Published in final edited form as:

J Acquir Immune Defic Syndr. 2012 October 1; 61(2): 158–163. doi:10.1097/QAI.0b013e3182615ad1.

Second-line antiretroviral therapy: long-term outcomes in South Africa

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Abstract

Background—Currently boosted protease inhibitor-containing regimens are the only option after first-line regimen failure available for patients in most resource-limited settings yet little is known about long-term adherence and outcomes.

Methods—We enrolled patients with virologic failure (VF) who initiated lopinavir/ritonavir-containing second-line ART. Medication possession ratios were calculated using pharmacy refill dates. Factors associated with 12-month second-line virologic suppression (viral load (VL) <50 copies/ul) and adherence were determined.

Results—136 patients (median CD4 count and VL at failure: 153 cells/uL and 28,548 copies/ml, respectively) were enrolled. Adherence improved after second-line ART switch (median adherence 6 months prior, 67%; median adherence during initial 6 months of second-line ART, 100%; $P=0.001$). Higher levels of adherence during second-line ART was associated with month 12 virologic suppression (OR 2.5 per 10% adherence increase, 95% CI 1.3 – 4.8, $P=0.01$). Time to virologic suppression was most rapid among patients with 91-100% adherence compared to patients with 80-90% and <80% adherence (log rank test, $P=0.01$). VF during 24 months of second-line ART was moderate (month 12, 25%, $n=32/126$; month 18, 21%, $n=23/112$; month 24, 25%, $n=25/99$).

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Potential conflicts of interest 1. D.R.K. is a consultant to, or has received research funding from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck and Siemens.

Richard A. Murphy (no conflicts), Henry Sunpath (no conflicts), Carmen Castilla (no conflicts), Shameez Ebrahim (no conflicts), Richard Court (no conflicts), Hoang Nguyen (no conflicts), Vincent C. Marconi (no conflicts), Jean B. Nachega (no conflicts)

Conferences: Presented February, 2011 at the Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA

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Conclusions—The switch to second-line ART in South Africa was associated with an improvement in adherence, however a moderate ongoing rate of virologic failure – among approximately 25% of patients receiving second-line ART patients at each follow-up interval – was a cause for concern. Adherence level was associated with second-line ART virologic outcome, helping explain why some patients achieved virologic suppression after switch and others did not.

Keywords

Second-line antiretroviral therapy; adherence; resource-limited settings; South Africa

Introduction

A growing proportion of patients in resource-limited countries who have initiated ART have experienced first-line regimen failure [1-3]. However, evidence shows that most patients identified early and switched to a boosted protease inhibitor (PI) containing second-line regimen – most commonly consisting in sub-Saharan Africa of lopinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors (NRTIs) – subsequently achieve early virologic suppression [4-6]. Currently, boosted PI-containing regimens are the only option after first-line regimen failure available for patients treated in the public sector in most resource-limited settings. Because most patients treated with boosted PI-containing ART regimens in low and middle-income countries have not had prior exposure to PIs, adherence to treatment will likely be the principle determinant of long-term virologic suppression.

South Africa has the largest HIV epidemic in the world. The demand for first-line and second-line ART continues to grow as ART coverage, now 37% nationally, is achieved in a greater proportion of eligible patients [23]. This study was performed in KwaZulu-Natal, an epicenter of the HIV epidemic in South Africa, where HIV incidence remains substantial and recent antenatal surveys continue to reveal a high prevalence of HIV among pregnant women, in some districts above 40% [24-25].

At a single antiretroviral clinic in Durban, the largest city in KwaZulu-Natal, we estimate adherence to second-line ART by calculating medication possession ratios (MPR) using pharmacy refill claims from an on-site pharmacy and explore the relationship between adherence and long-term clinical outcomes. MPR is a well-studied tool for estimating adherence; the validity of MPR in resource-limited settings has been supported by prior studies where it has been shown to be associated with virologic outcomes and mortality among patients receiving first-line ART [7, 8]. An improved understanding of second-line ART in resource-limited settings will be critical in maximizing the durability of second-line regimens, preventing disease progression and reducing long-term AIDS-related mortality in high HIV-prevalence countries without access to third-line ART regimens.

Methods

The Sinikithemba Outpatient HIV/AIDS Clinic at McCord Hospital provides HIV care for patients from Durban and the surrounding area with financial support from the President's Emergency Plan for AIDS Relief (PEPFAR) and the South African Department of Health. Approximately 8200 adults and 1200 children receive ART and related care, including tuberculosis treatment, at the clinic. ART initiation and monitoring follows South African Department of Health recommendations including both HIV-1 viral load (assay with detection limit of <50 copies/ml) and CD4 count testing six-monthly. Clinic counselors provide adherence training before first-line ART initiation and at the time of virological failure prior to regimen change.

Enrollment criteria

One hundred and sixty-five HIV-infected adults who initiated second-line ART after documented first-line ART virologic failure (HIV-1 RNA viral load ≥ 1000 copies/ml) were identified. After excluding 29 patients who received second-line ART for less than 6 months, we enrolled 136 patients. We did not include patients who were switched to second-line ART without documented virological failure.

During the period of the study, the standard South African second-line regimen consisted of lopinavir/ritonavir (fixed dose combination dosed twice daily) plus zidovudine and enteric-coated didanosine (each dosed once daily). Lamivudine and stavudine were available for use in a second-line regimen in the setting of prior adverse effect or contraindication to the standard second-line NRTI backbone.

Data collection and adherence measurement

Using a standardized instrument, we collected baseline demographic and clinical data from an electronic clinic database (TrakHealth™). Values for CD4 and viral load within 2 months of initiation of second-line ART initiation were considered to be the pre-switch baseline values.

To estimate adherence, a medication possession ratio was calculated by dividing the number of months that a patient submitted refill prescriptions by months since regimen initiation. The adherence estimates calculated for various time intervals were cumulative. For example, month 12 adherence reflected adherence during the initial 12 months of second-line ART. The measurement of adherence to ART at the Sinikithemba clinic was facilitated by the use of refill claims from an on-site pharmacy and an electronic clinical database. The dates of pharmacy refill were captured for the duration of second-line ART as well as for the final six months of first-line ART prior to virologic failure. Patients were routinely scheduled for clinic visits every 28 days, at which time they were given a 30-day supply of medication and patients accrued 2 extra days of pills (30 days of ART provided every 28 days) at each refill. Any missed refill visit resulted in a reminder phone call from the clinic within seven days.

Study design and endpoints

We conducted an observational, retrospective study of patients who initiated second-line ART after first-line ART virological failure. The primary outcomes were 12-month virological suppression (viral load <50 copies/ul) and 12-month adherence calculated using medication possession ratios. We also sought to determine factors – including medication adherence – associated with second-line virologic outcome, to determine risk factors for suboptimal second-line ART adherence, and to describe long-term virologic, immunologic and clinical outcomes among patients switched to second-line ART in South Africa.

Statistical analysis

We used a modified missing=failure rule for estimating rates of virologic failure; if a patient was in active follow-up but did not have a viral load measured at a six month interval, virologic failure was assumed. Patients who died, transferred care or were lost to follow-up were excluded from calculations of adherence, virologic or immunological outcomes after the patient's date of death, transfer or loss to follow-up, respectively. Patients who do not return to clinic were actively sought for six months and a disposition was ultimately determined (died, lost to follow-up, or transferred care).

We defined three strata of adherence based on medication refill pattern ($>90\%$, $80-90\%$, and $<80\%$). The Wilcoxon rank sum test was used to compare median levels of adherence across

time intervals. We analyzed the relationship between adherence and virologic suppression using a Kaplan-Meier analysis that estimated time to suppression by adherence strata.

Multivariable logistic regression modeling was used to explore the association between patient characteristics and month 12 virological suppression. Covariates included in the logistic regression model included age, gender, CD4 cell count at switch, viral load at switch, second-line NRTI backbone, first-line ART adherence in the 6 months prior to switch and second-line ART adherence. We also use multivariable logistic regression modeling to explore associations between patient characteristics and optimal month 12 second-line ART adherence of >90%. Analyses were performed using STATA software, version 10.

Ethical approval

This retrospective study was approved by the research ethics committee at McCord Hospital in Durban, South Africa and the requirement for informed consent was waived.

Results

Patient characteristics

We analyzed 136 adult patients – 65% female, median age 36 years (IQR, 31-43) – who initiated second-line ART with a lopinavir/ritonavir-containing second-line regimen after first-line ART virological failure. The median pre-ART nadir CD4 cell count was 70 cells/mm³ (IQR, 20-118 cells/mm³) and median prior duration of first-line ART was 13 months (IQR, 7-20 months). At the time of first-line ART regimen failure, the median CD4 count and viral load at failure was 153 cells/mm³ (IQR 89-232 copies/mm³) and 28,548 copies/ml (IQR, 7,000-89,000/ml), respectively.

The most common second-line ART NRTI backbones were: AZT + DDI, n=88 (65%); AZT + 3TC, n=30 (22%); 3TC alone, n=7 (5%) and D4T + 3TC, n=6 (4%) and the median duration of second-line ART follow-up was 34 months (IQR, 20-44 months). The median adherence in the 6 months prior to switch to second-line ART switch (during NNRTI-based first-line ART) was 67% (IQR, 33-67%). Median adherence improved significantly in the first 6 months of second-line ART (median adherence 6 months prior to switch, 67%; median adherence during initial 6 months of second-line ART, 100%; $P=0.001$). The median adherence remained high at months 12, 18, and 24 at 92% (IQR, 92-100%), 94% (IQR, 89-100%) and 96% (IQR, 88-100%), respectively.

Outcomes during second-line ART

Virological, immunological and clinical outcomes during the initial 24 months of second-line ART including events are described (Table 1). The rate of virological failure during the first 24 months of second-line therapy was low (month 6, 26%, n=36/136; month 12, 25%, n=32/126; month 18, 21%, n=23/112; and month 24, 25%, n=25/99). Median CD4 cell count rose to above 200 cells/mm³ rapidly by 6 months of second-line ART follow-up (month 6, median CD4 cell count 228 cells/mm³; month 12, median CD4 cell count 276 cells/mm³) and was greater than 300 cells/mm³ by month 18 of second-line ART (month 18 median CD4 cell count, 315 cells/mm³; and month 24, 330 cells/mm³).

We evaluated factors associated with virologic suppression at 12 months (Table 2). A higher rate of adherence during the first 12 months of second-line ART was independently associated with an increased odds of month 12 viral suppression (OR 2.5 per 10% increase in adherence, 95% CI 1.3 – 4.8, $P=0.01$). There was no significant association identified

between month 12 virological suppression and patient age, gender, second-line NRTI backbone, viral load at first-line failure or CD4 cell count at first-line failure.

Adherence and virologic outcome

We analyzed the relationship between adherence and virologic suppression using a Kaplan-Meier analysis that estimated time to suppression by adherence strata (Figure 2). Time to suppression was most rapid among patients with 91-100% adherence (log rank test, $P=0.01$). A plot of virologic suppression and adherence using three adherence strata suggested increasing rates of virologic suppression associated with progressively higher rates of adherence (adherence <80%; 80-90% and >90%) at 6, 12, 18 and 24 months of second-line ART (Figure 1). Among patients with an adherence of > 90%, the rate of virologic suppression at 6, 12, 18 and 24 months was 73% (IQR, 64-82), 87% (IQR, 80-93), 93% (IQR, 87-98), and 97% (IQR, 95-100), respectively. Among patients with adherence of <80%, the rate of virologic suppression to <50 copies/ml at 6, 12, 18 and 24 months was 20% (IQR, 2-38), 44% (IQR, 19-69), 67% (IQR, 44-89) and 83% (IQR, 61-100), respectively.

Multivariate analysis of risk factors associated with adherence of $\geq 90\%$

In multivariate analysis (Table 3), prior above the median adherence during the final 6 months first-line ART showed a borderline association with high level adherence of >90 during the first 12 months of second-line ART (OR: 2.5, 95% CI: 0.7–8.6, $P=0.15$). There was no significant association noted between age, gender, second-line NRTI backbone, CD4 cell count at first-line failure or with viral load at failure and high level adherence of >90 during the first 12 months of second-line ART.

Discussion

Among patients who initiated a boosted PI-containing second-line ART in South Africa, median adherence improved after switch to second-line ART from less than 70% to greater than 90%. Not surprisingly, time to second-line ART virologic suppression was most rapid among patients with 91-100% adherence (log rank test, $P=0.01$) and was least rapid among patients with second-line adherence of <80%. Further, a plot of virologic suppression according to adherence strata suggested a dose-response relationship between level of adherence and virologic suppression at each 6 month follow-up time point, with higher rates of suppression at progressively higher levels of adherence.

Additional studies will be needed to clarify factors leading to overall higher level adherence after second-line switch and the durability of the effect [11-13]. However factors that may have been contributed include peer-based adherence counseling received at the time of first-line virologic failure, informal doctor and nurse-driven adherence support during follow-up clinic visits and the role of improved regimen tolerability. Compared to first-line ART (at the time of the study, D4T + 3TC + EFV), patients may have found boosted PI-containing second-line ART to be associated with fewer adverse effects. D4T in particular has been associated in resource-limited settings with a high rate of metabolic complications including painful peripheral neuropathy and lipoatrophy [9, 10].

During second-line ART, at each six month interval, virologic failure was observed in about one quarter of patients who remained in active follow-up. Although resistance testing was not routinely performed, based on prior studies, virologic failure of second-line ART was unlikely to have been the result of acquired PI-associated drug resistance mutations. A large randomized trial showed that among patients without prior exposure to protease inhibitors – as is the case in most HIV-infected South Africans – virologic failure with boosted protease

inhibitor regimens is rarely associated with emergence of new protease inhibitor mutations [14]. Further, a recent study in South Africa found, among patients failing lopinavir/ritonavir-containing second-line regimens, a very low prevalence of major lopinavir resistance mutations [15, 16]. Taken together, these data suggest that adherence – not resistance – is the primary cause in South Africa of second-line ART failure in adults. As a result patients failing second-line ART would be expected to have a high likelihood of viral resuppression if adherence were to improve, and may therefore be an appropriate target for novel adherence interventions.

Another appropriate target for new adherence interventions may be patients identified to have poor adherence to first-line ART prior to switch. In evaluating for independent risk factors for suboptimal levels of second-line ART adherence, we found a borderline association suggesting that patients with first-line ART adherence below the median (in the 6 months prior to failure) were more likely, in multivariate analysis, to subsequently demonstrate suboptimal adherence to second-line ART. Of note, we had previously observed that South African patients found by viral genotype testing to have wild-type virus at the time of first-line ART failure experienced inferior second-line ART virologic outcomes compared to patients with at least one major resistance mutation. We observed that 84 (69%) of 122 patients with at least one major mutation achieved viral suppression 24-weeks after failure compared to 7 (37%) of 19 patients without a resistant virus ($P=0.01$) [5]. It is likely that wild-type viral genotype results was a proxy for poor first-line ART adherence which eventually undermined second-line ART outcome. Therefore, another opportunity for novel adherence intervention may be among patients with lower levels of first-line ART adherence prior to switch to second-line ART.

This study has several limitations. Adherence measured using medication possession ratios based on refill pattern is an indirect measure of behavior. It does not capture pill taking behavior directly and as a result is not sensitive to adherence interruptions resulting from behaviors such as pill sharing or “pill dumping.” [17]. However, it is an inexpensive and readily accessible monitoring tool has previously been shown to be associated with virologic outcome and mortality in sub-Saharan Africa [8, 18-22]. A second potential weakness was that our adherence estimates calculated at various time intervals were cumulative. For example, month 24 adherence reflected adherence during the entire first 24 months of second-line ART. If adherence declined substantially over time, it may not have been evident using a cumulative medication possession ratio. Lastly we cannot exclude the potential impact of survivorship bias. Patients remaining in active follow-up for 12 or 24 months after initiation of second-line ART may reflect a more adherent and overall healthier population of second-line ART patients in South Africa. By excluding patients from the study who completed less than 6 months of second-line ART, we risked underestimated second-line ART loss to follow-up and mortality because near the time of switch loss to follow-up and mortality tend to concentrate [5].

The switch to second-line ART in South Africa was associated with an improvement in adherence and a rapid immunological recovery. However a moderate ongoing rate of virologic failure – among approximately 25% of patients receiving second-line ART patients at each follow-up interval – is a cause for concern. Median adherence was not uniformly >90% after initiation of second-line ART and differences in second-line ART adherence help explain why some patients in South Africa achieved virologic suppression after switch and other patients did not. Novel adherence interventions may usefully target patients with second-line ART failure who – given a low likelihood of failure with major PI drug resistance mutations – have a high likelihood of achieving viral resuppression.

Acknowledgments

We acknowledge the immeasurable efforts of the nurses, doctors, counselors, administrators and volunteers at the Sinikithemba Clinic at McCord Hospital in Durban, South Africa. The clinic leadership offers vital ongoing support for studies to improve the lives of patients living with HIV/AIDS. We would like to note the contributions of Roma Maharaj in data collection.

Funding The project was supported in part by the IDSA Medical Scholars Program, the Arnold P. Gold Foundation Medical Student Scholarship, Partners AIDS Research Center, McCord Hospital, and by NIH grants K24-R016482 and P30 AI060354.

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Figure 1.

Figure 2.

Table 1

Long-term virologic, immunologic and clinical outcomes during second-line ART in South Africa

	Month 6	Month 12	Month 18	Month 24
Second-line patients remaining in active follow-up	136	126	112	99
Died during prior 6 months (no.)	N/A ²	0	0	1
Loss to follow-up during prior 6 months (no.)	N/A ²	4	7	6
Changed service provider during prior 6 months (no.)	N/A ²	6	7	6
Median CD4 cell count (cells/mm3) (IQR) ¹	228 (157–329)	276 (201–404)	315 (207–436)	330 (230–481)
Viral load >1000 copies/ml (%) ²	36/136 (26%)	32/126 (25%)	23/112 (21%)	25/99 (25%)

¹ Among patients in active follow-up. Missing=failure rule applied for patients in active follow-up but with no data during the interval.

² By definition, all patients included in this analysis completed six months of second-line ART.

Table 2

Factors associated with viral load <50 copies/ul at month 12 of second-line ART

Factor	N	Odds ration (95% CI)	P
Patients ^I	79		
Age (above the median)		2.0 (0.6 - 6.6)	0.3
Male gender		0.5 (0.2 - 1.6)	0.3
Adherence above median during final 6 months of first-line ART		1.6 (0.5 - 5.1)	0.4
CD4 cell count >100 cells/μL at second-line ART initiation		1.7 (0.4 - 7.1)	0.5
Viral load at second-line initiation of >4.5 log10 c/mL		0.5 (0.1 - 1.6)	0.2
NRTI backbone			
AZT/DDI		1	
AZT/3TC		1.6 (0.4-6.3)	0.5
Other		4.0 (0.4-46)	0.3
Adherence in first 12 months of 2 nd -line ART, per 10% increase		2.5 (1.3 – 4.8)	0.01

^I For this analysis, N was limited to patients in whom data on first-line ART medication possession ratio was also available.

Table 3

Factors associated with 90% adherence at month 12 to second-line ART

Factor	N	Odds ratio (95% CI)	P
All subjects ^I	80		
Age (above the median)		2.1 (0.6—7.3)	0.27
Male gender		1.1 (0.3—3.8)	0.85
Adherence during final six months of first-line ART (above the median)		2.5 (0.7—8.6)	0.15
CD4 cell count >100 cells/μL at second-line ART initiation		0.5 (0.1—2.3)	0.35
Viral load at second-line initiation of >4.5 log ₁₀ c/μL		0.4 (0.1—1.5)	0.19
NRTI backbone			
AZT/DDI		1	
AZT/3TC		0.6 (0.2—2.2)	0.42
Other		1.1 (0.1—13.4)	0.92

^IFor this analysis, N was limited to patients in whom data on first-line ART medication possession ratio was also available.