Published in final edited form as:
AIDS Care. 2011 May ; 23(5): 569–577. doi:10.1080/09540121.2010.525607.

Treatment switching in South Indian patients on HAART: What are the predictors and consequences

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Abstract

Early identification and management of treatment failure on highly active antiretroviral therapy (HAART) is crucial in maintaining a sustained response to therapy in HIV infection. However, HIV viral load and resistance testing, and second-line HAART regimens, are unaffordable to many patients in India, leaving them with limited treatment options. Predictors and reasons for antiretroviral switching, therefore, are likely to differ in settings of varying resources. A one-year, observational study of patients receiving antiretroviral therapy was conducted in a private, non-profit hospital in Bangalore. This paper examines the predictors and consequences of antiretroviral treatment switching in this setting and explores reasons for switching in a subset of patients. Data on demographics, drug regimens, adherence, and physical and psychosocial outcomes were collected quarterly. Tests of viral load and CD4 cell counts were performed every six months. One third of the patients switched therapy during the study period. Baseline predictors of switching included lower CD4 cell counts and more physical symptoms. Contrary to studies in other settings, a high viral load did not predict treatment switching, and only a minority of those experiencing drug failure were switched to second-line regimens. Both groups (switchers and non-switchers) improved significantly over time with respect to CD4 counts and showed a reduction in physical and depressive symptoms and psychological well-being, and any differences between the groups were no longer significant at the end of the study, once we controlled for baseline levels. Clinical, policy and research implications of these findings are discussed within the context of resource-limited settings.

Keywords

HIV/AIDS; antiretroviral therapy; HAART; treatment switch; India

Introduction

In India, the National AIDS Control Organization (NACO) supplies free first-line highly active antiretroviral therapy (HAART) and CD4 cell count monitoring for patients infected

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with HIV. Limited second-line treatment is provided through pilot programs, but widespread provision of free protease inhibitors (PIs) is not available.

HIV drug resistance remains a major threat for a sustained response to HAART, and regular HIV viral load (VL) testing provides one of the earliest indications of drug resistance. Global evidence suggests that resistance to first-line HAART starts in the first year of therapy, and that the prevalence of resistance increases throughout the course of treatment (Reynolds *et al.*, 2009; Tam *et al.*, 2007). Oyomopito *et al.* (2010) found that disease progression was accelerated in settings where VL testing was performed less than annually and experiences in resource-rich settings show that VL testing is cost-effective and improves patient outcomes (Sawe & McIntyre, 2009). Although the feasibility of ongoing VL monitoring is limited in many settings, the reliability of immunological (CD4 cell counts) and clinical monitoring strategies without VL is much debated (see e.g. Badri, Lawn*, &* Wood, 2008; Elliott *et al.*, 2008; Koethe *et al.*, 2010). A recent Cochrane review (Chang, Harris, & Humphreys, 2010) and an independent cost-effectiveness and survival analysis (Kimmel *et al.*, 2010) both demonstrated the superiority of clinical and laboratory monitoring, including VL testing, over clinical monitoring alone in the resource-limited setting.

There is no consensus on the optimal time to change HAART for virological failure even in settings with regular VL monitoring (Cohen, 2009). The most aggressive approach is to change therapy for two consecutive detectable HIV RNA measurements. Other approaches allow a rise in detectable viremia to an arbitrary level (1000-5000 copies/ml) prior to switching therapy (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2009). Treatment-naive patients initiated on HAART, who do not achieve VL suppression to <400 copies/ml after six months, should be considered as having primary virologic failure.

Though NACO has attempted to delay the development of drug resistance by building monitoring systems and addressing adherence barriers, VL testing is still not routinely available in India and resistance testing is unaffordable, even in high-prevalence areas (NACO, 2007). Furthermore, since second-line regimens are unaffordable for many, treatment options after documented virologic failure are limited. Given these realities, the triggers for switching HAART regimens may be different in resource-limited settings (Burgoyne & Tan, 2008; Kirstein *et al.*, 2002). Delays in treatment modification of virologically failing non-PI containing regimens are associated with increases in mortality (Petersen *et al.*, 2008). Further study of the predictors, rates and consequences of switching in resource-limited settings is therefore greatly needed.

The rates of and reasons for treatment switching in several Asian countries have been studied using data from the multi-site TREAT Asia HIV Observational Database (TAHOD). The rates of treatment modification in these Asian HIV patients were significantly associated with particular drug class combinations, number of previous regimen changes, number of drugs available, and type of exposure. The main reasons for switching were adverse events, treatment failure as assessed by physician report, and individual patient decisions (Srasuebkul *et al.*, 2007). Nearly half of the patients with documented treatment failure were still on the failing regimen one year later. In comparison with patients from low-income countries, those from high-income countries were more likely to change two or more drugs of the failing regimen and to change to a PI-containing regimen (Zhou *et al.*, 2009). For India in particular, previous studies have shown the majority of switches were treatment substitutions within the same class of drugs, driven primarily by concomitant tuberculosis (TB) infection and adverse reactions to antiretroviral agents (Kumarasamy *et al.*, 2006).

The consequences of switching have not been well-documented in the Indian setting, however. A study by Sherr *et al.* (2007) in the UK showed that successive switching was associated with a high psychological and physical burden. Studies pertaining to health-related quality-of-life indicators in HIV-positive patients show varied results in India, depending on the domains examined (Chandra, Satyanarayana, Satishchandra, Satish, & Kumar, 2009; Solomon *et al.*, 2009; Wig *et al.*, 2006, 2008), but the psychological impact of HAART switching has not been studied. The purpose of the present paper is (1) to describe the patterns of treatment switching in a cohort of HIV-positive patients in South India, (2) to examine the impact of VL and other factors on treatment switching, and (3) to test if there were differences in physical and psychosocial outcomes between switchers and non-switchers over time.

Methods

Study design and sample

Data were collected as part of a HAART adherence study at a private hospital in Bangalore, India (Ekstrand, Chandy, Heylen, Steward, & Singh, 2010; Steward *et al.*, 2008). A cohort of 229 participants was interviewed every three months for one year (12-month retention 91%). All participants were at least 18 years old, HIV positive, and on HAART medications for at least one month at baseline. Participants were interviewed about demographics, regimen details, adherence behaviors and barriers, stigma, depression, and quality of life. The instrument was developed in English and translated into Kannada, Tamil and Telugu. Translations were independently back-translated into English to ensure semantic equivalence. Interviews were conducted by trained interviewers after obtaining informed consent and lasted approximately one hour. Participants also had blood drawn for CD4/CD8 and VL tests at baseline, 6-month and 12-month visits.

A medical chart review was attempted for all participants who switched HAART regimens during the study period to look for reasons for switching. When medical charts were unavailable, we attempted to contact the patient's physician directly for information.

For the analyses reported here, we examined a subset of 185 participants with data at all five time-points.

Measures

Treatment switching—This was assessed during every study visit. Any change in antiretroviral agents between one interview and the next was considered a switch.

Adherence to HAART was assessed using a Visual Analogue Scale (VAS), which has been validated in multiple settings including our previous work in India (see Amico *et al.*, 2006; Ekstrand *et al.*, 2010; Giordano, Guzman, Clark, Charlebois, & Bangsberg, 2004; Kalichman *et al.*, 2009; Oyugi *et al.*, 2004). Participants were shown a line with numbers from 0-100 and asked to point to the place that best indicated the proportion of pills taken during the past month. The variable was dichotomized at 95% adherence, which was found to predict treatment outcome in a previous analysis (Ekstrand *et al.*, 2010).

CD4 cell counts were performed by Reliance Life Sciences™ on whole blood specimens using a single platform flow cytometry assay (Guava PCA system). The number of cells was reported per microliters(μl) of blood. We used a dichotomized version with a cut-off of 200 cells/μl, the level at which HAART should be initiated per NACO (2007).

Viral Load—HIV plasma VL tests were performed by Reliance Life Sciences laboratories using a real-time PCR assay with a fluorescein-labelled Taqman probe for the quantitation

of HIV particles. The test was developed and its performance characteristics determined at Molecular Diagnostics and Genetics, Reliance Life Sciences, Mumbai, India. The specificity of the assay is >98% and its sensitivity enables detection of an HIV RNA level to 100copies/milliliter (mL) of blood (Palmer *et al.*, 2003). A detectable VL is therefore defined as >100 copies/mL.

Symptom check list—At each visit, participants indicated whether they had experienced any of 21 symptoms (e.g. fever, nausea, fatigue) in the past three months. This list was a modified version of the HIV symptom index developed by the AIDS Clinical Trials Group (Justice *et al.*, 2001). An overall index was created by summing the endorsed items.

Benefits of HAART—This index consisted of 13 perceived benefits of HAART, such as feeling more energetic, more hopeful, or having a better appetite. For each item, participants indicated whether they had experienced the benefit. Again, an overall index was created by summing the endorsed items (Cronbach's $\alpha = 0.84$).

Depression was measured with a version of the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) previously validated in a South Indian population (Chandra *et al.*, 2006). Participants with a score of ≥16 were considered clinically depressed (Cronbach's $\alpha = 0.91$).

Quality of life was assessed with a modified version of the Quality of Life Enjoyment and Satisfaction Questionnaire (Endicott, Nee, Harrison, & Blumenthal, 1993) validated in an Indian population (Ekstrand *et al.*, 2004). Participants indicated on a 4-point scale past week satisfaction with eleven aspects of their life (e.g. health, work, relationships). A mean score was computed with higher scores reflecting better quality of life (Cronbach's $\alpha = 0.87$).

Demographics—Data were collected on gender, age, marital status, number of children, employment status, education, and place of residence (see Table 1).

Analyses

Bivariate analyses consisted of cross-tabulations and chi-square tests to check associations between treatment switching status and other categorical variables, and Mann-Whitney *U*-tests for continuous variables.

Comparisons of switchers and non-switchers on 12-month follow-up outcomes were done via regression models that included baseline levels of these variables as a predictor. To compare 12-month follow-up outcomes to baseline outcomes, we used generalized estimating equations (GEE) to estimate the regression parameters while accounting for the correlated nature of the data (Liang & Zeger, 1986; Zeger, Liang, & Albert, 1988). In both sets of regressions, a logistic regression model was specified for the dichotomous outcomes (VL, CD4 cell count, adherence, and depression), and a linear model for the other outcomes (quality of life, number of symptoms, and benefits of HAART). Demographic variables were not included in the regression models, as bivariate associations between treatment switching status and age, gender, education and employment were not significant.

We first ran the GEE regressions with an interaction between treatment switching status and time included, but this effect never reached statistical significance, and was therefore removed. Results reported here are based on models without this interaction effect. All regression models were done with SAS's GENMOD procedure.

Results

As seen in Table 1, the sample was two-thirds male, mostly married (76%) with children (74%), and living in or around Bangalore (86%). The vast majority of participants (91%) were taking a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non nucleoside reverse transcriptase inhibitor (NNRTI). There were no significant demographic differences between participants who switched treatment during the study period and participants who did not switch.

Fifty-nine participants (32%) switched treatment during the study, with fifteen (25%) of them switching twice, resulting in a total of 74 switches. Most switches were substitutions of one first-line antiretroviral agent for another. Only 7 switches (10%) were to second-line medication. Table 2 presents an overview of the frequency and types of switches.

Twenty-three patients (12%) had a VL >1000 copies/ml at both the baseline and 6-month follow-up sessions, and a VAS score ≥95% during both visits. One participant had just started HAART at baseline, and had a VL >400 copies/ml at the 6-month follow-up. According to the previously mentioned guidelines for resistance testing, these 24 patients were eligible to switch to a second-line regimen for presumed treatment failure. Only two of these 24 (8%) actually switched to a second-line regimen. Fourteen (58%) never switched at all, and the other eight (33%) had their first-line regimen adjusted.

Clinical and psychological outcomes, broken down by switching status and time of assessment, are presented in Table 3. At baseline, the participants who switched treatments during the study had a significantly lower median CD4 cell count than those who did not switch (221 vs. 306 cells/μl, Mann-Whitney U = 2704, p = 0.003). The only other baseline characteristic significantly associated with subsequent treatment switching was number of symptoms reported (median of 4 vs. 3, Mann-Whitney U = 2959, p = 0.025). In regression analyses comparing the two groups on their 12-month follow-up outcomes, we controlled for baseline levels of the outcomes. Results showed that no significant differences remained between the switching and the non-switching group on any of the variables reported in Table 3.

Comparing 12-month follow-up to baseline in Table 3, most outcomes showed improvement between the two visits for both the participants who switched treatment during the study, and those who did not. GEE regression models with time (baseline vs. 12-month follow-up) and switching status (switch vs. no switch) as predictors, showed that, on average, participants of both groups had significantly better outcomes at the 12-month follow-up than at baseline on all outcomes except adherence in the past month. At the 12-month follow-up, participants, on average, were 4.6 times more likely to have an undetectable VL than at baseline, 3.1 times more likely to have CD4 cell counts >200 cells/μl, and only 0.2 as likely to be depressed (BDI score ≥16). Quality of life scores and number of perceived benefits increased by, on average, 0.17 and 0.83 respectively, and the number of symptoms decreased by an average of 1.13 between beginning and end of the study (see Table 4 for details). There was a significant effect of switching status on CD4 cell counts, with those who switched having lower odds (OR = 0.4) of CD4 levels >200 cells/μl than those who did not switch, but not on any other variables in the model. Given this difference and the fact that the baseline differences between switchers and non-switchers were no longer significant at the 12-month follow-up, it may appear that the two groups experienced different rates of improvement. However, the interaction effect between time and switching status in the GEE regression model was not significant, indicating that, on average, the changes observed in the two groups over time were similar. The effect of switching status on CD4 counts is thus likely to reflect baseline differences between the two groups.

Finally, we were able to determine the charted reason for the treatment switches for only 35 (47%) of the study participants. The main reason (n=15, 43%) provided by the physicians was side effects. These switches were primarily between stavudine and zidovudine, in both directions. In addition, seven (20%) switches occurred for financial reasons. Drug failure/ treatment intensification was the reason for another seven (20%) switches, mostly 'other/ multiple' switches and switches to second-line regimens. The remaining six (17%) switches were regimen modifications due to a concomitant TB infection, and all but one were between nevirapine and efavirenz, in both directions. Virologic failure was not noted as a reason for any switches in the medical charts.

Discussion

About one third of our sample of HIV-infected patients in a South Indian cohort switched HAART agents during the study period, usually substituting one first-line antiretroviral agent for another. Predictors of treatment switching were lower baseline CD4 cell count and a higher number of symptoms, primarily attributed to medication side effects. The reported switches were primarily between stavudine and zidovudine (in both directions), which is consistent with a recent study from India reporting that the most common toxicities of first-line regimens are attributable to the thymidine analogues, (Sivadasan *et al.*, 2009). Earlier studies in resource-limited settings (Hawkins, Achenbach, Fryda, Ngare, & Murphy, 2007) found lower baseline CD4 cell counts to be an independent predictor of medication-related toxicities that ultimate lead to changes in HAART. Patients who are more immunocompromised at baseline are more susceptible to toxicities from multiple drugs, but are also more likely to have HIV-related symptoms, which can be misdiagnosed as toxicities. Therefore, switches due to symptomatology may not always be related to treatment toxicities. Drug-drug interactions, secondary to concomitant TB infection, constituted a third reason for treatment switches. Patients on rifampicin-containing TB treatment must switch from nevirapine to efavirenz during TB treatment. Due to cost, most patients switch back to nevirapine afterwards by the current clinical guidelines (NACO, 2007).

Virologic failure was neither a predictor nor noted as a reason for switches in any medical charts. Based on their study VL levels, 13% of our total sample (24/185) should have switched to second-line drugs in order to improve virologic outcome. However, only two of these patients did, presumably due to cost. Although second-line therapy is more expensive in the short-term, research suggests that their use may be cost-effective in the long-term (Bender *et al.*, 2010). In settings where VL monitoring is part of routine clinical practice, patients tend to switch therapies earlier and at higher CD4 cell counts than in sites without VL monitoring (ART-LINC of IeDEA Study Group, 2009). However, multicohort studies in other resource-limited settings (ART-LINC of IeDEA Study Group, 2009) have shown that CD4 count was the prime predictor of treatment switching to second-line regimens in programs with or without access to VL monitoring and the majority of patients who switched changed both the NRTI and the anchor drug to second-line agents. Further research is needed to determine the optimal frequency of measuring VL, in order to make an informed decision to change to second-line regimens, both in resource-limited and resource-rich settings. Low-cost, reliable VL testing strategies (Stevens, Scott, & Crowe, 2010), durable first line regimens with minimal adverse effects, and validated adherence monitoring strategies should be in place for all free HAART programs. Since HAART programs in India deliver standardized fixed-dose first-line drugs, common resistance patterns can be imputed to decide on which appropriate second-line regimens should be made available to optimize subsequent patient outcomes.

The multivariate analyses demonstrate that both switchers and non-switchers improved over time using both clinical and psychological indicators. There was a significant difference between the two groups in terms of CD4 cell counts when controlling for time, which appeared to be due primarily to differences in baseline scores between the groups. Although the data collected do not allow us to draw conclusions about the underlying factors that resulted in improvements in physical or mental health over time in both groups, anecdotal reports from patients suggest that the study tracking procedures and frequent interviews may have had an unintended intervention effect. Participants frequently reported they found it helpful to reflect on treatment-related issues with a supportive interviewer on a regular basis. This may in turn have led to improved nutrition, communication skills, more regular clinic visits, or other behaviors that may be associated with improvements in well-being. Additional research is needed to examine this hypothesis directly and should include measures of treatment switching or adherence to clinic appointments prior to study enrollment.

In conclusion, although switching between first-line HAART agents appears to have led to some improvement in CD4 count and perceived side effects, an expansion of HIV VL testing, routine adherence monitoring, and greater availability of second-line regimens are needed in order to improve virologic outcome among patients experiencing treatment failure in resource-limited settings.

Acknowledgments

Funding for this study was provided by the United States National Institute of Mental Health (1R01MH067513; PI:Ekstrand) and the data was collected as part of the project designed to study Adherence issues to Anti-retroviral Therapy in South India.

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Table 1

Demographic and treatment details at baseline (n=185)

Male: % (n)	67 (124)
Married: % (n)	76 (141)
Has children: % (n)	74 (137)
Place of Residence: % (n)	
Bangalore	44 (82)
Other Karnataka	42 (77)
Other state	14 (26)
Education: % (n)	
< 10 yrs	30 (56)
10 yrs	31 (57)
> 10 yrs	39 (72)
Employed: % (n)	72 (133)
Age (years): median (IQR)	35 (30 – 42)
Months since HIV diagnosis: median (IQR)	36 (15 – 71)
Months on ART: median (IQR)	14 (7 – 28)
Antiretroviral therapy regimen: % (n)	
1st line: 2 NRTI + 1 nNRTI	91 (169)
1st line: NRTI only	4 (8)
2nd line	4 (8)

(n)NRTI: (non) nucleoside analogue reverse transcriptase inhibitors.

There were no significant differences between the switch and no-switch group on any of these variables at baseline.

Table 2

Frequencies of different types of treatment switches

	% (n) of subjects with treatment switch (n=59)*	% (n) of treatment switches (n=74)
d4T to AZT	42 (25)	34 (25)
AZT to d4T	14 (8)	11 (8)
NVP to EFV	7 (4)	5 (4)
EFV to NVP	10 (6)	8 (6)
1st to 2nd line therapy	12 (7)	10 (7)
Other switches	31 (18)	32 (24)

d4T: Stavudine, AZT: Zidovudine, NVP: Nevirapine, EFV: Efavirenz

*Percentages do not add up to 100 %, because some subjects had multiple switches.

Table 3

Clinical and psychological data at baseline and 12 mo follow-up, by treatment switching group

	Tx switch (n=59)		No Tx switch (n=126)	
	Baseline	**12 mo FU**	**Baseline**	**12 mo FU**
Detectable VL (> 100c/ml): % (n)	64 (38)	34 (20)	59 (74)	21 (27)
CD4 cell count > 200 cells/μl: % (n)	51 (30) **	80 (47)	75 (94)	89 (112)
Adherence past month ≥ 95 %: % (n)	80 (47)	83 (49)	86 (108)	85 (107)
BDI score ≥ 16: % (n)	27 (16)	5 (3)	29 (37)	10 (13)
Quality-of-life score (range 1-4): median (IQR)	2.8 (2.5 – 3.0)	3.0 (2.8 – 3.0)	2.9 (2.6 – 3.0)	3.0 (2.9 – 3.0)
Nº side effects ART (range 0-21):median (IQR)	4 (2 – 7) *	2 (0 – 5)	3 (1 – 6)	2 (0 – 4)
Nº benefits of ART (range 0-13): median (IQR)	12 (10 – 13)	13 (12 – 13)	12 (11 – 13)	13 (12 – 13)

Tx: treatment; FU: follow-up; VL: viral load; BDI: Beck Depression Inventory; ART: antiretroviral therapy.

** Significant difference at baseline between switchers and non-switchers, p = 0.001.

* Significant difference at baseline between switchers and non-switchers, p = 0.025.

AIDS Care. Author manuscript; available in PMC 2013 April 23.

Table 4

Results GEE regression analyses with time and switching status as predictors

	Regression coefficient	*z*	*p*	Odds ratio	95 % CI for OR
Undetectable VL					
Time	1.52	8.06	<.0001	4.57	3.16 – 6.61
Switching status	n.s.				
CD4 Count > 200					
Time	1.14	5.20	<.0001	3.14	2.04 -4.83
Switching status	-0.94	-3.13	0.0018	0.39	0.22 -0.70
Depressed (BDI ≥16)					
Time	-1.45	-5.16	<.0001	0.24	0.14 -0.41
Switching status	n.s.				
Non-adherence (VAS <95%)					
Time	n.s.				
Switching status	n.s.				
Quality of life					
Time	0.17	4.42	<.0001	-	-
Switching status	n.s.				
No. of symptoms					
Time	-1.13	-4.00	<.0001	-	-
Switching status	n.s.				
No. of perceived HAART benefits					
Time	0.83	3.33	0.0009	-	-
Switching status	n.s.				

GEE: generalized estimating equations.

Reference groups: time: baseline; switching status: non-switchers