Delaying second line antiretroviral therapy after first line failure in South Africa: Moderating effect of CD4 count

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INTRODUCTION

BACKGROUND

- 10 years after the launch of South Africa's national antiretroviral therapy (ART) program, 8.2% of HIV patients ever initiated on first line have failed treatment.
- After treatment failure is detected through viral load monitoring, delay in switching to second line ART is common.
- Delays in second line may be associated with poor outcomes on second line if resistance mutations accumulate or CD4 count declines.

OBJECTIVE

The goal of this study is to evaluate the impact of delays from first line ART failure until initiation of a second line regimen on the success of second line ART. This question is important given the limited treatment options if second line fails.

METHODS

- Observational cohort study
- Medical record data from 9 public HIV clinics across South Africa.
- Included adult patients
  - Initiating first line ART in 2004-2012
  - With virologic failure on first line (2 consecutive viral loads >1,000 copies/mL)
  - With at least 1 year of potential follow-up time after failure
- Patients censored if they failed to follow routine viral load monitoring

Exposure groups: Time to switch to second line ART after first line failure (2nd viral load >1,000 copies/mL):

- Never, 0-1.5 months, 1.5-3 months, 3-6 months, 6-12 months, >12 months

Primary outcome: Hazards of virologic failure on second line ART among patients who switched to second line.

- Adjusted for confounding using Cox proportional hazards models

Secondary outcome: Hazards of death after first line ART failure for all patients who failed first line ART.

- Addressed survivor bias by including patients who never switched to second line in marginal structural models

COHORT DESCRIPTION

Initiated first line: 88,305 patients → Failed first line: 7,265 patients (Median time until failure: 17.4 months) → Had ≥1 year of potential follow-up after failure: 5,895 patients

- 3,706 (63%) switched to second line in:
  - 0-1.5 mo: 1114 patients
  - 1.5-3 mo: 669 patients
  - 3-6 mo: 688 patients
  - 6-12 mo: 593 patients
  - >12 mo: 642 patients
- 2,189 (37%) never switched to second line

Median time to switch: 3.4 months
Median follow-up time on second line after switch: 1.4 years

RESULTS

OUTCOMES ON SECOND LINE ART AMONG PATIENTS WHO SWITCHED TO SECOND LINE

Table 1. Cox proportional hazards models of virologic failure after switch to second line.

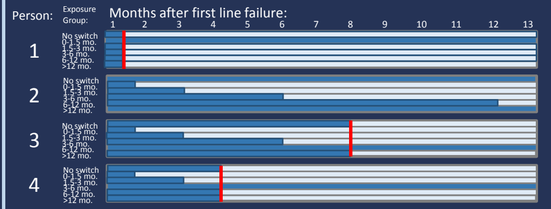
	Peak CD4 on first line ≤ 100 cells/mm^3		Peak CD4 on first line > 100 cells/mm^3	
Time to switch to second line	N	aHR* (95% CI)	N	aHR* (95% CI)
0 to 1.5 mo	156	Ref	884	Ref
1.5 to 3 mo	99	2.26 (1.12, 4.55)	524	0.87 (0.67, 1.14)
3 to 6 mo	101	2.13 (1.01, 4.47)	552	1.03 (0.78, 1.35)
6 to 12 mo	87	1.54 (0.68, 3.46)	460	0.87 (0.63, 1.20)
>12 mo	53	1.35 (0.49, 3.73)	519	0.73 (0.52, 1.02)

*Adjusted for gender, age, viral load at failure, BMI at failure, missed visits before failure, year of failure, time on treatment, clinic

ACCOUNTING FOR PATIENTS WHO DID NOT SWITCH TO SECOND LINE

- 43% lost from care & 6% died in one year
- Sickest patients lost most quickly
- Marginal structural models can account for these patients
- Each person contributes person time to each exposure group
- Artificial censoring is corrected using inverse probability of censoring weighting (equivalent to inverse probability of treatment)

Figure 1. Hypothetical person time contributed to each of the 6 exposure groups in marginal structural models. Time of switch to second line is represented by a red line.



OUTCOMES FOR ALL PATIENTS WHO FAILED FIRST LINE

Table 2. Marginal structural model results showing hazards of death after first line treatment failure.

		Peak CD4 on first line ≤ 100 cells/mm^3	Peak CD4 on first line >100 cells/mm^3
Variables		aHR (95% CI)	aHR (95% CI)
Time to switch to second line	No switch	1.55 (0.95, 2.53)	1.20 (0.82, 1.76)
	0-1.5 months	Ref	Ref
	1.5-3 months	1.39 (0.85, 2.27)	0.93 (0.64, 1.34)
	3-6 months	1.31 (0.81, 2.15)	0.98 (0.68, 1.42)
	6-12 months	1.49 (0.91, 2.42)	1.22 (0.82, 1.79)
	>12 months	1.52 (0.94, 2.46)	1.11 (0.77, 1.62)
Gender	Female	Ref	Ref
	Male	0.81 (0.46, 1.42)	1.37 (0.92, 2.02)
Age	18-25	0.92 (0.37, 2.29)	0.87 (0.31, 2.38)
	25-30	0.76 (0.34, 1.68)	1.22 (0.64, 2.33)
	30-35	Ref	Ref
	35-40	0.58 (0.23, 1.46)	1.26 (0.73, 2.16)
	40-45	0.39 (0.15, 0.99)	1.02 (0.53, 1.97)
	45-50	0.65 (0.23, 1.84)	0.91 (0.40, 2.08)
	50-55	1.06 (0.35, 3.22)	1.75 (0.70, 4.37)
	55+	0.65 (0.19, 2.24)	1.53 (0.55, 4.25)
Failing viral load	1000-9999	0.39 (0.19, 0.80)	0.51 (0.31, 0.84)
	10,000-59,999	0.82 (0.42, 1.63)	0.57 (0.35, 0.95)
	60,000+	Ref	Ref
CD4 count at failure	0-49		2.46 (1.20, 5.04)
	50-99		Ref
	100-250		0.72 (0.41, 1.28)
	>250		0.42 (0.20, 0.85)

CONCLUSIONS

- Even small delay in switch to second line ART was associated with increased death and increased virologic failure on second line among patients with low CD4 count on first line.
- Among patients with higher CD4 count on first line, death was slightly increased for patients who switched in >6 months.
- Results are consistent with survivor bias present in the Cox proportional hazards models, where longer time to switch groups were comprised of healthier patients by definition. Marginal structural models addressed this bias.

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