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Social and behavioral factors associated with failing second-line ART – results from a cohort study at the Themba Lethu Clinic, Johannesburg, South Africa

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Abstract

Poor adherence is a main challenge to successful second-line ART in South Africa. Studies have shown that patients can re-suppress their viral load following intensive adherence counselling. We identify factors associated with failure to re-suppress on second-line ART.

The study was a retrospective cohort study which included HIV-positive adults who experienced an elevated viral load > 400 copies/ml on second-line ART between January 2013–July 2014, had completed an adherence counselling questionnaire and had a repeat viral load result recorded within 6 months of intensive adherence counselling. Log-binomial regression was used to evaluate the association between patient characteristics and social, behavioral or occupational factors and failure to suppress viral load (> 400 copies/ml).

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DE, RB and EL were involved in conception and design. IJ and RB were involved in study implementation while DE and SD undertook data collection and management. SD, CG, and TS were involved in data collection and review of patient files. EL and DE were the supervisor and co-supervisor of SD's Master's in Medicine research project. MPF, DE, RB, SD were involved in data analysis and interpretation of data. IJ and RB were involved clinical interpretation and contributed to the Discussion and Limitations sections. SD drafted the first manuscript and all authors were involved in revising it critically for important intellectual content and final approval of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

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A total of 128 patients were included in the analysis, and of these 39% ($n = 50$) failed to re-suppress their viral load. Compared to those who suppressed, far more patients who failed to suppress reported living with family (44.2% vs. 23.7%), missing a dose in the past week (53.3% vs. 30.0%), using traditional/herbal medications (63.2% vs. 34.3%) or had symptoms suggestive of depression (57.7% vs. 34.3%).

These patient-related factors could be targeted for interventions to reduce the risk for treatment failure and prevent switching to expensive third-line ART.

Keywords

second-line antiretroviral therapy; resource limited setting; virologic failure; viral suppression; intensive adherence counselling

Introduction

In South Africa, an estimated 10% of patients started on antiretroviral therapy (ART) will switch to second-line ART, and a further 33–40% of patients are expected to fail treatment in the first 12 months of second-line ART (Fox, Brennan, Maskew, MacPhail, & Sanne, 2010; Onoya et al., 2016). This is similar to the high rates (21–38%) of second-line treatment failure described for other low- and middle-income countries (Ajose, Mookerjee, Mills, Boule, & Ford, 2012). Poor adherence rather than drug resistance is the main driver for virologic failure on protease-inhibitor (PI)-based second-line (Ajose et al., 2012; Court et al., 2014) and reports show that two-thirds of patients can re-suppress following intensive adherence counselling (IAC) (Cox, 2015; Evans et al., 2016; Fox et al., 2016). With rapid expansion of the ART program in South Africa, understanding factors that contribute to second-line treatment failure is essential to the future success of the national treatment program and highlights the importance of improving adherence on second-line ART. A better understanding of the reasons for failure to re-suppress can lead to the design of targeted interventions that reduce the risk of treatment failure among these patients, and ultimately prevent switching to more expensive third-line regimens. This study aims to identify factors associated with failure to suppress viral load (> 400 copies/ml) among a cohort of patients with an elevated viral load on second-line ART.

Methods

Study site

Themba Lethu Clinic (TLC) is a large, urban public-sector clinic located in Johannesburg, South Africa. Since the start of the national ART program in April 2004, more than 30,000 adults have been part of the TLC cohort, of whom more than 28,000 have started on first-line and over 3000 on second-line ART. The cohort has been described elsewhere (Fox et al., 2013, 2016). TLC follows the South African National Department of Health adult ART treatment guidelines which call for second-line treatment with the boosted protease inhibitor, lopinavir/ritonavir (Department of Health, 2013)

Study design and population

This was a retrospective cohort study. After July 2012 TLC introduced IAC as part of a standardized, targeted approach for all patients with an elevated viral load (> 400 copies/ml) on second-line ART. The IAC intervention for patients failing second-line has been described elsewhere (Fox et al., 2016). Briefly, patients are identified from the electronic medical record called TherapyEdge-HIV™ and are flagged by clinic staff for IAC at their upcoming clinic visit in 1–2 months. At this visit patients bypass the normal clinic queue and undergo detailed IAC with an experienced counsellor or social worker who completes a standardized questionnaire. The questionnaire consists of several open- and closed-ended questions relating to adherence and side-effects, social situation, behavioral characteristics, occupational situation and depression-related symptoms. All patients also complete a standardized adherence screen. The form was developed in the clinic and therefore has not been validated but does allow the provider to assess potential barriers to adherence (Fox et al., 2016).

After counselling patients meet with a senior clinician to discuss adherence and possible side-effects. Patients return in 2–4 months for a repeat viral load test. Patients who suppress their viral load <400 copies/ml continue with second-line treatment, those who do not undergo genotype resistance testing.

Inclusion criteria

All HIV-positive adults (≥ 18 years) with an elevated viral load (> 400 copies/ml) on second-line ART at TLC between January 2013–July 2014 were included. The analysis was restricted to patients who underwent IAC and for whom an adherence counselling questionnaire could be located in their medical file and those with a repeat viral load within six months of intensive adherence counselling.

Data collection

For each patient, data from the adherence counselling questionnaire was linked to the patient's electronic medical record (TherapyEdge-HIV™) and patient-level data including information on demographics, medications, laboratory test results and other clinical information were extracted. In our study, any symptom suggestive of depression was defined as reporting at least one of the following; feeling sad or anxious, crying frequently, feeling hopeless, having difficulty sleeping or using alcohol to feel better.

Statistical analysis

Our primary outcome of interest was failure to suppress viral load; defined as a repeat viral load > 400 copies/ml within 6 months of IAC. Numerous studies have used a cut-off of <400 copies/ml to define viral suppression (Johnston et al., 2014; Levison, Losina, Lu, Freedberg, & Wood, 2011). We identified factors associated with failure to suppress using log-binomial regression to estimate relative risks (RR) with corresponding 95% confidence intervals. Factors identified in univariate models ($p < 0.2$) and variables *a priori* considered important (i.e., age and gender) were included in the multivariate model. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

Ethical considerations

The study protocol was reviewed by University of the Witwatersrand Human Research Ethics Committee (M141187), who approved the use of routine clinical data without informed consent. All patient records and information was anonymized and de-identified prior to analysis.

Results

For the study period, 298 patients had a single viral load ≥ 400 copies/ml on second-line ART. Of those, 154 (51.7%) patients had an adherence counselling questionnaire and could be linked to clinical data. Of the 154 patients, 128 (83.1%) had a repeat viral load, of which 61% (78/128) suppressed their viral load after IAC (Figure 1). More patients who failed to suppress had a viral load more than 100,000 copies/ml at their first elevated viral load on second-line ART (20% vs. 2.6%) (Table 1).

In terms of missing data, characteristics were similar between those included in the analysis ($n = 128$) and those not included ($n = 26$; $p < 0.05$). Compared to those with a repeat viral load, patients without a repeat viral load were more likely to be lost from care (3 months late for the last scheduled visit; RR 7.38 95%CI 2.24–24.34), and explains the missing laboratory results (Table 1).

From univariate analyses, we identified factors associated with failure to suppress viral load after intensified adherence counselling (Table 2). These included reporting a missed dose in the past week (RR 1.78 95%CI 1.15–2.74) and using traditional/herbal medications (RR 1.84 95%CI 1.20–2.84). Living with family vs. separated from them (RR 1.87 95%CI 1.01–3.46) was the only social factor associated with failure to suppress. Any symptom suggestive of depression was associated with failure to suppress viral load (RR 1.68 95%CI 1.10–2.57). On their own, only feeling sad or anxious (RR 1.53 95%CI 1.10–2.34) and feeling hopeless (RR 1.73 95%CI 1.12–2.67) were associated with failure to suppress.

After adjusting for gender, age and viral load at first elevated viral load on second-line ART, none of the variables were associated with failure to suppress viral load. Despite this, four variables were prominent among those who failed to suppress. Compared to those who suppressed, more patients who failed to suppress reported living with family (44.2% vs. 23.7%; $p = 0.048$), missing a dose in the past week (53.3% vs. 30.0%; $p = 0.010$), using traditional/herbal medications (63.2% vs. 34.3%; $p = 0.006$) or any symptom suggestive of depression (57.7% vs. 34.3%; $p = 0.017$).

Discussion

Results from this study show that 61% of patients could suppress their viral load after IAC, which is consistent with other reports (Cox, 2015; Fox et al., 2016; Garone et al., 2013; Khan et al., 2014). Higher viral loads among those who failed to re-suppress supports the view that unresolved poor adherence, not drug resistance, drives second-line failure (Boyd et al., 2015; Ndahimana et al., 2016).

The main factors we identified undermining adherence in patients on second-line ART were patient-related factors such as use of traditional/herbal medicine and depression. We found that far more patients who failed to suppress reported living with family – which could suggest fear of stigmatization or poor family and social support which compromise adherence (Wood, Tobias, & McCree, 2004). In line with other reports, we found that having any symptom suggestive of depression was associated with failure to suppress viral load (Langebeek et al., 2014; Marconi et al., 2013). Our study also found that far more patients who failed to suppress reported using traditional/herbal medicine. However, the kind of herbal/traditional medicine a person was using was not documented in this study nor the reasons for taking them. A previous South African study conducted in South Africa showed the main reasons for taking these traditional/herbal medications was for pain relief, as an immune booster or to stop diarrhoea (Peltzer et al., 2011). Commonly used herbal medicines can result in drug-interactions with ART or reduce ART adherence (Kiguba, Karamagi, Ssali, Mugenyi, & Katabira, 2007; Mills et al., 2005). Our study found that patients using traditional/herbal medication commonly (>60%) report missing doses or interrupting treatment.

As expected, poor adherence, in our study measured by a missed dose in the past week, was more common among those who failed to suppress. Results from this study and in line with other reports which have demonstrated a connection between poor adherence and elevated viral load (Ajose et al., 2012; Lima et al., 2008; Martin et al., 2008).

The findings should be considered in light of the study limitations. First, we did not have an objective measure of ART adherence (e.g., pill counts) or information relating to ART adherence. For example we did not have information on alcohol or drug use and did not measure factors such quality of healthcare services (e.g., lack of confidentiality and privacy, distance to clinic, drug stock outs, staff shortages etc.). Second, there was limited data to evaluate depression as a risk factor of failing second-line ART. In our study, any symptom of depression reported was used to classify a patient as possibly depressed. Therefore, it is possible that this may have led to misclassification. Third, 48% (144/298) of patients eligible for the study did not have an adherence counselling questionnaire and close to 17% (26/154) of patients included in the analysis did not have a repeat viral load. There were however no major differences observed between those included and not included in the analysis. Fourth, since the study only considers patients engaging in care, the factors identified and the estimate of adherence to ART may be different for those who are no longer in care. Lastly, it should be noted that we did not include information on drug resistance testing.

Conclusion

We demonstrate that patient-related factors (e.g., use of traditional/herbal medicine, depression, family/social support) and not necessarily provider-related factors, health system factors or treatment related factors contribute to poor adherence on second-line ART. Based on our findings, there is a need for on-going counselling and education of patients on second-line ART. Strategies to support patients, improved adherence evaluation and intensified monitoring need to be considered and evaluated in order to reduce the risk of virologic failure. Competing priorities and life circumstances can play a role in adherence

and suppression, and should be taken into consideration when thinking through strategies or interventions to address these.

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Figure 1.
Study enrollment and study outcomes.

Table 1.

Demographic and clinical characteristics of patients with an elevated viral load on second-line ART at Themba Lethu Clinic, stratified by the repeat viral load after intensified adherence counselling ($n = 154$).

	Suppressed ($N = 78$)	Not suppressed ($N = 50$)	No repeat VL ($N = 26$)	<i>P</i> value
Gender, Male, n %	35 (44.9%)	28 (56.0%)	10 (38.5%)	0.317
Age at first elevated viral load, years				
Median, IQR	42.9 (37.7–49.2)	38.7 (33.6–45.0)	41.7 (36.6–47.0)	0.826 [†]
<45	48/76 (63.2%)	39/50 (78.0%)	21/26 (80.8%)	0.230
45	28/76 (36.8%)	11/50 (22.0%)	5/26 (19.2%)	
CD4 count at first elevated viral load				
Median, IQR ^{&}	454 (274–593)	266 (201–472)	351 (195–501)	0.784 [†]
<250 cells/mm ³	13/60 (21.7%)	21/47 (44.7%)	4/15 (26.7%)	0.703
250–500 cells/mm ³	20/60 (33.3%)	18/47 (38.3%)	7/15 (46.6%)	
500 cells/mm ³	27/60 (45.0%)	8/47 (17.0%)	4/15 (26.7%)	
Viral load at first elevated viral load				
Median, IQR	2780 (1721–10,442)	4539 (1994–74,153)	12,606 (1684–47,924)	0.269 [†]
1000–10,000 copies/ml	57/77 (74.0%)	29/50 (58.0%)	15/25 (60.0%)	0.620
10,000–100,000 copies/ml	18/77 (23.4%)	11/50 (22.0%)	8/25 (32.0%)	
100,000 copies/ml	2/77 (2.6%)	10/50 (20.0%)	2/25 (8.0%)	
Transfer-in from another facility on second-line ART	9/78 (11.5%)	8/50 (16.0%)	3/26 (11.5%)	0.809
Second-line ART NRTI back-bone				
Abacavir	3/76 (4.0%)	3/49 (6.1%)	–	0.183
Zidovudine	29/76 (38.1%)	21/49 (42.9%)	14/24 (58.3%)	
Tenofovir	37/76 (48.7%)	25/49 (51.0%)	8/24 (33.4%)	
Stavudine	7/76 (9.2%)	–	2/24 (8.3%)	
Time on second-line ART prior to elevated viral load, months (IQR)	21.3 (9.4–35.0)	17.5 (7.8–25.7)	18.1 (10.1–26.2)	0.242 [†]
Time to repeat viral load, months (IQR)	4.6 (3.6–5.5)	4.6 (3.7–6.5)	N/A	N/A
Final treatment outcome ^{**}				
Alive and in care	69 (88.5%)	42 (84.0%)	19 (73.1%)	0.020
Dead	0 (0.0%)	1 (2.0%)	0 (0.0%)	
Lost to follow-up	1 (1.2%)	3 (6.0%)	6 (23.1%)	
Transfer	8 (10.3%)	4 (8.0%)	1 (3.8%)	

NRTI; Nucleoside Reverse Transcriptase Inhibitor. IQR; inter quartile range.

[†]Those without a repeat VL ($n = 26$) compared to those with a VL ($n = 128$) using Chi square test for proportions or as otherwise indicated using the Kruskal-Wallis test for non-normally distributed continuous data ().

^{**}Final treatment outcomes defined at the end of follow-up. These included alive and in care, dead (verified through linkage with the National Vital Registration System for patients with a valid South African national identification document (Fox, Ive, Long, Maskew, & Sanne, 2010; Shearer et al., 2014), lost to follow-up (defined as being > 3 months late for the last scheduled visit with no subsequent visit) and transferred to another facility.

[&]CD4 at first elevated viral load on second-line, extracted from the patient medical record and defined as the closest result, up to 180 days prior to but not more than 30 days after, the date the patient received the adherence intervention.

Bolded values are statistically significant at p value < 0.05 .

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Table 2.

Factors associated with failure to suppress viral load after intensified adherence counselling at Themba Lethu Clinic, Johannesburg.

Failure to suppress viral load (<i>n</i> = 50)			
Characteristic	Proportion not suppressed/ <i>N</i> (%)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Education			
Below tertiary	6/12 (50.0%)	1.0	
Tertiary and above	40/108 (37.0%)	0.74 (0.40–1.37)	
Employed			
Yes	30/82 (36.6%)	1.0	
No	17/42 (40.5%)	1.11 (0.70–1.76)	
Gender			
Female	22/65 (33.9%)	1.0	1.0
Male	28/63 (44.4%)	1.31 (0.85–2.03)	1.08 (0.86–1.33)
Age			
<45 years	39/89 (43.8%)	1.0	1.0
45 years	11/39 (28.2%)	0.64 (0.37–1.12)	0.86 (0.70–1.07)
CD4			
<250 cells/mm ³	21/34 (61.8%)	1.0	
250–500 cells/mm ³	18/38 (47.4%)	1.09 (0.69–1.70)	
500 cells/mm ³	8/35 (22.9%)	0.52 (0.27–1.03)	
Viral load at first elevated VL			
1000–10,000	29/86 (33.7%)	1.14 (0.66–1.98)	1.01 (0.83–1.23)
10,000–100,000	11/29 (37.9%)	1.0	1.0
100,000 copies/ml	10/12 (83.3%)	2.50 (1.69–3.69)	1.21 (0.80–1.82)
Second-line NRTI backbone			
d4T/AZT/ABC	24/63 (38.0%)	1.0	
TDF	25/62 (40.3%)	1.06 (0.69–1.64)	
Time on second-line ART			
<24 months	4/9 (44.4%)	1.22 (0.54–2.74)	
24–48 months	11/35 (31.4%)	1.0	
48 months	27/67 (40.3%)	1.10 (0.70–1.75)	
Year initiated second-line			
2010	8/31 (25.8%)	1.0	
>2010	34/80 (42.5%)	1.65 (0.86–3.15)	
Knows names of ARV's			
Yes	20/58 (34.5%)	1.0	
No	28/67 (41.8%)	1.21 (0.77–1.91)	
Regimen taken as prescribed			
Yes	37/97 (38.1%)	1.0	
No	9/26 (34.6%)	0.91 (0.51–1.63)	

Failure to suppress viral load (<i>n</i> = 50)			
Characteristic	Proportion not suppressed/ <i>N</i> (%)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Missed pills in last week			
No	24/80 (30.0%)	1.0	1.0
Yes	24/45 (53.3%)	1.78 (1.15–2.74)	1.10 (0.91–1.34)
Patient has interrupted ARV's			
No	26/69 (37.7%)	1.0	
Yes	23/57 (40.4%)	1.10 (0.69–1.66)	
ARV side effects reported			
No	27/79 (34.2%)	1.0	
Yes	21/46 (45.7%)	1.34 (0.86–2.07)	
Takes other chronic medication			
No	32/85 (37.7%)	1.0	
Yes	16/40 (40.0%)	1.06 (0.67–1.70)	
Ever had TB treatment			
No	21/65 (32.3%)	1.0	
Yes	28/60 (46.7%)	1.44 (0.93–2.25)	
Currently taking anti-TB drugs			
No	47/121 (38.8%)	1.0	
Yes	1/3 (33.3%)	0.86 (0.17–4.32)	
Uses traditional/herbal medicine			
No	37/108 (34.3%)	1.0	1.0
Yes	12/19 (63.2%)	1.84 (1.20–2.84)	1.20 (0.90–1.59)
Use of alcohol			
No	35/99 (35.4%)	1.0	
Yes	14/26 (54.9%)	1.52 (0.98–2.38)	
Use of drugs			
No	45/116 (38.8%)	1.0	
Yes	4/10 (40.0%)	1.03 (0.47–2.28)	
Financial support			
Employed	30/82 (36.6%)	1.0	
Social grants	3/7 (42.9%)	1.14 (0.46–2.81)	
Family	14/35 (40.0%)	1.07 (0.65–1.75)	
Other	3/6 (50.0%)	1.33 (0.57–3.12)	
Use tools to remember			
Yes	44/114 (38.6%)	1.0	
No	4/10 (40.0%)	1.04 (0.47–2.29)	
Difficulty reading or understanding instructions			
No	41/109 (37.6%)	1.0	
Yes	5/14 (35.7%)	0.95 (0.45–2.00)	
Married			
Yes	40/99 (40.4%)	1.0	
No	10/29 (34.5%)	0.85 (0.49–1.49)	

Failure to suppress viral load (<i>n</i> = 50)			
Characteristic	Proportion not suppressed/ <i>N</i> (%)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Partners			
Single	13/34 (38.2%)	1.0	
Multiple	32/87 (36.8%)	0.96 (0.58–1.60)	
Partner tested HIV			
Yes	26/70 (37.1%)	1.0	
No	2/13 (15.4%)	0.41 (0.11–1.54)	
Partner status			
HIV positive	21/53 (39.6%)	0.94 (0.60–1.48)	
HIV negative	2/11 (18.2%)	1.0	
Unknown	5/18 (27.8%)	0.66 (0.30–1.48)	
Use of condoms			
Yes	26/63 (41.3%)	1.0	
No	9/31 (29.0%)	0.70 (0.38–1.31)	
Desire for children			
Yes	16/42 (38.1%)	1.0	
No	21/67 (31.3%)	0.82 (0.49–1.39)	
Feel about clinic staff			
Bad	3/7 (42.9%)	0.94 (0.38–2.32)	
Good	18/41 (43.9%)	1.0	
Neutral	25/73 (34.3%)	0.75 (0.48–1.16)	
Disclosed to employer			
Yes	6/22 (27.3%)	1.0	
No	22/49 (44.9%)	1.65 (0.78–3.48)	
Difficulty getting time off for medical visits			
No	29/82 (35.4%)	1.0	
Yes	2/6 (33.3%)	0.94 (0.29–3.03)	
Frequently travels for work			
No	20/59 (33.9%)	1.0	
Yes	10/21 (47.6%)	1.40 (0.79–2.49)	
Afford transport costs to clinic			
Yes	42/113 (37.2%)	1.0	
No	1/4 (25.0%)	0.67 (0.12–3.73)	
Lives with family			
No	9/38 (23.7%)	1.0	1.0
Yes	38/86 (44.2%)	1.87 (1.01–3.46)	1.09 (0.88–1.33)
Patient hides pills			
No	41/109 (37.6%)	1.0	
Yes	5/13 (38.5%)	1.02 (0.48–2.11)	
Takes ARV's openly			
Yes	33/90 (36.7%)	1.0	
No	13/33 (39.4%)	1.07 (0.65–1.78)	

Failure to suppress viral load (<i>n</i> = 50)			
Characteristic	Proportion not suppressed/ <i>N</i> (%)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Religious practices that interfere with treatment			
Yes	26/76 (34.2%)	1.0	
No	18/45 (40.0%)	1.17 (0.73–1.88)	
Cultural practices that interfere with treatment			
No	35/100 (35.0%)	1.0	
Yes	12/23 (52.2%)	1.49 (0.93–2.39)	
Feel sad/anxious			
No	28/82 (34.2%)	1.0	
Yes	22/42 (52.4%)	1.53 (1.01–2.33)	
Cry frequently			
No	33/89 (37.1%)	1.0	
Yes	17/36 (47.2%)	1.27 (0.82–1.98)	
Feel hopeless			
No	32/96 (33.3%)	1.0	
Yes	15/26 (57.7%)	1.73 (1.12–2.67)	
Difficulty sleeping			
No	35/95 (36.8%)	1.0	
Yes	14/29 (48.3%)	1.31 (0.83–2.07)	
Use alcohol to feel better			
No	41/111 (36.9%)	1.0	
Yes	7/12 (58.3%)	1.58 (0.92–2.70)	
Any symptom suggestive of depression			
No	35/102 (34.3%)	1.0	1.0
Yes	15/26 (57.7%)	1.68 (1.10–2.57)	1.05 (0.80–1.38)

Bold text $p < 0.05$. NRTI; nucleoside reverse transcriptase inhibitor. d4T; stavudine.; AZT; zidovudine. ABC; abacavir. TDF; tenofovir. TB; tuberculosis. ART; antiretroviral therapy. ARV; antiretroviral. VL; viral load. HIV; human immunodeficiency virus.