816 (74.2%)	568 (99.8%)	121 (47.5%)	127 (45.0%)
Prior tuberculosis				
No	952 (83.8%)	481 (81.9%)	227 (88.3%)	244 (83.6%)
Yes	184 (16.2%)	106 (18.1%)	30 (11.7%)	48 (16.4%)
Baseline creatinine				
30–50 mL/min	160 (14.2%)	17 (2.9%)	47 (18.4%)	96 (34.2%)
>50 mL/min	775 (69.0%)	551 (93.9%)	115 (45.1%)	109 (38.8%)
Missing	189 (16.8%)	19 (3.2%)	93 (36.5%)	77 (27.1%)

*Data missing for 59 patients.
†Denominator includes only women.

majority had a creatinine drop of less than 10 mL/min, and all but 3 returned to normal on a subsequent measurement. This lower toxicity is particularly important for settings where detection of lactic acidosis is difficult (lactic acidosis was likely underestimated in our cohort for this reason), and monitoring of neuropathy and lipodystrophy is clinically challenging. Where access to routine laboratory monitoring is a challenge and human resources are scarce, the use of antiretrovirals with a lower risk of side-effects is supportive of a public health approach to delivering ART.¹² Reducing regimen switches is also desirable to maximize adherence¹³ and preserve drug options for the management of treatment failure.¹⁴

Our analysis is based on programmatic data in which treatment was allocated for clinical reasons, prescriber

preference, or drug availability. Important differences in baseline characteristics were observed, and we attempted to adjust for confounding that may have resulted from prescribing bias (notably differences in baseline renal function, gender, and pregnancy status) but cannot rule out residual confounding. The NNRTI component may have contributed to a degree of toxicity; however, this is unlikely to be an important source of bias as reported rates of toxicity associated with efavirenz and nevirapine are far lower than for stavudine and zidovudine.¹¹

In conclusion, our results provide further evidence that a tenofovir-based first-line regimen is supportive of simplified care by reducing the rate of regimen substitutions compared with stavudine-based and zidovudine-based regimens. These findings are encouraging for developing country governments currently considering implementation of the new WHO guidelines, in particular, the introduction of tenofovir as a preferred first-line option, given the advantages over zidovudine in terms of ease-of-use and availability as a once-daily formulation.

ACKNOWLEDGMENTS

We would like to thank Rachel Cohen, Sharonann Lynch, Prinitha Pillay, and Peter Saranchuk for their essential contributions in the establishment and evolution of the treatment program.

REFERENCES

1. Stone VE. Strategies for optimizing adherence to highly active antiretroviral therapy: lessons from research and clinical practice. *Clin Infect Dis.* 2001;33:865–872.
2. Ford N, Calmy A. Improving first-line antiretroviral therapy in resource-limited settings. *Current Opin HIV AIDS.* 2010;5:38–47.
3. Brinkman K. Stavudine in antiretroviral therapy: is this the end? *AIDS.* 2009;23:1727–1729.

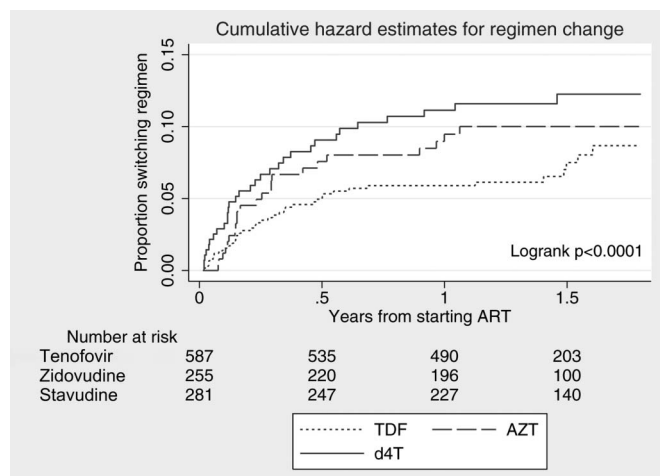


FIGURE 1. Cumulative hazard estimates for toxicity driven regimen change.

4. Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother*. 2002;46:716–723.
5. Grim SA, Romanelli F. Tenofovir disoproxil fumarate. *Ann pharmacother*. 2003;37:849–859.
6. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA*. 2004;292:191–201.
7. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med*. 2006;354:251–260.
8. Pozniak A. Tenofovir: what have over 1 million years of patient experience taught us? *Int J Clin Pract*. 2008;62:1285–1293.
9. Anon. *Rapid Advice: Antiretroviral Therapy for HIV Infection in Adults and Adolescents*. Geneva, Switzerland: World Health Organization; 2009.
10. Cohen R, Lynch S, Bygrave H, et al. Antiretroviral treatment outcomes from a nurse-driven, community-supported HIV/AIDS treatment programme in rural Lesotho: observational cohort assessment at two years. *J Int AIDS Soc*. 2009;12:23.
11. Davidson I, Beardsell H, Smith B, et al. The frequency and reasons for antiretroviral switching with specific antiretroviral associations: the SWITCH study. *Antiviral Res*. 2010;86:227–229.
12. Callaghan M, Ford N, Schneider H. A systematic review of task—shifting for HIV treatment and care in Africa. *Hum Resour Health*. 2010;8:8.
13. Mills EJ, Nachega JB, Bangsberg DR, et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. *PLoS Med*. 2006;3:e438.
14. Hawkins C, Achenbach C, Fryda W, et al. Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. *Journal of acquired immune deficiency syndromes (1999)*. 2007;45:304–310.