Successful Second Line Antiretroviral Therapy with High Rates of Survival, Immune Reconstitution and Virologic suppression in a Large Urban Clinic in Johannesburg, South Africa

Authors: Matthew Fox[€¥*], Prudence Ive[√], Lawrence Long[¥], Mhairi Maskew[£], Ian Sanne[£√]

Affiliations:
€ Center for International Health and Development, Boston University School of Public Health, Boston, MA, USA
¥ Health Economics Research Unit, University of the Witwatersrand, Johannesburg, South Africa
£ Right to Care, Johannesburg, South Africa
√ Clinical HIV Research Unit, Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa
** Corresponding Author*

Running Head: Second-line therapy in South Africa

Acknowledgments:
Funding was provided by USAID under the terms of agreement 674-A-00-08-00007-00 with Right to Care and by the South Africa Mission of the US Agency for International Development (USAID) under the terms of Cooperative Agreement GHSA-00-00020-00, Country Research Activity (G/PHN/HN/CS). We express our gratitude to the directors and staff of the Themba Lethu Clinic, who helped to collect and interpret the data; to Right to Care, the NGO supporting the study sites through a partnership with USAID and to the patients at the Themba Lethu Clinic. We also thank the Gauteng and National Department of Health for providing for the care of the patients at the Themba Lethu Clinic as part of the Comprehensive Care Management and Treatment plan. We are also extremely grateful to Professor Patrick MacPhail and Babatyi Malope-Kgokong for their work in creating the Themba Lethu Clinical Cohort dataset. The authors also thank Sydney Rosen and Donald Thea for their comments on earlier drafts of the manuscript. The opinions expressed herein are those of the authors and do not necessarily reflect the views of USAID, the Themba Lethu Clinic, Right to Care or the colleagues mentioned above. Most of all we thank the patients attending the clinic for their continued trust in the treatment provided at the clinic.

Key words: human immunodeficiency virus, antiretroviral therapy, South Africa, second-line therapy, viral load, CD4 count, sub-Saharan Africa

Word count: 3,414
Abstract word count: 345

ABSTRACT

Background: As rapid scale-up of ART programs continues in South Africa, more patients will fail first-line regimens. Currently little is known about survival and immunologic and virologic outcomes of second-line ART in resource-limited settings.

Methods: We conducted a cohort study among 328 patients initiated on second-line treatment, namely zidovudine, didanosine and lopinavir/ritonavir (AZT/ddI/LPVr). All patients failed first-line therapy at a large urban public-sector clinic in Johannesburg, South Africa. We investigated three outcomes in the year after initiating second-line therapy: 1) viral load suppression (≤400 copies/ml); 2) alive and in care; and 3) CD4 count increase. Predictors of treatment failure were assessed with proportional hazards regression and outcomes were compared to patients on first-line for an equivalent time.

Results: Excluding transferred patients, a year after initiating second-line therapy we estimated that 243/313 (78%; 95% CI 73-82%) were alive and in care. Of the 261 subjects with a viral load measurement after initiating second-line, 202 (77%; 95% CI 72-82%) had a suppressed viral load by one year. Mean gain in CD4 count by 12 months was 133 cells/µl (95% CI 106-160). Patients on second-line therapy had a small decreased likelihood of being alive and in care by one year (HR 0.84; 95% CI 0.73-0.97) as time matched comparisons on first-line ART. In multivariable analysis, patients with prior single drug substitution (HR 0.71; 95% CI 0.56-0.89), those with a history of TB (HR 0.70; 95% CI 0.48-1.01) and those who had >3 weeks delay between a second viral load > 1000 before switching (HR 0.60; 95% CI 0.43-0.83) were less likely to achieve virologic suppression by one year on second-line ART.

Conclusions: Rates of being alive and in care over the first year on second-line therapy in patients in our cohort were high and similar to that shown previously. Our study has demonstrated that viral load suppression is also being achieved on second-line therapy. Second line treatment appears to be similar to continued first-line therapy, and provision of such treatment to patients who fail their first ART regimen should be considered a high priority in resource poor settings.

INTRODUCTION

In 2004 the South African government began its large-scale Comprehensive Care Management and Treatment (CCMT) plan for provision of antiretroviral therapy (ART).[1] Over the next three years South Africa saw the number of patients on ART rise to nearly 300,000 by 2007.[2] Although the vast majority of patients remain on first-line therapy and are achieving positive clinical, immunologic, and virologic outcomes,[3-7], the absolute number of patients failing first-line therapy is likely to increase along with overall patient numbers and duration on ART. In addition, as women who receive single dose NVP (sNVP) for pMTCT appear to be more likely to fail first-line ART regimens that include NVP, the use sNVP may lead to an increased rate of first-line treatment failure.

Second-line regimens are far more expensive than standard first-line therapy, and concerns over the development of resistance to second-line regimens in developing countries have been raised particularly in the absence of viral load monitoring.[8;9] It is therefore critical to assess the effectiveness of second-line regimens in resource-limited settings, where treatment programs are still relatively new and viral load testing to confirm suppression is rate.[10-12] A search of the literature identified only one published analysis of the outcomes of second-line therapy in developing countries. The Médecins Sans Frontières cohort experienced high rates of survival and successful immunologic outcomes in 370 patients from different developing countries.[13] While very encouraging, this program had limited data on viral load to be able to assess virologic suppression.

South Africa, where treatment guidelines for public sector treatment[1] do allow for switching patients to second-line regimens after virologic confirmation of failure of first-line regimens is likely to see such a rise in the near future. We use data from a large urban HIV clinic in South Africa which conducts routine viral load tests after initiation of second-line therapy to assess survival and immunological and virologic outcomes over the first year of follow-up in a cohort of patients switched to standard public sector second-line therapy.

MATERIALS AND METHODS

Study Site

The study was conducted using data collected at the Themba Lethu Clinic (TLC) in Johannesburg, South Africa. TLC is a large urban public-sector ART clinic located at a secondary referral hospital. The clinic also receives support from a PEPFAR-supported South African non-governmental organization called Right to Care. All care at TLC has been provided completely free of charge to patients since October 2006.

TLC is one of the largest HIV clinics in South Africa with nearly 11,000 patients initiated on ART and 3,000 patients receiving pre-ART HIV wellness care with between 200-500 consultations per day. Treatment is conducted in accordance with the South African National Department of Health guidelines[1] for the provision of antiretroviral therapy. These include stavudine, lamivudine and efavirenz (d4T/3TC/EFV) as the standard first-line therapy with zidovudine (AZT) and nevirapine (NVP) as possible alternatives to d4T and EFV respectively. Patients are initiated on ART with a CD4 count ≤200 or a WHO

Stage IV condition. Standard public-sector second-line therapy is zidovudine, didanosine and lopinavir/ritonavir (AZT/ddI/LPVr). Treatment switching is undertaken based on toxicity and viral load >1000 copies/ml.

Study population

This analysis included all patients initiated on standard public-sector second-line therapy at TLC between April of 2004 and June 2008 who were ≥18 years old and who were initiated on a standard triple drug therapy and who did not have AZT/ddI/LPVr as their first known regimen. We excluded patients who initiated second-line therapy after November 2007 so that all subjects had the potential to complete a minimum of one year of follow-up.

Data collection

We conducted a cohort analysis of data collected prospectively as part of routine HIV care. All patient data at TLC is collected in a standardized way using an electronic patient management system. Demographic data are captured at initiation of first-line ART, and all visit information are collected in real-time in the clinic.

Patients are scheduled for medical visits every one to six months, though most patients return to the clinic every 1-2 months to collect ARVs. Visit scheduling is tracked electronically and allows for tracing of patients who have missed visits and for categorization of patients as lost to follow-up (LTF) (defined as is having missed a scheduled ARV pickup for >3 months). At each medical visit, patients are seen by a nurse, a doctor, and when appropriate, a counselor. Medical visit information is collected on TB symptom screen, weight, other vital signs and any new clinical conditions diagnosed including new opportunistic infections and tuberculosis.

Treatment monitoring is done with CD4 counts and viral loads at four months after initiation and then approximately six monthly thereafter unless clinically indicated. CD4+ T-cell lymphocytes counts are done using pan-leucogated CD4+ flow cytometry while HIV-1 RNA viral load tests are conducted using NucliSENS EasyQ® HIV-1 assay (bioMérieux Clinical Diagnostics, France).

Analysis of this data was approved by the Institutional Review Board of Boston University and the Human Research Ethics Committee of the University of the Witwatersrand.

Comparison population

To determine if outcomes on second-line therapy differed from outcomes on first-line therapy, we time-matched each index patient who switched to second-line to four comparison subjects who did not begin second-line therapy. For each index patient we calculated their duration on first-line therapy and then randomly sampled up to four comparison patients from all patients who did not go on to second-line therapy but who had been on first-line *at least as long as the index patient*. Four matches were found for all but 1 second-line patient. We then used the calendar time of initiating second-line for the index subject as the time we began calculating person time for all patients in the

matched set. For example if a patient initiated second-line drugs after 365 days on first-line drugs, we sampled four subjects who did not switch to second-line drugs from the list of all patients on first-line for ≥ 365 days. Each of the 5 subjects (the second-line patient and the four matched comparison subjects) began accumulating person time from day 365 through a maximum of 730 days.

Definition of analytic variables

Dependent variable

We examined two measures of treatment success by one year after initiating second-line ART: 1) alive and in care and on treatment (AIC), defined as not known to have died, not LTF (missed a scheduled ARV pickup for longer than three months) and no record of stopping standard second-line treatment; 2) achieving an undetectable viral load (UDVL) (<400 copies/ml); and 3) changes in CD4 count. For UDVL we only included patients with ≥1 viral load measure within 12 months after initiating second-line treatment. Patients transferred out of care were excluded from the AIC analysis unless they completed 1 year of follow-up before transfer and the UDVL analysis unless they had a viral load prior to transfer.

Follow-up time

Follow-up time for each subject began on the date of initiating second-line therapy for index subjects or the equivalent duration on first-line for time matched comparisons. For AIC, follow-up time ended at the date of the earliest of: 1) completion of one year of follow-up; and 2) closing the dataset; 3) death or LTF. For the AIC analysis the study population was limited to those 332 subjects who had the potential to complete one year of follow-up. For UDVL, follow-up time ended at the date of the earliest of: 1) last viral load while on second-line up to one year; 2) first UDVL on second-line.

Statistical analysis

We summarized treatment simple proportions achieving each outcome and corresponding 95% confidence intervals (CI). Changes in CD4 count after initiating second-line therapy were summarized as mean changes over time and 95% confidence intervals. We then looked for predictors of UDVL by one year among to those on second-line drugs. We calculated crude Kaplan-Meier curves of viral suppression stratified by predictors of interest and calculated crude and hazard ratios (HR) using Cox proportional hazards regression. We fit adjusted multivariable models adjusted for age and sex and other important predictors. To look for predictors of second line treatment failure, multivariable models included any variable with a Wald p-value <0.3. Potential predictors included variables related to initiation of any ARV (e.g. regimen, CD4 count, BMI, calendar year, history of TB, etc.), variables occurring during first-line (e.g. incident TB, development of toxicities, compliance, months on first-line, time from two consecutive viral loads >1000 to switching, etc.) as well as variables relating to the time of initiation of second-line (e.g. CD4 count, BMI, CD4 nadir, etc).

Finally, we calculated hazard ratios comparing subjects on second-line therapy to the time matched comparison group to determine whether outcomes on second-line therapy differed from those on first-line therapy for patients on ART for an equal duration.

RESULTS

Cohort Description

Roughly 3.5% of all patients initiated on ART at TLC initiated second-line treatment. Table 1 compares the 328 index patients initiated on second-line therapy to two other groups: 1) all the 9,694 patients initiated on first-line ART at TLC not switched to second-line therapy; and 2) the 1,311 time matched comparison patients (described under Methods).

Patients initiated on second-line had been on ART a median of 1.3 years at the time of treatment switch. Most patients were initiated on d4T-3TC-EFV (79%) as first-line therapy. Compared to those not switched to second-line or the time matched comparisons, patients switched were more immunosuppressed at initiation of first-line therapy as they were more likely to have had a CD4 count <50 than either comparison group (43% vs 35% and 32% respectively) and more likely to have a history of TB (19% vs. 9% and 11% respectively). While underreporting was common, 57 (18%) of patients experienced peripheral neuropathy before switching, 5 (2%) experienced lactic acidosis, and 40 (12%) were noted to have had non-compliance with their first regimen.

Outcomes on Second-line Therapy

Alive and In Care

Perhaps the most general measure of the success of treatment is being alive and in care (Figure 1a). After excluding 15 patients who were transferred out of care to another treatment facility, 78% (95% CI 73-82%) of patients switched to second-line treatment (243/313) were alive and in care at the end of one year on second-line therapy. Of the 70 patients who experienced a negative outcome, 17 died (24%) and 53 were LTF (76%)

Virologic Suppression

For treatment to show long term effectiveness patients must achieve and maintain viral suppression (Figure 1b). After excluding 5 transferred patients, we had viral load measures for 261 (77%) patients. Of the 62 with missing viral load measures, 57 (92%) died (N=8) or were LTF (N=39). We detected no differences in CD4 count, BMI, hemoglobin, and age at initiation of first-line ART between those who did and did not have a viral load outcome. Of the remaining 261 with a viral load measure, 202 (77%; 95% CI 72-82%) had achieved a suppressed viral load by one year after initiation of second-line treatment. Of the 59 patients who did not achieve viral suppression, median viral load was 7,000 (range 450 – 130,000). Of these 59, 30 (51%) were still alive and in care at the end of one year of follow-up. The remaining 29 (41%) 8 died while 19 were. Of the 202 subjects who reached virally suppression by one year, 18 (9%) had viral rebound within one year with a median viral load or 1700 (range 420-62,000).

Immunologic Success

Figure 2 shows population mean increases in CD4 counts from initiation of second-line therapy. At initiation of second-line therapy, 249 patients had a CD4 count up to four months before the switch. Among those the mean CD4 count was 203 cells/µl (95% CI 187-219). This increased to 266 cells/µl by 6 months (95% CI 241-292) and to 318

cells/mm^3 (95% CI 288-348) by one year on second-line treatment. The relatively small number of patient with a CD4 count reported after one year on second-line therapy (N=138) accounts for the wide confidence intervals. The mean increase from initiation of second-line when limited to the 110 patients with both an initiation of second-line and 6 month CD4 count was 59 cells/µl (95% CI 37–80) and the among the 102 with both an initiation of second-line and 12 month CD4 count was 133 cells/µl (95% CI 106–160). The increase was slightly larger by one year when limited to those who achieved viral suppression (129; 95% CI: 93 to 165) with little to no change among those not virally suppressed (44; 95% CI: -29 to 118).

Comparison to those on first-line for equal duration

To determine if one year outcomes on second-line therapy differed from outcomes among patients on first-line for an equivalent amount of time, we compared the proportion alive in care by one year of time to matched controls who did not switch to second-line to those on second-line (Table 2). A smaller proportion of patients on second-line therapy were alive and in care after one year on treatment compared to those time matched comparisons still on first-line (77% vs. 91%). After adjusting for age, sex, race and first-line regimen and year of initiating any ART, patients on second-line therapy were somewhat less likely to be alive and in care by one year (HR 0.84; 95% CI 0.73-0.97).

Predictors of Virologic Success

Figure 3 shows Kaplan-Meier curves of time to viral suppression by one year on second-line treatment stratified by various predictors and Table 3 summarizes predictors of virologic suppression. In adjusted analyses, we found that patients with at least one single drug substitution before switching to second-line (HR 0.71; 95% CI 0.56-0.89), a history of TB (HR 0.70; 95% CI 0.48-1.01) and those who had >3 weeks delay between a second viral load > 1000 before switching (HR 0.60; 95% CI 0.43-0.83) were less likely to achieve viral suppression by one year than those who had not. Interestingly, when we stratified our data into those who did and did not switch for reasons of compliance and those who did and did not experience toxicity before failure of first-line, single drug substitution was the largest predictor of treatment failure in all four models.

While not statistically significant, those with a lowest CD4 count <50 before initiating second-line ART and those who were non-compliant with their first-line regimen were also somewhat less likely to achieve viral suppression by one year. We did not detect any prior toxicity as being predictive of failure.

DISCUSSION

As the scale up of ART in developing countries continues, the number of patients switching to second-line therapy will inevitably increase. Decision about the use of second-line regimens in these areas will depend, in part, on the success of these regimens, but to date there has been little evidence to assess the effectiveness of these regimens in patients failing first-line therapies.[12] We have demonstrated in a large urban cohort in South Africa that outcomes on second-line therapy, whether measured in terms of remaining alive and in care or by virologic suppression showed between 77-78% success rates by one year after initiating second line treatment. In comparison, a pooled analysis

of mortality on first-line regimens in low-income countries showed one year survival rates of roughly 94% when actively tracing patients.[14]

Our results are very similar to the recent findings by Pujades-Rodriguez[13] using the Médecins Sans Frontières (MSF) cohort encompassing countries throughout the developing world. Our data are not strictly comparable as their data included several second-line regimens and the majority of those patients had d4T-3TC-NVP as first-line. In their cohort of 370 patients on second-line therapy, 86% (95% CI 81-90%) were alive and in care by one year, similar, though somewhat higher than our finding (78%; 95% CI 73-82%). Our ability to show viral load suppression in 77% (95% CI 72-82%) of patients demonstrates that patients are not only surviving but are achieving maximum viral suppression. Equally important, we found that, while outcomes among patients on second-line therapy were not as positive as patients who were still on first-line therapy but of equal total duration on any ART, differences were small. Taken together these findings suggest that patients who are switched to second-line treatment have a positive prognosis, at least through on year after initiation.

We have also demonstrated a substantial mean increase in CD4 count in patients on second-line therapy. Patients on second-line therapy increased an average of 102 cells/µl over the first year on treatment. This is again similar to the MSF cohort, where patients had a median CD4 count increase at 12 months of 135 cells/µl.[13] While not universally accepted, an increase of 100 cell/µl over the first year on therapy can be seen as a marker of treatment success on first-line therapy when most patients are initiated at CD4 counts below 200. In comparison, the average gain of over 102 cells in one year on second-line seen in our study represents substantial immune recovery.

As more patients are initiated on second-line regimens, being able to identify which patients fail these regimens and why will be critical to the long term durability of these regimens. In our study, patients who had at least on single drug substitution prior to switching to second-line and those with a delay of more than three weeks between failure of first-line and switching were less likely to achieve viral suppression by one year. Single drug substitution is likely a marker of toxicity in our database as toxicities tend to be underreported. Such substations are often undertaken for toxicity, either nucleoside related mitochondrial toxicity or Nevirapine related hypersensitivity. Intermittent therapy provided during the toxicity either due to patient non-adherence or provider directed may lead to the accumulation of resistance mutation. Delays between failure of first-line and switching can also lead to increased resistance mutations. Prolonged treatment during first-line treatment failure is associated with higher rates of thymidine analogue mutations, which may impact the second line treatment response.[15;16] Thus our data suggest that monitoring patients with first-line failure is important to success of second-line regimens.

We did not have data on adherence to second-line therapy, potentially the most important predictor of achieving viral suppression. Overall adherence was likely high as treatment success rates were high, but over time adherence rates may decline leading to more failures.

Our findings should be considered in light of its limitations. In particular, each of our outcome measures was subject to some misclassification. We have used alive and in care as a proxy for vital status. The realities of working in a large urban treatment facility are that some patients will be lost and no outcome can be recorded for them. In many settings being lost means no longer on ART,[17] as most patients who discontinue care will likely die within one year of stopping treatment.[18;19] In two studies of patients who dropped out of care at clinics in Johannesburg, 27% and 48% of those who could be traced had died.[20;21] It thus seems reasonable to use alive and in care as a proxy for vital status, particularly as this would be a conservative estimate of overall treatment success.

In addition, our comparison of patients who were on second-line therapy with those on first-line for equivalent times likely suffers from some survivor bias. Patients who are failing first line but survive long enough to be switched to second line may be at reduced risk of poor outcomes and death, compared to those who were eligible for second-line but either chose not to initiate, or died before receiving it. This would tend to bias mortality rates on second-line towards those on first-line and cause us to underestimate whether those on second-line do worse. Still, the lack of effect observed suggests that the bias would have to be substantial to lead to a strong increased risk in those on second-line.

The South African CCMT program for antiretroviral therapy includes the monitoring of treatment using CD4+ count and viral load. Whereas the national treatment program advocates treatment switching for virologic failure as defined by two consecutive viral loads >5000 copies/ml, the Themba Lethu Clinic cohort switches treatment based on two detectable viral loads>1000 copies/ml. The results presented here may therefore reflect a more stringent monitoring policy.

In conclusion, we found that patients who were initiated on second-line therapy in a large urban HIV clinic in Johannesburg, South Africa had high rates of immunologic and virologic success and low rates of mortality over the first year on second-line treatment. Further research is needed to determine if these findings can be extended to different settings and longer follow-up will be needed to determine if these early outcomes can be sustained over the following years of treatment.

Table 1 – Demographic, social and clinical characteristics of a cohort of 328 patients initiating second-line therapy at the Themba Lethu Clinic in Johannesburg, South Africa between 2004-2008.

Variable	**Exposure**	**Second line (N=328)**	**Did not begin second line (N=9,694)**	**Time matched comparison (N=1,311)**
Sex	Male	112 (34.1%)	3298 (34.0%)	446 (34.0%)
	Female	216 (65.9%)	6396 (66.0%)	865 (66.0%)
Race	Black	309 (94.2%)	9244 (95.3%)	1244 (94.9%)
	Other	19 (5.8%)	451 (4.7%)	67 (5.1%)
Year of initiation of first line	2004	124 (37.8%)	1378 (14.2%)	260 (19.8%)
	2005	115 (35.1%)	2140 (22.1%)	333 (25.4%)
	2006	81 (24.7%)	2734 (28.2%)	384 (29.3%)
	2007	8 (2.4%)	2692 (27.8%)	291 (22.2%)
	2008	0 (0.0%)	751 (7.7%)	43 (3.3%)
ART regimen at ART initiation	d4T-3TC-EFV	259 (79.0%)	7509 (77.5%)	1023 (78.0%)
	d4T-3TC-NVP	46 (14.0%)	793 (8.2%)	100 (7.6%)
	Other	23 (7.0%)	1393 (14.4%)	188 (14.3%)
CD4 category at ART initiation	0-50	118 (43.2%)	2853 (34.7%)	355 (31.6%)
	51-100	68 (24.9%)	1686 (20.5%)	233 (20.8%)
	101-200	65 (23.8%)	2822 (34.3%)	392 (34.9%)
	>200	22 (8.1%)	867 (10.5%)	142 (12.7%)
History of TB	No	267 (81.4%)	8811 (90.9%)	1162 (88.6%)
	Yes	61 (18.6%)	884 (9.1%)	149 (11.4%)
Number of single drug substitutions∫	0	184 (56.1%)	5850 (60.3%)	677 (51.6%)
	1	93 (28.4%)	2617 (27.0%)	427 (32.6%)
	2 or more	51 (15.5%)	1228 (12.7%)	207 (15.8%)
Incident peripheral neuropathy	No	263 (80.2%)	8375 (86.4%)	1073 (81.8%)
	Yes	65 (19.8%)	1320 (13.6%)	238 (18.2%)
Had two consecutive viral loads	No	69 (21.7%)		

Variable	Exposure	Second line (N=328)	Did not begin second line (N=9,694)	Time matched comparison (N=1,311)
> 1000 before switch	Yes	249 (78.3%)		
			MEAN (STD) N	
CD4 at ART initiation		84.7 (82.1) 273	105.4 (99.2) 8228	114.4 (111.2) 1122
BMI at ART initiation		22.4 (4.2) 254	22.4 (4.6) 7470	22.6 (4.6) 1069
Hemoglobin at ART initiation		11.4 (2.2) 284	11.6 (4) 8231	11.6 (2.2) 1135
Age at ART initiation		35.8 (8.1) 328	36.5 (8.6) 9695	36.8 (8.8) 1311
Total months on treatment		37.5 (11.6) 328	23.5 (15.1) 9695	31 (13.2) 1311
Age at initiation of second line		37.2 (8.1) 328		
CD4 at initiation of second line		203.3 (128.3) 249		
BMI at initiation of second line		24.9 (5.6) 311		
Days from second viral load > 1000 to switch		88.3 (83) 249		

* CI: Confidence interval
∫ For patients on second-line this is up to the time of switching to second-line

Table 2 – Crude and adjusted predictors of being alive and in care in a cohort of 328 patients initiating second-line therapy at the Themba Lethu Clinic in Johannesburg, South Africa between 2004-2008.

Exposure	Level	Number alive and in care	Person years	Rate/ 100 py*	IRR (95% CI)*	HR adjusted (95% CI)*∞
Began second line?						
	No	1155	991.5	116.5	1	1
	Yes	243	253.8	95.7	0.84 (0.73-0.97)	0.84 (0.73-0.97)
Sex						
	Male	462	405.5	113.9	1	1
	Female	936	839.7	111.5	0.93 (0.83-1.04)	0.93 (0.83-1.05)
Age at second line						
	<=35	665	584.4	113.8	1	1
	>35	733	660.9	110.9	0.97 (0.87-1.08)	0.96 (0.86-1.07)
Black						
	Yes	1328	1172.5	113.3	1	1
	No	70	72.8	96.2	0.90 (0.71-1.15)	0.90 (0.70-1.15)
Regimen at ART initiation						
	Other	306	277.0	110.5	1	1
	d4T-3TC-EFV	1092	968.2	112.8	1.04 (0.91-1.18)	1.04 (0.91-1.19)

* IRR -Incidence Rate Ratio, HR = Hazard Ratio, CI = Confidence Interval, py= person years
∞ adjusted for all other variables in the model

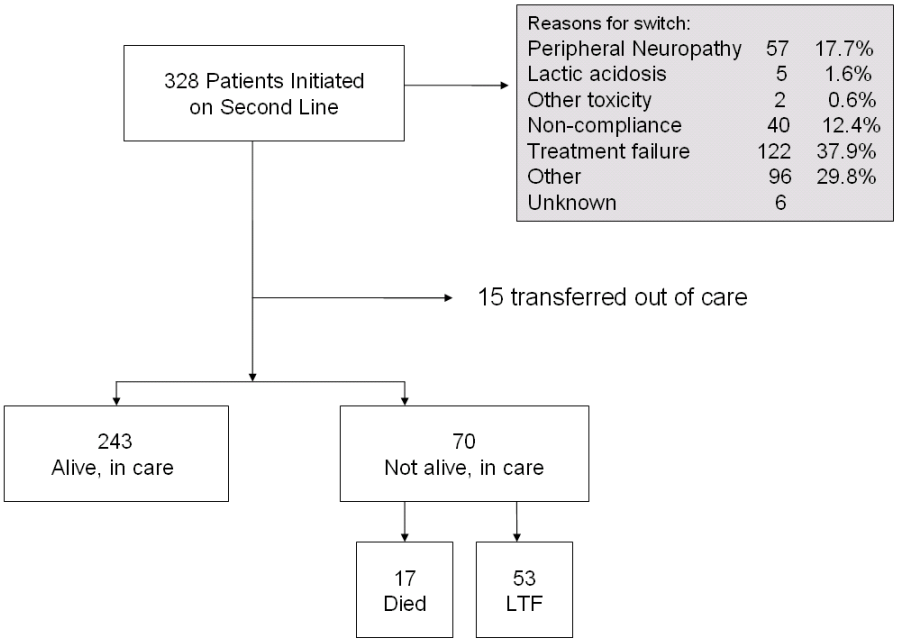
Table 3 – Crude and adjusted predictors of viral suppression∫ in a cohort of 328 patients initiating second-line therapy at the Themba Lethu Clinic in Johannesburg, South Africa between 2004-2008.

Exposure	Level	Number suppressed∫	Person years	Rate/ 100 py*	Crude HR* (95% CI)*	HR adjusted (95% CI)*∞
History of TB before initiation of first-line ART						
	No	166	80.9	205.2	1	1
	Yes	36	22.4	160.7	0.74 (0.52-1.06)	0.70 (0.48-1.01)
Sex						
	Male	69	35.5	194.4	1	1
	Female	133	67.8	196.2	1.07 (0.80-1.44)	1.06 (0.78-1.45)
Lowest CD4 before initiation of second-line						
	>= 50 cell/ml3	109	52.2	208.8	1	1
	< 50 cell/ml3	93	51.2	181.6	0.84 (0.64-1.11)	0.80 (0.60-1.07)
Age at second-line						
	<=35	82	43.3	189.4	1	1
	>35	120	60.0	200.0	1.01 (0.76-1.34)	0.94 (0.70-1.26)
Single drug substitution before initiation of second-line						
	No	127	56.3	225.6	1	1
	Yes	54	28.8	187.5	0.71 (0.58-0.87)	0.71 (0.56-0.89)
In treatment > 3 yrs before initiation of second-line						
	No	72	33.6	214.3	1	1
	Yes	130	69.8	186.2	0.79 (0.59-1.06)	0.86 (0.64-1.16)
> 3 weeks from second viral load > 1000 to switch to second-line						
	No	55	19.8	277.8	1	1
	Yes	147	83.6	175.8	0.56 (0.41-0.77)	0.60 (0.43-0.83)
Prior non-compliance						
	No	180	87.6	205.5	1	1
	Yes	22	15.8	139.2	0.59 (0.38-0.92)	0.85 (0.52-1.39)

* IRR -Incidence Rate Ratio, HR = Hazard Ratio, CI = Confidence Interval, py= person years
∫ viral load ≤ 400 copies/µl
∞ adjusted for all other variables in the model

Figure 1 – Treatment outcomes over the first year of second-line ART in cohort of 328 patients at the Themba Lethu Clinic in Johannesburg, South Africa between 2004-2008.

1a) Alive, in care and on standard second line treatment



1b) Viral suppression

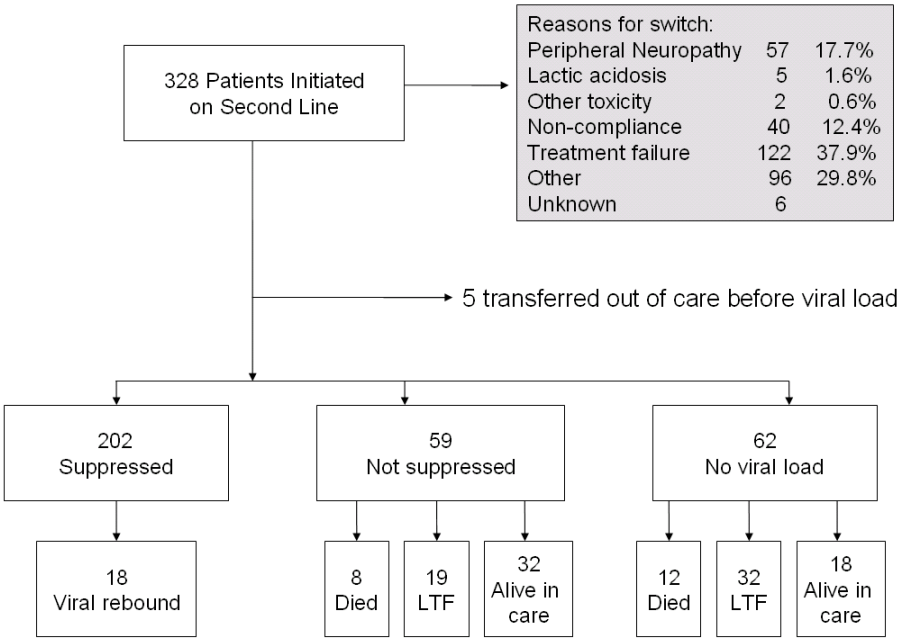


Figure 2 – Mean CD4 count/µl over the first year of second-line ART in cohort of 328 patients at the Themba Lethu Clinic in Johannesburg, South Africa between 2004-2008.

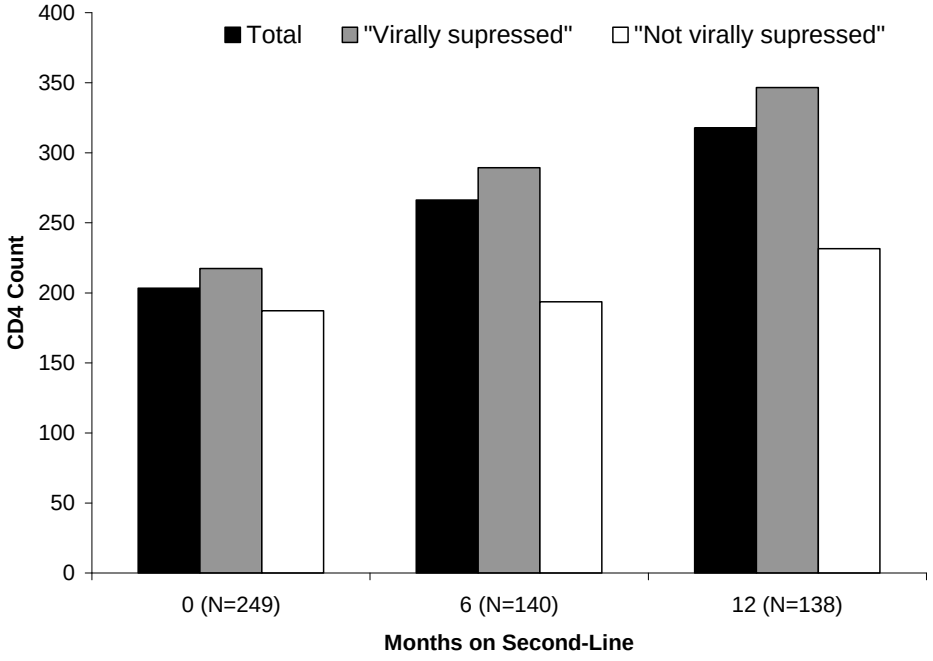
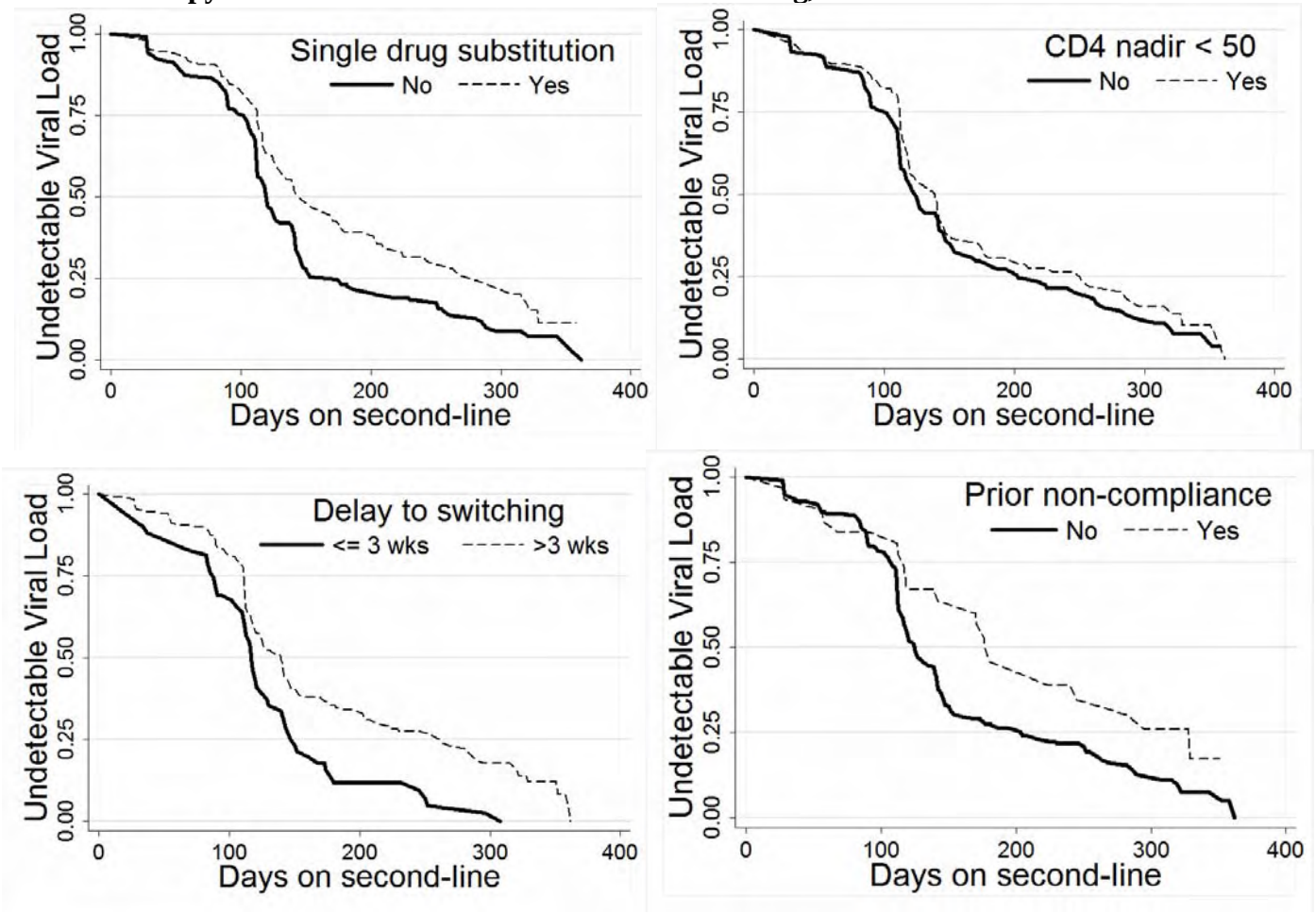


Figure 3 – Kaplan-Meier survival plots of time to first undetectable viral load among 261 patients with viral loads after initiating second-line therapy at the Themba Lethu Clinic in Johannesburg, South Africa between 2004-2008.*



* Stratified by a) prior single drug substitutions; b) CD4 nadir below 50 before switching to second-line; c) delay from second detectable viral load > 1000 to switching to second line > 3 weeks; and d) prior non-compliance. Log rank p-value < 0.05 for all except CD4 nadir < 50 (p=0.20)

Reference List

1. National Department of Health. National Antiretroviral Treatment Guidelines, First Edition, 2004. 2004.

2. Progress report on declaration of commitment of HIV and AIDS. Republic of South Africa. Prepared for the United Nations General Assembly Special Session on HIV and AIDS. 2008.

3. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, Costagliola D, D'Arminio MA, de Wolf F, Reiss P, Lundgren JD, Justice AC, Staszewski S, Leport C, Hogg RS, Sabin CA, Gill MJ, Salzberger B, Sterne JA. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002;360:119-29.

4. Coetzee D, Hildebrand K, Boulle A, Maartens G, Louis F, Labatala V, Reuter H, Ntwana N, Goemaere E. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004;18:887-95.

5. Laurent C, Ngom Gueye NF, Ndour CT, Gueye PM, Diouf M, Diakhate N, Toure Kane NC, Laniece I, Ndir A, Vergne L, Ndoye I, Mboup S, Sow PS, Delaporte E. Long-term benefits of highly active antiretroviral therapy in Senegalese HIV-1-infected adults. *J Acquir Immune Defic Syndr* 2005;38:14-17.

6. Ivers LC, Kendrick D, Doucette K. Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature. *Clin Infect Dis* 2005;41:217-24.

7. Lawn SD, Myer L, Wood R. Efficacy of antiretroviral therapy in resource-poor settings: are outcomes comparable to those in the developed world? *Clin Infect Dis* 2005;41:1683-84.

8. Gallant JE. Drug resistance after failure of initial antiretroviral therapy in resource-limited countries. *Clin Infect Dis* 2007;44:453-55.

9. Vekemans M, John L, Colebunders R. When to switch for antiretroviral treatment failure in resource-limited settings? *AIDS* 2007;21:1205-6.

10. Galarraga O, O'Brien ME, Gutierrez JP, Renaud-Thery F, Nguimfack BD, Beusenberg M, Waldman K, Soni A, Bertozzi SM, Greener R. Forecast of demand for antiretroviral drugs in low and middle-income countries: 2007-2008. *AIDS* 2007;21 Suppl 4:S97-103.

11. Boyd MA, Cooper DA. Second-line combination antiretroviral therapy in resource-limited settings: facing the challenges through clinical research. *AIDS* 2007;21 Suppl 4:S55-S63.

12. Renaud-Thery F, Nguimfack BD, Vitoria M, Lee E, Graaff P, Samb B, Perriens J. Use of antiretroviral therapy in resource-limited countries in 2006: distribution and uptake of first- and second-line regimens. *AIDS* 2007;21 Suppl 4:S89-S95.

13. Pujades-Rodriguez M, O'Brien D, Humblet P, Calmy A. Second-line antiretroviral therapy in resource-limited settings: the experience of Medecins Sans Frontieres. *AIDS* 2008;22:1305-12.

14. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, Miotti P, Wood R, Laurent C, Sprinz E, Seyler C, Bangsberg DR, Balestre E, Sterne JA, May M, Egger M. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 2006;367:817-24.

15. Wallis, CL, Bell, C, Boulme, R, Sanne I, Venter F, Papathanasopoulos, M, and Stevens, W. Emerging ART Drug Resistance in Subtype C: Experience from the 2 Clinics in Johannesburg, South Africa. CROI 661. 2007.

16. Hosseinipour M, van Oosterhout J, Weigel R, Mzigangira D, Saukila N, Mhango B, Phiri R, Phiri S, Kumwenda J, and SAFEST 2 study Team. Validating clinical and immunological definitions of antiretroviral treatment failure in Malawi. International AIDS Society Conference . 2007.

17. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. *PLoS Med* 2007;4:e298.

18. Mocroft AJ, Lundgren JD, d'Armino MA, Ledergerber B, Barton SE, Vella S, Katlama C, Gerstoft J, Pedersen C, Phillips AN. Survival of AIDS patients according to type of AIDS-defining event. The AIDS in Europe Study Group. *Int J Epidemiol* 1997;26:400-407.

19. Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R, Whitworth JA. HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS* 2002;16:597-603.

20. Maskew M, MacPhail P, Menezes C, Rubel D. Lost to follow up: contributing factors and challenges in South African patients on antiretroviral therapy. *S Afr Med J* 2007;97:853-57.

21. Dalal RP, MacPhail C, Mqhayi M, Wing J, Feldman C, Chersich MF, Venter WD. Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in johannesburg, South Africa. *J Acquir Immune Defic Syndr* 2008;47:101-7.