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Treatment outcomes of over 1000 patients on second-line, protease inhibitor-based antiretroviral therapy from four public-sector HIV treatment facilities across Johannesburg, South Africa

Kate Shearer[1], Denise Evans[1], Faith Moyo[1], Julia K. Rohr[2], Rebecca Berhanu[3], Liudmyla Van Den Berg[3], Lawrence Long[1], Ian Sanne[1,3,4] and Matthew P. Fox[1,5]

1 *Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
2 *Center for Global Health & Development, Boston University, Boston, MA, USA*
3 *Right to Care, Johannesburg, South Africa*
4 *Clinical HIV Research Unit, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
5 *Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA*

Abstract

OBJECTIVES To report predictors of outcomes of second-line ART for HIV treatment in a resource-limited setting.

METHODS All adult ART-naïve patients who initiated standard first-line treatment between April 2004 and February 2012 at four public-sector health facilities in Johannesburg, South Africa, experienced virologic failure and initiated standard second-line therapy were included. We assessed predictors of attrition (death and loss to follow-up [≥3 months late for a scheduled visit]) using Cox proportional hazards regression and predictors of virologic suppression (viral load <400 copies/ml ≥3 months after switch) using modified Poisson regression with robust error estimation at 1 year and ever after second-line ART initiation.

RESULTS A total of 1236 patients switched to second-line treatment in a median (IQR) of 1.9 (0.9-4.6) months after first-line virologic failure. Approximately 13% and 45% of patients were no longer in care at 1 year and at the end of follow-up, respectively. Patients with low CD4 counts (<50 vs. ≥200, aHR: 1.85; 95% CI: 1.03–3.32) at second-line switch were at greater risk for attrition by the end of follow-up. About 75% of patients suppressed by 1 year, and 85% had ever suppressed by the end of follow-up.

CONCLUSIONS Patients with poor immune status at switch to second-line ART were at greater risk of attrition and were less likely to suppress. Additional adherence support after switch may improve outcomes.

keywords HIV, antiretroviral therapy, second-line, death, loss to follow-up, virologic suppression

Introduction

The South African public-sector health system supports the world's largest antiretroviral therapy programme (ART) with an estimated 7 million HIV-infected and 3.1 million on ART [1, 2]. Estimates from WHO suggest that among patients on ART in low-and middle-income settings, approximately 95% are on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimens, and estimates of first-line treatment failure range between 6% and 32% [3–5]. Recently published estimates from a mathematical model note that in South Africa alone, there were approximately 128 000 individuals on second-line ART in 2014. By 2020, that number is expected to expand to approximately 450 000 and to >900 000 by 2030 [6]. Thus, as treatment programmes across Southern Africa continue to grow, the absolute number of patients requiring second-line regimens will continue to increase.

Numerous programmes in resource-limited settings have demonstrated successful treatment outcomes of first-line therapy. Fewer, however, have described the treatment outcomes of second-line therapy, with evidence

mainly restricted to smaller cohorts with limited information on efficacy and durability of second-line ART beyond 1 year [7–12]. Nonetheless, programmes that have reported outcomes have shown mixed results. The mortality rate after the initiation of second-line treatment has been fairly low, with estimates of approximately 4–5%, but virologic failure estimates have remained higher, with many programmes reporting second-line failure rates of more than 15% [8–14].

Given the increasing need for second-line therapy in resource-limited settings, it is critical to assess the effectiveness of such treatment now that ART programmes are more experienced. As poor response to treatment is likely to put patients at increased risk for mortality, and may increase risk of further transmission, understanding why certain patients fail to respond to treatment and how that impacts their risk for death and loss to follow-up is of great importance. Thus, we update our previous work, which was conducted at a single public-sector HIV treatment facility under more stringent ART initiation criteria, and report predictors of short- and long-term outcomes of more than 1200 HIV-infected patients receiving second-line therapy at four public-sector HIV treatment facilities across Johannesburg, South Africa [12].

Methods

Study sites

Data from four public-sector facilities located across Johannesburg were used for this analysis. Since 2004, when ART provision began in the public sector, these clinics have initiated over 40 000 patients onto ART. All demographic and clinical information, including data on drug regimens and dates of regimen changes as well as co-infections and comorbidities, at each of these sites is captured in an electronic medical record, TherapyEdge-HIV™, during the patient encounter. This system is integrated with the National Health Laboratory Service (NHLS) and all laboratory data, including CD4 counts and viral loads, are downloaded directly into the electronic record [15].

All public-sector facilities follow the guidelines of the South African National Department of Health. From April 2004 to August 2011, patients were initiated onto first-line ART when their CD4 count fell below 200 cells/mm^3 or when a WHO Stage IV condition was present [16, 17]. Patients presenting for care between August 2011 and December 2014 were initiated when their CD4 count fell below 350 cells/mm^3 [18].

Second-line treatment is available for patients who fail first-line ART. Clinics follow the algorithm laid out by the guidelines which call for switch to a protease inhibitor-based second-line regimen after two consecutive failing viral loads (viral load >1000 copies/ml) [17].

Study population

We conducted a retrospective cohort analysis using routinely collected data. All ART-naïve, adult (≥18 years old) patients who initiated a standard first-line ART regimen between April 2004 and February 2012, experienced virologic failure and then initiated a standard second-line ART regimen within 1 year of failure were included. Patients who initiated second-line ART during pregnancy or those who were switched to second-line without evidence of virologic failure were excluded.

Study variables

Standard ART regimens were defined based on the national ART guidelines in use during the period of analysis. First-line ART was defined as stavudine (d4T), zidovudine (AZT) or tenofovir (TDF), with lamivudine (3TC) and either nevirapine (NVP) or efavirenz (EFV). Patients on TDF could also have received emtricitabine (FTC) instead of 3TC [16, 17]. Standard second-line ART was defined as AZT with lopinavir–ritonavir (LPVr) and either 3TC or didanosine (ddI) or TDF with LPVr and either 3TC or FTC [16, 17].

Under the 2004 guidelines, viral load testing was conducted at ART initiation and then every 6 months thereafter [16]. In 2010, the monitoring schedule was shifted to 6 months, 1 year and then yearly thereafter [17]. However, patients who experience an elevated viral load should have a repeat viral load test conducted 3 months later. Thus, we defined virologic failure as two consecutive failing viral loads (>1000 copies/ml) between 2 weeks and 6 months apart at least 4 months after ART initiation.

Clinical characteristics at second-line initiation, including body mass index (BMI), anaemia, CD4 count and viral load, were defined as the values closest to the date of second-line initiation up to 7 days after the date of switch. WHO standards were used to define anaemia as severe (Hb <8 g/dl), moderate (Hb 8–10 g/dl), mild (males: Hb 11–12 g/dl; females: Hb 11–11.9 g/dl) or none (males: Hb ≥13 g/dl; females: Hb ≥12 g/dl). In addition, to account for the effect of Johannesburg's altitude (approximately, 1750 m above sea level) on haemoglobin values, we applied a downward adjustment of 0.65 g/dl before creating anaemia categories [19].

Table 1 Demographic and clinical characteristics of patients who switched to second-line antiretroviral therapy between 2005 and 2013 at four public-sector HIV treatment facilities in Johannesburg, South Africa

Characteristic	Total	2005/2006	2007/2008	2009/2010	2011/2012/2013
Total	1236	71	269	266	630
Sex (%)					
Male	505 (40.9)	24 (33.8)	109 (40.5)	116 (43.6)	256 (40.6)
Female	731 (59.1)	47 (66.2)	160 (59.5)	150 (56.4)	374 (59.4)
Age at second-line initiation (%)					
Median (IQR)	37.7 (32.5–44.4)	38.5 (32.0–44.1)	35.8 (31.8–42.8)	37.2 (32.2–44.3)	38.3 (33.1–45.0)
<30	195 (15.8)	13 (18.3)	46 (17.1)	50 (18.8)	86 (13.7)
30–34	264 (21.4)	12 (16.9)	76 (28.3)	53 (19.9)	123 (19.5)
35–39	278 (22.5)	15 (21.1)	52 (19.3)	55 (20.7)	156 (24.8)
40–44	218 (17.6)	17 (23.9)	44 (16.4)	50 (18.8)	107 (17.0)
≥45	281 (22.7)	14 (19.7)	51 (19.0)	58 (21.8)	158 (25.1)
Confirmatory failing viral load (copies/ml) (%)					
Log_{10} Median (IQR)	4.11 (3.62–4.80)	4.08 (3.64–5.04)	4.08 (3.71–4.57)	3.86 (3.49–4.49)	4.27 (3.66–4.92)
<5000	360 (29.1)	18 (25.4)	65 (24.2)	107 (40.2)	170 (27.0)
5000–9999	192 (15.5)	13 (18.3)	56 (20.8)	44 (16.5)	79 (12.5)
10 000–49 999	331 (26.8)	15 (21.1)	92 (34.2)	57 (21.4)	167 (26.5)
50 000–99 999	129 (10.4)	6 (8.5)	25 (9.3)	23 (8.7)	75 (11.9)
≥100 000	224 (18.1)	19 (26.8)	31 (11.5)	35 (13.2)	139 (22.1)
Viral load at second-line initiation (copies/ml) (%)					
Log_{10} Median (IQR)	4.18 (3.64–4.81)	4.28 (3.88–5.05)	4.08 (3.66–4.61)	4.00 (3.52–4.59)	4.31 (3.66–4.93)
<5000	340 (27.5)	10 (14.1)	73 (27.1)	89 (33.5)	168 (26.7)
5000–9999	171 (13.8)	13 (18.3)	46 (17.1)	45 (16.9)	67 (10.6)
10 000–49 999	361 (29.2)	23 (32.4)	90 (33.5)	74 (27.8)	174 (27.6)
50 000–99 999	134 (10.8)	5 (7.0)	24 (8.9)	21 (7.9)	84 (13.3)
≥100 000	230 (18.6)	20 (28.2)	36 (13.4)	37 (13.9)	137 (21.8)
CD4 count (cells/mm^3) (%)					
Median (IQR)	202.5 (114–305)	152 (88–223)	186 (111–274)	195 (131–260)	218 (113–345)
Missing	10	0	0	5	5
<50	129 (10.4)	9 (12.7)	24 (8.9)	20 (7.7)	76 (12.2)
50–99	130 (10.5)	11 (15.5)	32 (11.9)	27 (10.3)	60 (9.6)
100–199	342 (27.7)	27 (38.0)	88 (32.7)	85 (32.6)	142 (22.7)
≥200	625 (50.6)	24 (33.8)	125 (46.5)	129 (49.4)	347 (55.5)
Co-infected with TB (%)					
Yes	45 (3.6)	2 (2.8)	4 (1.5)	3 (1.1)	36 (5.7)
BMI (kg/m^2) (%)					
Median (IQR)	24.4 (21.4–28.3)	24.4 (22.2–28.5)	24.3 (21.4–28.4)	23.7 (21.2–27.6)	24.6 (21.4–28.4)
Missing	56	2	19	9	26
<18.5	69 (5.6)	5 (7.3)	17 (6.8)	16 (6.2)	31 (5.1)
18.5–24.9	588 (47.6)	34 (49.3)	121 (48.4)	131 (51.0)	302 (50.0)
25–29.9	320 (25.9)	19 (27.5)	70 (28.0)	68 (26.5)	163 (27.0)
≥30	203 (16.4)	11 (15.9)	42 (16.8)	42 (16.3)	108 (17.9)
Anaemia* (%)					
Median (IQR)	12.7 (11.6–13.8)	12.6 (11.3–13.6)	12.8 (11.7–13.9)	12.6 (11.4–13.6)	12.8 (11.6–13.9)
Missing	24	1	1	2	20
None	705 (57.0)	39 (55.7)	169 (63.1)	133 (50.4)	364 (59.7)
Mild	297 (24.0)	17 (24.3)	53 (19.8)	81 (30.7)	146 (23.9)
Moderate	196 (15.9)	13 (18.6)	41 (15.3)	44 (16.7)	98 (16.1)
Severe	14 (1.1)	1 (1.4)	5 (1.9)	6 (2.3)	2 (0.3)
First ART regimen (%)					
TDF-3TC-EFV	217 (17.6)	0 (0.0)	0 (0.0)	5 (1.9)	212 (33.7)
d4T-3TC-EFV	827 (66.9)	58 (81.7)	237 (88.1)	216 (81.2)	316 (50.2)
Other†	192 (15.5)	13 (18.3)	32 (11.9)	45 (16.9)	102 (16.2)

Table 1 (*Continued*)

Characteristic	Total	2005/2006	2007/2008	2009/2010	2011/2012/2013
Second-line ART regimen (%)					
TDF-3TC/EMT-LPVr‡	374 (30.3)	1 (1.4)	4 (1.5)	93 (35.0)	276 (43.8)
AZT-3TC-LPVr	366 (29.6)	0 (0.0)	1 (0.4)	13 (4.9)	352 (55.9)
AZT-ddI-LPVr	496 (40.1)	70 (98.6)	264 (98.1)	160 (60.2)	2 (0.3)
Time on first-line ART (months)					
Median (IQR)	18.8 (12.9–30.9)	14.4 (10.3–18.3)	18.3 (12.9–25.3)	20.8 (13.3–34.2)	19.9 (13.0–36.2)
Time from virologic failure to switch (months)					
Median (IQR)	1.9 (0.9–4.6)	2.3 (0.9–5.3)	2.0 (1.0–4.1)	1.8 (0.9–4.6)	2.0 (0.9–4.6)
Time from second-line switch to outcome or close of data set					
Median (IQR)	23.6 (14.0–36.1)	48.1 (20.1–92.9)	34.5 (15.2–66.3)	32.4 (12.5–45.2)	20.4 (14.0–27.4)

*None: males: ≥13 g/dl, females: ≥12 g/dl; Mild: males: 11–12 g/dl, females: 11–11.9 g/dl; Moderate: 8–10 g/dL; Severe: <8 g/dl.
†Other regimens include AZT-3TC-NVP/EFV, d4T-3TC-NVP, TDF-3TC-NVP, TDF-EMT-EFV.
‡11 patients initiated TDF-EMT-LPVr0.

Patients were followed from the date of second-line ART initiation until transfer to another HIV treatment facility, loss to follow-up (defined as ≥3 months late for a scheduled visit), death, or close of the dataset (at 12 months for the one-year outcome or February 28, 2014 for the final outcome). The primary outcome for this analysis was attrition, defined as mortality and loss to follow-up combined, at 1 year and ever after second-line ART initiation. For patients who report a South African national identification number (approximately 61%), mortality is ascertained primarily through routine linkage with the South Africa National Vital Registration System, which is estimated to have a record of approximately 90% of deaths [20]. For patients without a national ID number or those who choose to not report their number, mortality is ascertained primarily through routine loss to follow-up tracing.

The secondary outcome was virologic suppression (any viral load <400 copies/ml), at least 3 months after the initiation of second-line treatment with only those patients with at least one viral load recorded after second-line ART initiation included. All patients with complete covariate information were included in one-year analyses of attrition. For virologic suppression, patients were included in one-year outcome analyses if they also had at least one viral load between 3 and 12 months on treatment. For final outcomes, only those patients who initiated second-line ART between 2005 and 2008 were included to ensure that patients could have been followed for at least 5 years.

Statistical analysis

We present baseline demographic and clinical characteristics as proportions for categorical variables and as medians with interquartile ranges (IQR) for continuous variables. We conducted a complete case analysis using Cox proportional hazards regression to evaluate predictors of attrition and modified Poisson regression with robust error estimation to assess predictors of virologic suppression. Potential risk factors were chosen *a priori* based on the literature, and results are presented as both unadjusted and adjusted hazard or risk ratios with 95% confidence intervals (CI).

Ethical approval

Approval for the use of anonymised data from TherapyEdge-HIV™ was provided by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand and the Institutional Review Board of Boston University.

Results

A total of 1236 people initiated standard second-line ART within 1 year of first-line failure and were included in the analysis. Patients were on first-line ART for a median (IQR) of 18.8 (12.9–30.9) months prior to the initiation of second-line therapy with switch occurring in a median (IQR) of 1.9 (0.9–4.6) months after the second failing viral load. Patients were followed for a median (IQR) of 23.6 (14.0–36.1) months after second-line initiation. About 59.1% of patients were female. At second-line initiation, the median (IQR) age was 37.7 (32.5–44.4) years, the median (IQR) CD4 count was 202.5 (114–305) cells/mm^3 and the median viral load was 4.18 (3.64–4.81) $\log_{10}$ copies/ml. The CD4 count at switch increased from a median of 152 cells/mm^3 in 2005–2006 to 218 cells/mm^3 in 2011–2013 and more patients were

Table 2 Unadjusted and adjusted estimates of attrition at one year and ever after second-line initiation among patients at four public-sector HIV treatment facilities in Johannesburg, South Africa.

	At one year after second-line initiation (n = 1150)*			Ever after second-line initiation (n = 318)†		
Characteristic	Dead or LTF/*N* (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Dead or LTF/*N* (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Year of second-line initiation						
2005/2006	8/68 (11.8)	Reference	Reference	27/68 (39.7)	Reference	Reference
2007/2008	39/250 (15.6)	1.36 (0.64–2.91)	1.47 (0.68–3.18)	117/250 (46.8)	1.51 (0.98–2.33)	1.64 (1.04–2.60)
2009/2010	30/251 (12.0)	1.09 (0.50–2.38)	1.11 (0.48–2.57)	–	–	–
2011/2012/2013	68/581 (11.7)	1.03 (0.50–2.15)	0.77 (0.27–2.16)	–	–	–
Sex						
Male	69/460 (15.0)	Reference	Reference	67/122 (54.9)	Reference	Reference
Female	76/690 (11.0)	0.74 (0.54–1.03)	0.89 (0.61–1.30)	77/196 (39.3)	0.75 (0.54–1.04)	0.73 (0.49–1.08)
Age at initiation						
<30	33/180 (18.3)	Reference	Reference	33/54 (61.1)	Reference	Reference
30–34	33/245 (13.5)	0.72 (0.44–1.17)	0.77 (0.47–1.27)	35/82 (42.7)	0.58 (0.36–0.93)	0.59 (0.36–0.99)
35–39	20/256 (7.8)	0.40 (0.23–0.70)	0.41 (0.23–0.73)	26/63 (41.3)	0.52 (0.31–0.88)	0.52 (0.30–0.91)
40–44	24/207 (11.6)	0.61 (0.36–1.02)	0.61 (0.35–1.06)	25/60 (41.7)	0.47 (0.28–0.79)	0.49 (0.28–0.85)
≥45	35/262 (13.4)	0.70 (0.44–1.13)	0.76 (0.46–1.26)	25/59 (42.4)	0.55 (0.33–0.93)	0.48 (0.27–0.84)
Viral load (copies/ml)						
<5000	29/319 (9.1)	Reference	Reference	30/81 (37.0)	Reference	Reference
5000–9999	22/158 (13.9)	1.59 (0.91–2.77)	1.50 (0.85–2.64)	27/56 (48.2)	1.73 (1.03–2.91)	1.91 (1.12–3.28)
10 000–49 999	34/337 (10.1)	1.12 (0.68–1.84)	1.00 (0.60–1.67)	42/102 (41.2)	1.22 (0.76–1.95)	1.11 (0.68–1.81)
50 000–99 999	17/122 (13.9)	1.59 (0.87–2.90)	1.55 (0.84–2.87)	12/26 (46.2)	1.47 (0.75–2.87)	1.39 (0.70–2.74)
≥100 000	43/214 (20.1)	2.36 (1.47–3.78)	1.85 (1.08–3.18)	33/53 (62.3)	2.17 (1.32–3.56)	1.64 (0.94–2.88)
CD4 count (cells/mm^3)						
<50	26/121 (21.5)	2.19 (1.38–3.46)	1.43 (0.83–2.46)	20/31 (64.5)	2.18 (1.30–3.64)	1.85 (1.03–3.32)
50–99	14/112 (12.5)	1.21 (0.68–2.17)	0.78 (0.42–1.47)	22/37 (59.5)	1.57 (0.95–2.57)	1.33 (0.77–2.32)
100–199	44/323 (13.6)	1.35 (0.92–1.99)	1.16 (0.77–1.75)	48/108 (44.4)	1.24 (0.84–1.83)	1.22 (0.80–1.86)
≥200	61/594 (10.3)	Reference	Reference	54/142 (38.0)	Reference	Reference
Co-infected with tuberculosis						
No	134/1109 (12.1)	Reference	Reference	141/313 (45.1)	Reference	Reference
Yes	11/41 (26.8)	2.41 (1.31–4.46)	2.11 (1.11–4.01)	3/5 (60.0)	1.35 (0.43–4.23)	0.98 (0.29–3.27)
BMI						
<18.5	15/66 (22.7)	1.66 (0.96–2.88)	1.66 (0.94–2.92)	15/22 (68.2)	1.71 (0.98–2.97)	1.31 (0.72–2.38)
18.5–24.9	83/568 (14.6)	Reference	Reference	76/154 (49.4)	Reference	Reference
25–29.9	34/315 (10.8)	0.72 (0.49–1.08)	0.83 (0.55–1.25)	32/89 (36.0)	0.65 (0.43–0.99)	0.69 (0.45–1.05)
≥30	13/201 (6.5)	0.42 (0.24–0.76)	0.47 (0.26–0.87)	21/53 (39.6)	0.70 (0.43–1.14)	0.81 (0.48–1.39)
Anaemia‡						
None	82/670 (12.2)	Reference	Reference	84/195 (43.1)	Reference	Reference
Mild	38/279 (13.6)	1.14 (0.78–1.68)	0.97 (0.65–1.45)	28/68 (41.2)	1.00 (0.65–1.54)	0.90 (0.57–1.41)
Moderate	23/187 (12.3)	1.03 (0.65–1.64)	0.82 (0.49–1.37)	28/49 (57.1)	1.64 (1.07–2.52)	1.43 (0.87–2.34)
Severe	2/14 (14.3)	1.16 (0.29–4.73)	0.98 (0.23–4.08)	4/6 (66.7)	1.86 (0.68–5.07)	1.42 (0.48–4.18)

Table 2 (*Continued*)

Characteristic	At one year after second-line initiation (n = 1150)*			Ever after second-line initiation (n = 318)†		
	Dead or LTF/N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Dead or LTF/N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
First ART regimen						
TDF-3TC-EFV	32/196 (16.3)	1.44 (0.96–2.15)	1.57 (0.86–2.88)	–	–	–
d4T-3TC-EFV	93/781 (11.9)	Reference	Reference	123/276 (44.6)	Reference	Reference
Other§	20/173 (11.6)	0.99 (0.61–1.61)	1.13 (0.68–1.88)	21/42 (50.0)	1.11 (0.70–1.77)	1.07 (0.64–1.79)
Second-line ART regimen						
TDF-3TC/EMT-LPVr¶	36/350 (10.3)	0.75 (0.50–1.13)	1.21 (0.61–2.42)	4/5 (80.0)	–	–
AZT-3TC-LPVr	46/335 (13.7)	1.03 (0.70–1.51)	1.16 (0.50–2.70)	0/1 (0)	–	–
AZT-ddI-LPVr	63/465 (13.6)	Reference	Reference	140/312 (44.9)	–	–

*One-year analyses include all patients with complete covariate information.
†Final analyses included only those patients who initiated second-line ART between 2005 and 2008 and had complete covariate information.
‡None: males: ≥13 g/dl, females: ≥12 g/dl; Mild: males: 11–12 g/dl, females: 11–11.9 g/dl; Moderate: 8–10 g/dl; Severe: <8 g/dl.
§Other regimens include AZT-3TC-NVP/EFV, d4T-3TC-NVP, TDF-3TC-NVP, TDF-EMT-EFV.
¶11 patients initiated TDF-EMT-LPVr.

co-infected with TB at switch in 2011–2013 than in 2009-2010 (5.7% *vs.* 1.1%). Patients had otherwise similar clinical characteristics with different drug regimens prescribed over time reflecting changing guidelines (Table 1).

Attrition from care

A total of 1150 patients had information on all covariates of interest and were included in the analysis of one-year outcomes, and 12.6% died (1.9%) or were lost to follow-up (10.7%). Older patients were less likely to leave care than younger patients (35–39 *vs.* <30, HR: 0.40; 95% CI: 0.23–0.70) and patients with high viral loads (≥100 000 *vs.* <5000, HR: 2.36; 95% CI: 1.47–3.78), low CD4 counts (<50 *vs.* ≥200, HR: 2.19; 95% CI: 1.38–3.46) and those co-infected with TB (HR: 2.41; 95% CI: 1.31–4.46) were at greater risk for attrition. After adjustment, including for sex, BMI, anaemia, TB co-infection and ART regimen, the association was attenuated for viral load (aHR: 1.85; 95% CI: 1.08–3.18) while no association was observed for CD4 count (Table 2).

Patients who initiated second-line ART from 2005 to 2008 were included in long-term analyses. By the end of follow-up, 45.3% of 318 patients had died (14.2%) or were lost (31.1%). Patients who initiated in 2007–2008 were more likely to leave care than patients who initiated in 2005–2006 (aHR: 1.64; 95% CI: 1.04–2.60), as were patients with low CD4 counts (<50 *vs.* ≥200, aHR: 1.85; 95% CI: 1.03–3.32), while being of older age was protective (≥45 vs. <30, aHR: 0.48; 95% CI: 0.27–0.84) (Table 2).

Virologic suppression

A total of 927 patients were included in one-year analyses of virologic suppression and 74.9% suppressed (Table 3). Patients whose first-line regimen consisted of TDF-3TC-EFV were slightly more likely to suppress than patients on d4T-3TC-EFV (aRR: 1.22; 95% CI: 1.07–1.39), while patients with high viral loads at switch were less likely to suppress (≥100 000 *vs.* <5000, aRR: 0.79; 95% CI: 0.68–0.92). No associations were observed between second-line ART regimen and virologic suppression. Few characteristics were associated with suppression in long-term analyses, and rates of suppression were moderately high (85.3%). Patients with low CD4 counts at the time of switch (<50 *vs.* ≥200, RR: 0.62; 95% CI: 0.44–0.87) and those with high viral loads (≥100 000 vs. <5000, RR: 0.79; 95% CI: 0.64–0.97) were less likely to suppress, but the relationship between a high viral load

Table 3 Unadjusted and adjusted estimates of virologic suppression at one year and ever after second-line initiation among patients at four public-sector HIV treatment facilities in Johannesburg, South Africa.

	At one-year after second-line initiation (n = 927)*			Ever after second-line initiation (n = 272)†		
Characteristic	Suppressed/N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Suppressed/N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Year of second-line initiation						
2005/2006	45/59 (76.3)	Reference	Reference	54/61 (88.5)	Reference	Reference
2007/2008	160/205 (78.1)	1.02 (0.87–1.20)	0.99 (0.85–1.15)	178/211 (84.4)	0.95 (0.86–1.06)	0.91 (0.83–1.01)
2009/2010	142/197 (72.1)	0.95 (0.80–1.12)	0.88 (0.74–1.05)	–	–	–
2011/2012/2013	347/466 (74.5)	0.98 (0.84–1.14)	0.82 (0.65–1.03)	–	–	–
Sex						
Male	266/370 (71.9)	Reference	Reference	88/104 (84.6)	Reference	Reference
Female	428/557 (76.8)	1.07 (0.99–1.16)	1.06 (0.97–1.15)	144/168 (85.7)	1.01 (0.91–1.12)	1.02 (0.91–1.14)
Age at initiation						
<30	91/129 (70.5)	Reference	Reference	33/43 (76.7)	Reference	Reference
30–34	153/196 (78.1)	1.11 (0.97–1.27)	1.12 (0.98–1.27)	61/72 (84.7)	1.10 (0.91–1.34)	1.13 (0.94–1.35)
35–39	165/223 (74.0)	1.05 (0.92–1.20)	1.09 (0.95–1.25)	44/52 (84.6)	1.10 (0.90–1.35)	1.09 (0.90–1.31)
40–44	125/169 (74.0)	1.05 (0.91–1.21)	1.08 (0.93–1.24)	49/54 (90.7)	1.18 (0.98–1.42)	1.19 (0.99–1.43)
≥45	160/210 (76.2)	1.08 (0.94–1.24)	1.12 (0.98–1.29)	45/51 (88.2)	1.15 (0.95–1.39)	1.20 (0.99–1.47)
Viral load (copies/ml)						
<5000	207/264 (78.4)	Reference	Reference	67/74 (90.5)	Reference	Reference
5000–9999	99/126 (78.6)	1.00 (0.90–1.12)	1.02 (0.91–1.14)	39/43 (90.7)	1.00 (0.89–1.13)	0.99 (0.88–1.12)
10 000–49 999	222/286 (77.6)	0.99 (0.91–1.08)	1.00 (0.91–1.10)	78/91 (85.7)	0.95 (0.85–1.06)	1.00 (0.90–1.12)
50 000–99 999	66/92 (71.7)	0.91 (0.79–1.06)	0.92 (0.79–1.06)	18/22 (81.8)	0.90 (0.73–1.12)	0.94 (0.76–1.16)
≥100 000	100/159 (62.9)	0.80 (0.70–0.92)	0.79 (0.68–0.92)	30/42 (71.4)	0.79 (0.64–0.97)	0.85 (0.69–1.04)
CD4 count (cells/mm^3)						
<50	57/91 (62.6)	0.82 (0.69–0.97)	0.86 (0.72–1.03)	15/27 (55.6)	0.62 (0.44–0.87)	0.65 (0.46–0.91)
50–99	70/91 (76.9)	1.00 (0.89–1.14)	1.05 (0.92–1.19)	29/31 (93.6)	1.04 (0.93–1.15)	1.08 (0.96–1.20)
100–199	191/254 (75.2)	0.98 (0.90–1.07)	1.00 (0.92–1.10)	76/90 (84.4)	0.93 (0.84–1.04)	0.96 (0.86–1.07)
≥200	376/491 (76.6)	Reference	Reference	112/124 (90.3)	Reference	Reference
Co-infected with tuberculosis						
No	672/899 (74.8)	Reference	Reference	229/268 (85.5)	Reference	Reference
Yes	22/28 (78.6)	1.05 (0.86–1.28)	1.06 (0.86–1.29)	3/4 (75.0)	0.88 (0.50–1.55)	0.90 (0.55–1.48)
BMI						
<18.5	30/44 (68.2)	0.93 (0.76–1.15)	0.99 (0.80–1.22)	12/15 (80.0)	0.99 (0.76–1.29)	1.15 (0.87–1.48)
18.5–24.9	327/448 (73.0)	Reference	Reference	105/130 (80.8)	Reference	Reference
25–29.9	204/265 (77.0)	1.05 (0.97–1.15)	1.03 (0.94–1.12)	72/78 (92.3)	1.14 (1.03–1.27)	1.11 (1.00–1.23)
≥30	133/170 (78.2)	1.07 (0.97–1.18)	1.02 (0.92–1.13)	43/49 (87.8)	1.09 (0.95–1.24)	1.05 (0.92–1.21)

Table 3 (*Continued*)

Characteristic	At one-year after second-line initiation (n = 927)*			Ever after second-line initiation (n = 272)†		
	Suppressed/N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Suppressed/N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Anaemia‡						
None	408/540 (75.6)	Reference	Reference	149/167 (89.2)	Reference	Reference
Mild	167/227 (73.6)	0.97 (0.89–1.07)	0.99 (0.91–1.09)	49/61 (80.3)	0.90 (0.79–1.03)	0.94 (0.83–1.07)
Moderate	109/148 (73.7)	0.97 (0.88–1.09)	0.99 (0.88–1.11)	30/39 (76.9)	0.86 (0.72–1.03)	0.89 (0.74–1.07)
Severe	10/12 (83.3)	1.10 (0.85–1.43)	1.12 (0.86–1.47)	4/5 (80.0)	0.90 (0.58–1.39)	1.08 (0.62–1.88)
First ART regimen						
TDF-3TC-EFV	117/145 (80.7)	1.12 (1.02–1.23)	1.22 (1.07–1.39)	–	–	–
d4T-3TC-EFV	461/639 (72.1)	Reference	Reference	200/235 (85.1)	Reference	Reference
Other§	116/143 (81.1)	1.12 (1.03–1.23)	1.15 (1.04–1.26)	32/37 (86.5)	1.02 (0.89–1.17)	1.03 (0.90–1.18)
Second-line ART regimen (%)						
TDF-3TC/EMT-LPVr¶	204/284 (71.8)	0.95 (0.87–1.05)	1.07 (0.91–1.26)	3/3 (100)	–	–
AZT-3TC-LPVr	204/263 (77.6)	1.03 (0.94–1.12)	1.13 (0.93–1.39)	0/1 (0.0)	–	–
AZT-ddI-LPVr	286/380 (75.3)	Reference	Reference	229/268 (85.5)	–	–

*One-year analyses include all patients with at least one viral load conducted between 3 and 12 months after second-line ART initiation and complete covariate information.
†Final analyses included only those patients who initiated second-line ART between 2005 and 2008 had at least one viral load conducted at least 3 months after second-line ART initiation and had complete covariate information.
‡None: males: ≥13 g/dl, females: ≥12 g/dl; Mild: males: 11–12 g/dl, females: 11–11.9 g/dl; Moderate: 8–10 g/dl; Severe: <8 g/dl.
§Other regimens include AZT-3TC-NVP/EFV, d4T-3TC-NVP, TDF-3TC-NVP, TDF-EMT-EFV.
¶11 patients initiated TDF-EMT-LPVr.

and suppression was attenuated after adjustment (aRR: 0.85; 95% CI: 0.69–1.04) (Table 3).

Discussion

The number of people living with HIV in resource-limited settings who require second-line treatment to effectively manage their HIV infection is expanding, with close to 1 million people living with HIV anticipated to be on second-line treatment by 2030 in South Africa alone [6]. Thus, understanding the factors associated with good second-line treatment outcomes is imperative to the continued success of South Africa's national ART programme. In this cohort of 1236 HIV-infected adult patients on second-line ART, we found overall low mortality 1 year after second-line initiation, with just 2% of patients reported to have died, and moderately high rates of virologic suppression.

The low levels of mortality observed after second-line ART initiation in this cohort may reflect some under-ascertainment of deaths. Among included patients, approximately 64% provided a national ID number that could be linked with the national death registry. Therefore, losses to follow-up among patients without a national ID number may be masking mortality. While routine loss to follow-up tracing does mitigate this under-ascertainment, studies of loss to follow-up tracing have reported that 10–47% of patients who are lost from care cannot be traced [21–24]. In addition, the low mortality may also be indicative of some survivor bias as not all patients who failed first-line treatment switched to second-line ART. Thus, sicker patients may have died before being able to switch to a second-line regimen. In our cohort, when mortality was combined with loss to follow-up to form our primary outcome of attrition, 12.6% of patients had left care 1 year after second-line ART initiation, increasing to nearly half of all patients by the end of follow-up.

Patients with higher viral loads and lower CD4 counts at the time of switch to second line were at greater risk for attrition and were less likely to experience virologic suppression. These findings are similar to those reported elsewhere, but the larger sample size and longer follow-up time aid in making inferences [7, 12, 13]. While drug resistance testing is not routinely conducted, previous research has shown that suboptimal adherence is likely to be the primary driver of virologic failure on second-line ART [25–27]. Thus, further adherence support may improve treatment outcomes for patients who are on second-line treatment. The higher proportion of TB co-infection at second-line switch observed in more recent years may be reflective of the expanded use of a more sensitive TB diagnostic, Xpert MTB/RIF [28, 29]. While national scale-up of Xpert MTB/RIF was completed in 2013, some facilities had access to Xpert MTB/RIF for initial TB diagnosis from as early as 2011.

This analysis should be viewed in the light of several limitations. As not all patients who are lost to follow-up are able to be successfully traced, some patients may also have self-transferred to another HIV treatment facility and, thus, may represent loss from the original treating facility but not loss from the national ART programme. In addition, only those patients with a viral load recorded were included in analyses of virologic suppression. This may have resulted in a biased estimate of suppression if patients with a viral load result were systematically different from those who remained in care but did not have a viral load measurement recorded.

Our analysis also has several strengths. Our cohort of over 1200 patients initiated on second-line therapy is one of the largest analyses presented from sub-Saharan Africa. Including only those patients who initiated standard regimens for both first- and second-line treatment, and limiting the analysis to patients who switched within 1 year of virologic failure, protected our results from potential biases that may occur from including patients who switched to second-line for reasons other than virologic failure. Finally, the integration of the clinics' electronic medical record systems with the NHLS improved the ascertainment of clinical indicators and limited data entry errors.

Conclusions

HIV-infected patients initiated on standard second-line ART in South Africa can experience overall low rates of attrition and moderately high rates of virologic suppression shortly after second-line initiation; however, individuals with poorer immune status at the time of initiation of second-line treatment are at greater risk for attrition, were less likely to suppress and may need additional adherence support to improve treatment outcomes.

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Corresponding Author Kate Shearer, Health Economics and Epidemiology Research Office, 39 Empire Road, Parktown, Johannesburg, South Africa. Tel: +27 10 001 7930; E-mail: kshearer@heroza.org