Predictors of time to switch to second line ART after first line failure in Johannesburg, South Africa

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INTRODUCTION

Background

In South Africa, national treatment guidelines state that patients with two consecutive failing viral load measurements on first line antiretroviral therapy (ART) should be switched to a second-line protease inhibitor based regimen. Yet, there are often long delays in switching treatment regimens if it occurs at all. The causes of these delays are not well understood.

Objective

The goal of this study is to better understand why delays from first line ART failure to switch to second line regimen occur. We explored whether clinic attendance or disease progression was more likely to explain delays in second line initiation.

METHODS

Study Population

We conducted an observational cohort study using prospectively collected data from Themba Lethu Clinic in Johannesburg, South Africa, a large, public sector HIV clinic. We included HIV+ adult patients ≥18 years old initiating first line ART after April 2004 with virologic failure on first-line (date of 2nd consecutive viral load ≥ 1,000 copies/mL) at least 1 year before the end of the study period in 2013. First-line ART regimens were defined as standard regimens in the National Treatment Guidelines, including 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI).

Statistical Methods

We looked for demographic, clinical, and visit adherence predictors of time to switch to second line ART after first line failure using Kaplan-Meier curves and Cox proportional hazards regression to adjust for confounders.

The following variables were considered as potential predictors of time to switch to second line:

Age, sex, time on first line treatment, year of failure, proportion of visits missed before failure, time between consecutive first line failing viral load dates, history of TB, and values at failure of CD4 count, viral load, hemoglobin, and BMI.

RESULTS

Predictors of Time to Switch

Figure 1. Kaplan-Meier curves showing time to second line switch by failing viral load, CD4 count at failure, and proportion of missed visits before failure

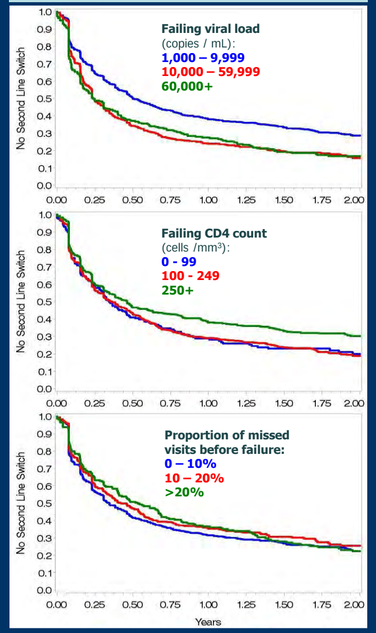


Table 1. Cox proportional hazard ratios predicting shorter time to second line switch from first line failure.

Predictor	Crude HR (95% CI)	Adjusted* HR (95% CI)
Male	1.09 (0.96, 1.22)	1.16 (0.99, 1.35)
Viral load (copies/mL) at failure:		
1,000 to 9,999	Reference	
10,000 to 59,999	1.42 (1.24, 1.62)	1.29 (1.08, 1.55)
60,000+	1.44 (1.24, 1.67)	1.27 (1.04, 1.56)
CD4 count (cells/mm³) at failure:		
0-99	1.25 (1.03, 1.52)	1.15 (0.90, 1.47)
100-250	1.23 (1.06, 1.42)	1.27 (1.06, 1.52)
>250	Reference	
Time on first line treatment before failure:		
0-1 years	1.46 (1.19, 1.78)	1.54 (1.14, 2.09)
1-2 years	1.08 (0.90, 1.30)	1.14 (0.86, 1.49)
2-3 years	1.08 (0.88, 1.32)	1.09 (0.81, 1.46)
3-4 years	0.99 (0.78, 1.25)	0.95 (0.68, 1.32)
4+ years	Reference	
Visits missed before treatment failure by >7 days:		
<10%	1.09 (0.91, 1.29)	1.19 (0.95, 1.47)
10-20%	1.01 (0.83, 1.23)	1.10 (0.87, 1.39)
>20%	Reference	

** Adjusted for all variables in table plus year of failure*

Cohort Characteristics

- 19670 patients initiated first line ART after 2004
- 1874 (9.5%) failed first line
- 1562 had at least 1 year of follow-up after failure
- Median (IQR) time from ART initiation until first line failure was 22.4 (13.7-38.2) months
- 61% were female
- At failure the median (IQR):
  - Age: 37.3 (32.3-43.5)
  - CD4 count: 216.5 (127.5-329.5)
  - Viral load: 8,835 (2,800-40,000)
- 1161 (74.3%) of failing patients switched to second line ART in a median (IQR) of 2.8 (0.9-6.9) months

Medical Visits After Treatment Failure

Table 2. Differences in patients' medical visits after first line ART failure, by time to switch to second line group.

Time from first line failure to second line switch:	Did not switch	0 to 1.5 months	1.5 to 3 months	3 to 6 months	6 to 12 months	>12 months
N	401	404	240	199	143	175
Had missed visits in the 6 months following failure	40.5%	22.7%	25.7%	40.2%	43.9%	46.9%
Had next visit within 1 month after failure	68.3%	83.7%	70.4%	72.9%	71.3%	74.3%
Lost from care within 12 months after failure	27.2%	9.7%	5.4%	5.5%	4.2%	0%

Key Findings

- Faster rate of switching was seen in patients with higher viral load and lower CD4 count at failure (Table 1, Figure 1).
- Males and patients with a shorter duration on first line ART prior to failure switched more quickly (Table 1, Figure 1).
- Missed visits prior to failure was weakly associated with a longer delay until second line switch (Table 1, Figure 1).
- Patients who switched most quickly had fewer missed visits after failure and were more likely to have their next visit within a month following treatment failure (Table 2).
- The majority of patients, including patients who did not switch to second line for a year or longer, did not miss visits in the 6 months following first line failure (Table 2).
- Among 401 patients who did not switch, 27% were lost from care in 1 year after failure (Table 2).

CONCLUSION

We found that disease severity at first line failure predicted faster switching, with patients with higher viral load levels and lower CD4 counts being switched to second line more quickly. Lack of visit adherence before failure had a minimal effect on delaying second line ART, and the majority of patients remained in care and did not miss visits within the 6 months following failure, indicating delay in second line treatment initiation is only partially explained by patients missing visits.

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