Long-term outcomes of over one thousand patients on second-line antiretroviral therapy in South Africa

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ABSTRACT

Background: While most resource-limited settings provide access to second-line antiretroviral therapy (ART) for patients failing first-line, there has been little assessment of long-term outcomes. Early reports showed positive outcomes; however, it remains to be seen if such positive outcomes will continue as second-line care becomes more routine. We assessed second-line outcomes under routine care over eight years in four public-sector clinics in South Africa.

Methods: We conducted a retrospective study of patients who initiated standard government first-line ART, failed first-line ART, and then switched to a standard second-line regimen between April 2004 and September 2012. Patients were followed from second-line ART initiation until the earliest of death, loss to follow-up, transfer, or dataset closure (September 2013). We looked for differences in one-year treatment outcomes by year of cohort initiation and outcomes over the entire eight years of follow-up.

Results: Overall, 1304 patients initiated second-line ART, ranging from 26 in 2005 to 359 in 2011. The cohort was 60.4% female and initiated ART with a median (IQR) CD4 count of 74.5 (25-144.5) cells/mm^3, lower than for the overall population (median 121; IQR 56-186). Patients were followed for a median (IQR) of 23.1 (14.2-36.9) months on second-line. At the end of follow-up, 52.5% of patients were alive and in care at censoring, 7.4% had died, 19.5% were lost to follow-up and 20.6% transferred to another site. Over eight years, using Kaplan-Meier analysis, we estimated attrition (death and loss to follow-up) was 54.7% (95% CI: 47.8-62.0).

Over time rates of attrition at one-year on second-line were stable between 102.5/1000 person-years (95% CI: 48.9-215.0) for patients who initiated second-line treatment in 2005/2006 and 109.6 (95% CI: 85.6-140.3) for patients who initiated in 2011/2012 (Figure). Patients who initiated in 2007 and 2008 did see a slight increase in attrition with a rate of 138.3 (95% CI: 100.6-190.1).

In adjusted analyses, there was a slight increased risk of one-year attrition after second-line initiation for patients who initiated in 2007/2008 compared to patients initiating in 2005/2006 (aHR: 1.33; 95% CI: 0.56-3.18); however, there was limited precision around the estimate. In addition, patients who initiated second-line with a viral load >50,000 copies/mL were over twice as likely to die or become lost after second-line initiation vs. patients with a viral load <5,000 copies/mL (aHR: 2.34; 95% CI: 1.43-3.83).

Conclusions: Second-line therapy has become widely accessible in resource-limited settings but treatment outcomes in large cohorts of patients haven't been evaluated. We found little increased risk of poor treatment outcomes as scale-up for second-line increased but as we saw poorer outcomes associated with higher viral load at switch, interventions for earlier switch should be considered.

BACKGROUND

While most resource-limited settings provide access to second-line antiretroviral therapy (ART) for patients failing first-line, there has been little assessment of long-term outcomes. Early reports showed positive outcomes; however, it remains to be seen if such positive outcomes will continue as second-line care becomes more routine.

METHODS

We conducted a retrospective cohort study of HIV-infected patients who initiated standard first-line ART, failed first-line ART, and then switched to second-line treatment at public-sector facilities in Johannesburg, South Africa from April 2004 – September 2012

Study Population

- Inclusion criteria:
  - HIV-infected, treatment naïve, adult (≥18) at one of four public sector facilities in Johannesburg, South Africa
  - Initiated standard first-line ART, experienced virologic failure (2 consecutive viral loads >1000 copies/ml between 2 weeks and 6 months apart), and then initiated standard second-line ART
- Patients followed from second-line ART initiation until the earliest of death, loss to follow-up, transfer, or dataset closure (September 2013)

Definitions

- Standard first-line ART: d4T-3TC-EFV/NVP, TDF-3TC/FTC-EFV/NVP, AZT-3TC-EFV/NVP
- Standard second-line ART: AZT-3TC/ddI-LPVr, TDF-3TC/FTC-LPVr
- Loss to follow-up (LTF): ≥3 months late for a scheduled visit with no subsequent visit
- Attrition: death or loss to follow-up

Statistical Methods

- Continuous variables are presented as medians with corresponding interquartile ranges (IQR) and categorical variables are expressed as simple proportions
- Kaplan-Meier analysis was utilized to estimate attrition over eight years and one-year incidence rates of attrition are presented per 1000 person-years
- Cox proportional hazards regression was used to examine predictors of one-year attrition and results are presented as unadjusted (HR) and adjusted hazard ratios (aHR) with corresponding 95% confidence intervals (CI)

RESULTS

- 1304 patients initiated standard second-line ART and were included in the analysis. 60.4% of patients were female and the median (IQR) CD4 count at second-line ART initiation was 226 (137-335) cells/mm^3
- Most patients initiated d4T-3TC-EFV (68.9%) at ART initiation and AZT-ddI-LPVr (42.1%) at second-line initiation
- Patients were followed for a median (IQR) of 23.1 (14.2-36.9) months on second-line ART
- At the end of follow-up, 52.5% of patients were alive and in care, 7.4% of patients had died, 19.5% of patients were LTF, and 20.6% had transferred to another site

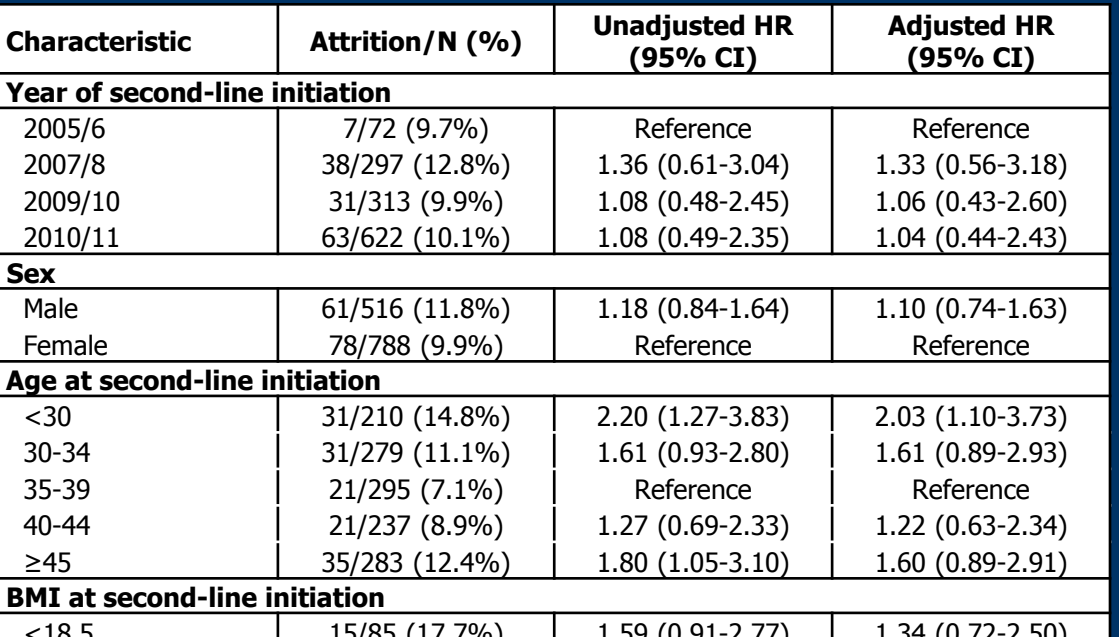
Table 1 – Baseline demographic and clinical characteristics at second-line ART initiation

Characteristic	Exposure	Total
TOTAL	n (%)	1304 (100%)
Sex	Female	788 (60.4%)
Age	Median (IQR)	37.6 (32.4-44.0)
CD4 count (cells/mm^3)	Median (IQR)	226 (137-335)
Viral load (copies/mL)	Median (IQR)	13000 (3200-63000)
BMI	Median (IQR)	24.4 (21.3-28.0)
Hemoglobin (g/dL)	Median (IQR)	12.6 (11.4-13.6)
Year of second-line initiation	2005/6	72 (5.5%)
	2007/8	297 (22.8%)
	2009/10	313 (24.0%)
	2011/12	622 (47.7%)
First-line ART Regimen	d4T-3TC-EFV	899 (68.9%)
	AZT-3TC-EFV	35 (2.7%)
	TDF-3TC-EFV	188 (14.4%)
	Other	182 (14.0%)
Second-line ART Regimen	AZT-3TC-LPVr	345 (26.5%)
	AZT-ddI-LPVr	549 (42.1%)
	TDF-3TC-LPVr	400 (30.7%)
	TDF-FTC-LPVr	10 (0.8%)

Table 2 – Predictors of 1 year attrition after second-line initiation

Characteristic	Attrition/N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Year of second-line initiation			
2005/6	7/72 (9.7%)	Reference	Reference
2007/8	38/297 (12.8%)	1.36 (0.61-3.04)	1.33 (0.56-3.18)
2009/10	31/313 (9.9%)	1.08 (0.48-2.45)	1.06 (0.43-2.60)
2010/11	63/622 (10.1%)	1.08 (0.49-2.35)	1.04 (0.44-2.43)
Sex			
Male	61/516 (11.8%)	1.18 (0.84-1.64)	1.10 (0.74-1.63)
Female	78/788 (9.9%)	Reference	Reference
Age at second-line initiation			
<30	31/210 (14.8%)	2.20 (1.27-3.83)	2.03 (1.10-3.73)
30-34	31/279 (11.1%)	1.61 (0.93-2.80)	1.61 (0.89-2.93)
35-39	21/295 (7.1%)	Reference	Reference
40-44	21/237 (8.9%)	1.27 (0.69-2.33)	1.22 (0.63-2.34)
≥45	35/283 (12.4%)	1.80 (1.05-3.10)	1.60 (0.89-2.91)
BMI at second-line initiation			
<18.5	15/85 (17.7%)	1.59 (0.91-2.77)	1.34 (0.72-2.50)
18.5-24.9	72/611 (11.8%)	Reference	Reference
25-29.9	35/364 (9.6%)	0.81 (0.54-1.22)	0.85 (0.54-1.32)
≥30	15/205 (7.3%)	0.61 (0.35-1.05)	0.71 (0.39-1.29)
Viral load at second-line initiation			
<5000	24/382 (6.3%)	Reference	Reference
5000-9999	18/153 (11.8%)	1.88 (1.02-3.47)	1.73 (0.93-3.23)
10000-49999	26/301 (8.6%)	1.41 (0.81-2.46)	1.36 (0.78-2.37)
≥50000	53/353 (15.0%)	2.52 (1.56-4.08)	2.34 (1.43-3.83)

Figure – Kaplan-Meier survival curve for 1 year attrition after switching to second-line therapy by year switched to second-line



- Over time rates of attrition at one-year on second-line were stable between 102.5/1000 person-years (95% CI: 48.9-215.0) for patients who initiated second-line treatment in 2005/2006 and 109.6 (95% CI: 85.6-140.3) for patients who initiated in 2011/2012 (Figure).
- There was an increased risk of one-year attrition after second-line initiation for patients aged 18-29 compared to patients aged 35-39 (aHR: 2.03; 95% CI: 1.10-3.73)
- Patients who initiated second-line with a viral load >50,000 copies/mL were over twice as likely to die or become lost after second-line initiation vs. patients with a viral load <5,000 copies/mL (aHR: 2.34; 95% CI: 1.43-3.83).

CONCLUSIONS

Second-line therapy has become widely accessible in resource-limited settings but treatment outcomes in large cohorts of patients haven't been evaluated. We found little increased risk of poor treatment outcomes as scale-up for second-line increased but as we saw poorer outcomes associated with higher viral load at switch, interventions for earlier switch should be considered.

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