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Reasons for and correlates of antiretroviral treatment interruptions in a cohort of patients from public and private clinics in southern India

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Abstract

Understanding the prevalence and correlates of treatment interruptions (TIs) in resource-limited settings is important for improving adherence. HIV-infected adults on highly active antiretroviral therapy (HAART) in Bangalore, India, were enrolled into a prospective cohort study assessing HAART adherence. Participants underwent a structured interview assessing adherence, including occurrence of TI > 48 hours since HAART initiation, length of TI, and self-reported reasons for TI. Serum HIV viral load (VL) and CD4 was measured at 6-month intervals. Baseline data are presented in this article. For the 552 participants mean age was 37.8, 32% were female, 70% were married, 45% earned < \$2/day. Eighty-four percent were on nevirapine-based antiretroviral therapy; median duration on HAART was 18 months (range: 1–175) and median CD4 count was 318 cells/μl (IQR: 195–460) at time of study enrollment. Twenty percent ($n = 110$) reported at least one TI; of these, 33% ($n = 36$) reported more than one TI. Median length of most recent TI was 10 days (range: 2–1095). TI was associated with a higher probability of having VL > 400 copies/ml (43% versus 12%; $p < 0.001$). After controlling for time on HAART, TI was more likely among those who were unmarried (OR: 1.9; CI: 1.2–3.1), those treated in a private clinic setting (OR: 2.7; CI: 1.6–4.6 compared with public, and OR: 4.1; CI: 1.9–9.0 compared with public–private setting), and those on efavirenz-based therapy (OR: 2.0; CI: 1.1–3.6). The most common self-reported reason for TI was “side effects” ($n = 28$; 25%), followed by cost of therapy ($n = 24$; 22%). We discuss implications for both individual and structural level interventions to reduce TIs.

Keywords

treatment interruptions; adherence; India; resource-limited settings; side effects; cost; HAART

Introduction

The number of HIV-infected individuals receiving highly active antiretroviral therapy (HAART) in resource-limited settings have increased dramatically over the last decade,

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from 300,000 people in 2002 to over 5.5 million in 2009 (World Health Organization [WHO], 2009a). In India alone, over 350,000 individuals were started on HAART between 2004, when the Government of India began its free antiretroviral therapy program, and 2010 [National AIDS Control Organization [NACO], 2010). Although the rapid scale up of HAART has led to dramatic declines in mortality (Herbst et al., 2009; Jahn et al., 2008; Kumarasamy et al., 2005b; Mwagomba et al., 2010; Reniers et al., 2009) concerns remain regarding loss to follow up, ongoing access to treatment, and adherence to treatment (Bachani et al., 2009; Kranzer et al., 2010).

Adherence to treatment is one of the most important determinants of treatment outcome (Bangsberg et al., 2001; Hogg et al., 2002; Parienti et al., 2004; Chesney 2003). Nonadherence can lead to development of drug resistance, virologic failure, and eventually, clinical failure (Gardner et al., 2008; Nachega et al., 2007). Prior studies have shown that nearly one in four patients in resource-limited settings has less than optimal adherence (Mills et al., 2006). With the extremely limited availability of second line antiretroviral therapy in these settings, it is crucial to understand how to improve adherence and prevent drug resistance.

Recent work suggests that not all types of non-adherence are the same. Parienti and colleagues found that among patients with < 80% adherence on nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, sustained interruption resulted in a greater degree of viral rebound compared to missing an equivalent number of interspersed doses. Loss of viral suppression began as early as 48 hours into a treatment interruption (TI) and there was a 50% risk of virologic failure after 15 days of interruption (Parienti et al., 2008). Given these data, there is growing interest in understanding this specific type of nonadherence, with particular interest in identifying TIs lasting longer than 48 hours.

We have previously shown that TIs of over 48 hours is the most common form of nonadherence in India (Ekstrand, Chandy, Heylen, Steward, & Singh, 2010), and that presence of TI was significantly associated with development of drug resistance (Ekstrand et al., 2011). The objective of the present study is to describe the frequency, duration, reasons, and risk factors of TIs in a cohort of HIV-infected patients on HAART in southern India.

Methods

The analysis presented in this article includes baseline data from an ongoing 2-year cohort study of adherence to HAART among HIV-infected adults attending public and private hospitals in Bangalore, India. Primary study outcomes were virologic failure and development of drug resistance.

Setting

The study was conducted at two hospitals, one public and one private, in Bangalore, India. Bangalore is a major metropolitan city in the state of Karnataka and home to the highest number of HIV-infected individuals in the state. Karnataka is one of six states in India with a high HIV prevalence; in 2006, the prevalence of HIV in antenatal clinics was 1.0%. HIV prevalence is estimated to be 9.6% among female sex workers in Karnataka, and 19.2% among men who have sex with men (NACO 2006). According to the Indian National AIDS Control Organization's (NACO) estimates, 46,500 patients are enrolled in the government-sponsored anti-retroviral therapy program in Karnataka (NACO 2010).

Within the two hospitals, there are three types of care settings. (1) *The public clinic* is located in the public hospital. Patients attending this clinic receive free clinical care according to local standards, and antiretroviral therapy is supplied to them for free each

month, according to the NACO protocol. Patients pay for certain lab tests not included in the NACO package, and for non HIV-related medications. (2) *The private clinic* is located in the private hospital. In this clinic, patients pay out of pocket for all clinical services, lab monitoring, and antiretroviral therapy and non HIV-related medications. (3) *The public-private clinic* is located in the private hospital as well. Some of the staff from the private clinic overlaps with the public-private clinic and patients receive all the same services as those in the private clinic, but patients in this setting receive free point of care services and antiretroviral therapy through the government-sponsored antiretroviral therapy program by NACO protocol. This public-private clinic was the among the first of its kind in India and was created due to the high demand for HIV care, the recognition by NACO that certain private and nongovernmental agencies were already providing excellent HIV care, and the desire to expand antiretroviral access to patients who were already seeking care at these facilities.

According to the 2007 NACO guidelines, all individuals with CD4 cell count < 200 cells/ μ l and symptomatic individuals with CD4 count < 350 cells/ μ l are eligible for HAART (NACO 2007). The most commonly prescribed antiretroviral therapy in this setting is a generic nevirapine-based regimen, usually including lamivudine and either zidovudine or stavudine; this fixed-dose combination costs approximately \$20 per month. In some instances, patients at the private clinic receive tenofovir in place of d4T or AZT at a cost of \$30 for triple drug therapy that includes nevirapine. Patients with a concurrent diagnosis of active tuberculosis infection are placed on efavirenz-based regimens to minimize drug interactions (Chandy, Singh, Heylen, Gandhi, & Ekstrand, 2011). Access to second line therapy is greatly limited and the medications are much more expensive. Only selected government HIV treatment centers designated as Centers for Excellence, including the public hospital included in this study, can dispense second line antiretroviral therapy. If paying out of pocket, the cheapest protease inhibitor-based therapy costs approximately \$100 per month. Viral load (VL) monitoring is not available in these clinics except through research studies.

Participants

Five hundred and fifty-two participants are included in this analysis of baseline data (533 participants enrolled in the cohort, and 19 patients recruited during the pilot phase of the study). Participants were interviewed between August 2007 and November 2009. Eligibility criteria included age $\geq$ 18 years, ability to communicate verbally in English, Kannada, Tamil or Telugu, HIV infection and on antiretroviral therapy for at least one month, and willingness to participate in all follow-up visits.

Procedures

Potential participants were referred to the study interviewers by their physician, the outpatient clinic clerk or a screener at outpatient clinic registration. Following referral, participants were brought to a separate room next to the clinic (private, and public-private clinic participants) or to a nearby study office (public clinic participants) for eligibility confirmation and the study interview. All patients provided written informed consent.

A face-to-face interview was administered by trained study staff using a standard survey instrument. The survey instrument was developed in English, translated into Kannada, Tamil and Telugu, and independently back-translated into English to ensure semantic equivalence. The interview lasted approximately one hour and covered a variety of topics, including demographics and health history, medical regimen, adherence behaviors and barriers, as well as psychosocial factors. Participants were asked about their HAART start date as well as their current and past HAART regimens. Adherence was assessed in multiple ways including self-reported TIs of > 48 hours since starting HAART. If participants reported any

TIs, they were asked about number, length, and reasons for interrupting. A sizable proportion of those reporting TI, said “doctor told me to” was the reason for their TI. Since this category could include a number of underlying reasons, we reviewed the medical charts of these participants to look for documentation of TI on the dates given by the participant, and the reason recorded by the physician. Reasons for TI were then recorded if a more specific cause could be identified from the medical record (e.g., side effects of HAART). If chart review did not reveal a more specific reason, the reason for the TI was left as “doctor told me to.”

Participants' blood was drawn by trained staff phlebotomists and analyzed for CD4 count, VL, and if applicable, HIV genotype. CD4 cell counts were performed on whole-blood specimens collected in an EDTA tube using a single platform flow cytometry assay (PCA system; Guava Technologies Inc., Hayward, CA, USA) and the number of cells were reported as cells/ μ l of blood. HIV plasma VLs were determined using a real-time PCR assay with a fluorescein-labeled TaqMan probe for quantitation of HIV particles. This assay can reliably detect an HIV RNA level of 100 copies/ml of blood (Palmer et al., 2003).

The study was approved by the institutional review boards of the University of California, San Francisco and St John's National Academy of Health Sciences.

Definitions

Treatment interruptions were defined as an episode of stopping HAART for > 48 hours with subsequent resumption of the same, or a different combination of antiretroviral therapy. In the present analyses, virologic failure was defined as having a VL > 400 copies/ml after at least six months on HAART.

Data analysis

Baseline data from the prospective cohort study were used in the current analyses. We calculated descriptive statistics for continuous variables, and assessed differences between participants with and without TI via Mann–Whitney *U* test. Analysis of categorical variables consisted of frequencies and cross-tabulations, with χ^2 or Fisher's exact tests to assess the significance of the associations. Multivariate logistic regression was used to identify independent predictors of TI. Only demographic variables that were significantly associated with reporting TI at the bivariate level at $p < 0.05$ were included in the multivariate analysis and were entered as one block. The logistic regression was performed in SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA), all other analyses in SPSS, version 18.0.2. (SPSS Inc., Chicago, IL, USA). All significance levels reported are two-sided.

Results

Baseline demographic and clinical characteristics

Demographic and clinical characteristics of the cohort are described in Table 1. The mean age of the participants was 37.8 (SD: 8.8) and a majority were male. Almost half of the participants had < 10 years of formal education. Nearly half reported an individual income that was < \$2/day (criteria for living below the poverty level, as defined by the World Bank). A majority of participants was married and lived in urban Bangalore. Approximately half of participants received their care in the public clinic.

A vast majority of participants were on a nevirapine-based regimen and nearly half were on stavudine-containing regimens. Participants had been on HAART for a median of 18 months (range: 1–175 months) at study enrollment. All but four participants were on a first-line

HAART regimen at the time of study enrollment. Median CD4 cell count at the time of enrollment into the study was 318 cells/ μ l.

Frequency of TI

Of the 552 participants, 20% ($n = 110$) reported at least one TI of more than 48 hours since they started HAART (see Table 2). One out of every three participants who reported a TI, stated that they interrupted therapy more than once. The median length of the longest TI was 15 days and the median length of the last TI was 10 days. Those with a TI in the last three months had been on HAART for a longer duration compared to those without TI in the last three months (median of 23 months versus 16 months, respectively, ($p < 0.05$)). Among those who had been on HAART for six or more months, 20% ($n = 85/419$) had detectable VL (>400 copies/ml) at study entry. Reporting a TI was associated with a significantly higher probability of virologic failure: 43% ($n = 43/100$) of those reporting a TI had a detectable plasma VL compared to 13% ($42/319$) of those not reporting a TI ($p < 0.001$).

Correlates of TI

After controlling for time on HAART, several demographic and clinical characteristics factors predicted TIs in a multivariate model (Table 2). Those receiving care in the private clinic had 2.7 times the odds of having TI compared to those receiving care at the public clinic, and 4.1 times the odds compared to participants receiving care at the public-private partnership clinic. Compared with those not on efavirenz-based therapy, those on efavirenz-based therapy had twice the odds of TI (OR: 2.0). Finally, unmarried participants had nearly twice the odds of TI compared with married participants (OR: 1.9). Participants who reported that their spouse reminded them to take their HIV medications were less likely to have a TI: 17% ($n = 55/324$) of those with a supportive spouse had a TI compared to 24% ($n = 55/228$) of those with no spouse or a nonsupportive spouse ($p = 0.04$). Gender, place of residence, education, income, and age were not significantly associated with reporting a TI in bivariate analyses.

Self-reported reasons for TI

The most common reason reported by participants for TI was “side effects” (25%) (see Table 3). Compared to participants with TIs for reasons other than side effects, those who reported TI due to medication side effects were marginally more likely to be on stavudine-containing regimens (36% vs. 56%, respectively) ($p = 0.06$). Cost of therapy was the second most common reason given by participants for TIs (22%). Not surprisingly, of the participants with a TI, those seeking care in a private setting were more likely to cite cost of care as a reason for the TI (33%) compared to those in a public and public-private setting (18%) ($p = 0.05$). The type of first-line regimen was not significantly associated with reporting cost as a reason for TI. A number of individuals indicated that they did not take their medication because they were “away from home” (12%). A sizable minority of participants reported pharmacy stock outs (5%) or that there was a delay in getting to a doctor for a prescription refill (6%). Finally, nine participants (8%) reported depression as a reason for TIs.

Discussion

This is the first study from India to examine the reasons for and correlates of TIs of > 48 hours, precisely the type of nonadherence that is associated with increased risk of virologic failure. We found that approximately 20% of participants reported such a TI at some point during the duration of HAART and that one-third of those reporting a TI experienced more than one TI. Given that the median length of these TIs was 10 days for the last TI and 15 days for the longest TI, a significant proportion of these participants were at risk for

virologic failure, and in fact, 43% of those reporting TIs had VLs > 400 copies/ml even after 6 or more months on HAART. From our previous work, we know that participants reporting TIs are also at increased risk for significant mutations (Ekstrand et al., 2010).

Several studies have looked at risk factors for suboptimal adherence in India, and the results have included younger age, lack of family support, higher CD4 cell count, longer duration on HAART, alcohol use, and low general health perception (Shah et al., 2007; Venkatesh et al., 2010). In our study, those on efavirenz-based therapies were more likely to have experienced a TI than those on nonefavirenz-based therapies. Being on efavirenz-based therapy is a marker for co-infection with tuberculosis, and high pill burden from treatment of HIV TB co-infection, and generally being more ill from dual infection may explain the higher prevalence of TI among those taking efavirenz. Close follow up and special adherence counseling may be warranted in this subgroup of patients on efavirenz-based therapy.

We found that being unmarried was associated with a higher odds of reporting a TI, and those with a supportive spouse were less likely to have TIs. Several studies have shown the importance of social support systems in improving adherence to HIV medications (Ammassari et al., 2002; Kunutsor et al., 2010). In fact, in many antiretroviral distribution programs in India, patients are required to bring a friend or relative with them to clinic appointments to be started on antiretroviral therapy.

Side effects of HAART, particularly for those on stavudine-containing regimens were the most common reason for TI. Stavudine has been shown to result in higher rates of regimen change due to toxicity than other antiretroviral medications in patients of India (Sivadasan et al., 2009). Because of the toxicity associated with stavudine, the developed world has long abandoned the use of this medication in HAART regimens. The WHO revised its antiretroviral therapy guidelines in 2009 to use tenofovir in place of stavudine as part of the nucleoside reverse transcriptase inhibitor backbone in HAART even in resource-limited settings (WHO 2009b). However, uptake of this recommendation has been slow in resource-limited settings due to cost. A recent costeffectiveness analysis of the use of tenofovir in place of stavudine or zidovudine in India showed that use of tenofovir would be cost-effective by international standards in the long run (Bender et al., 2010). There is a need to intensify efforts to phase out stavudine as part of HAART in resource-limited settings to avoid unnecessary TIs from treatment-related adverse events; these TIs can end up costing more because they can lead to virologic failure, and development and transmission of drug resistance. Adherence interventions need to take into account side effects, and encourage patients to talk with their care providers about side effects they may be experiencing so that treatment substitutions can be made in a timely manner without interruptions.

Cost was the second most common self-reported reason for TI of > 48 hours in this study. In addition, receiving care at a private clinic, where patients bear a greater burden of medical expenses, was associated with increased odds of TI. Despite the expansion of access to antiretroviral therapy through government programs, cost of therapy has repeatedly been found to be a barrier to adherence in multiple studies from India, especially ones done in settings where patients pay for their own medications (Kumarasamy et al., 2005a; Kumarasamy et al., 2006; Wanchu, Kaur, Bamberg, & Singh, 2007). In addition, no-cost antiretroviral therapy has been shown to improve adherence (Batavia et al., 2010). Although fixed dose combinations of first-line antiretroviral therapy costs as “little” as \$20/month, this is still out of reach for many HIV-infected individuals in our cohort. This is especially true when more than one member of the family is HIV-infected. It represents at least one-third of the income of the 44% of individuals in our cohort making < \$2 per day. Patients may prefer to attend private clinics because of shorter wait times and more convenient facilities, but the

burden of paying for antiretroviral therapy appears to result in increased TI. This finding speaks for the need to expand the model of public–private partnerships, such as the one described in this article, to decrease the economic barrier to interruption-free HAART.

Other reasons for TIs in this cohort, including “being busy with other things”, and “being away from home”, suggesting lack of, or interruption of daily routine, have been cited commonly in studies both in resource-limited settings, and in the developed world (Batavia et al., 2010; Kumarasamy et al., 2005a; Shah et al., 2007). This suggests that adherence strategies found to effectively deal with these more universal barriers could be adapted to the Indian setting and tested as part of future interventions here. Additionally, depression was reported as a fairly common reason for TIs. Others have demonstrated that it is feasible and effective to treat depression as a means of improving adherence (Tsai et al., 2010) and therefore should be a part of adherence interventions.

Participants who had been on treatment for a longer duration were more likely to report a TI in the last 3 months. This finding is consistent with other health behavior literature that shows that it is more challenging to maintain a behavior over time than to make initial behavior changes, and that lapses continue to occur over time (Dimeff & Marlatt, 1998; Gill, Hamer, Simon, Thea, & Sabin, 2005). It supports the need for ongoing adherence support, especially among those who have been on therapy for longer periods of time.

There are several limitations to the study. Although the 20% of the cohort reporting a TI had a higher risk of having virologic failure, there was still a sizable proportion (12%) of those not reporting a TI who also had virologic failure after at least 6 months on HAART. Although our interviewers were well-trained in asking questions in a nonjudgmental manner, and questions regarding adherence were preceded by statements that tried to “normalize” some amount of nonadherence, there is always a possibility of substantial under-reporting of TI. This potential problem is not one unique to our cohort. It has been well established that due to recall bias or social desirability bias, or both, patient self-report of adherence tends to be overly optimistic (Gao & Nau, 2000). Additionally, in this baseline analysis, we were not able to assess the incidence of TIs and incidence of virologic failure. However, the prospective cohort design of the study will allow us to explore this issue in the future. The participants in this study were limited to one geographical area in India. However, in order to make the results more broadly applicable, we recruited a fairly large number of participants from both public and private clinic settings to more accurately represent the types of settings in which HIV-infected persons seek care in resource-limited settings.

In conclusion, we demonstrated that HIV TIs of >48 hours are fairly common among HIV-infected individuals accessing care in India, and that those reporting TIs are at higher risk of virologic failure compared with those who do not report TIs. Side effects of treatment seem to be a driver for TIs. Cost of therapy was also given as a significant reason for TI, especially for those seeking care at private clinics, indicating a need for greater public–private partnerships where patients can continue to access their private providers of choice for care, but are able to access medications through a publicly funded program. TIs longer than 48 hours should be assessed in future adherence research. Adherence interventions in India need to focus on reasons for TIs that seem specific to local settings, such as side effects from stavudine-containing regimens and cost as well as barriers to adherence that are more universal across all settings including in the developed world, such as lack of social support, depression, lack of routine, and simply forgetting to take medications.

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Table 1

Baseline demographic and clinical characteristics of 552 patients on HAART, Bangalore, India (2007).

	<i>N</i> (%)
Patient age: mean (SD)	37.8 (8.8)
Patient gender	
Female	177 (32)
Marital status	
Married	388 (70)
Single	58 (11)
Divorced/separated	19 (3)
Widowed	87 (16)
Education	
< 10 years	242 (44)
10 years	156 (28)
> 10 years	154 (28)
Self-reported personal monthly income	
0 Rs. (\$0/day)	145 (26)
1–2499 Rs. (< ~\$2/day)	104 (19)
2500–4999 Rs. (~\$2–\$4/day)	159 (29)
5000–9999 Rs. (~\$4–\$8/day)	97 (18)
10,000 Rs. (>~\$8/day)	46 (8)
Place of Residence	
Urban Bangalore	361 (65)
Other areas of Karnataka	136 (25)
Other states	55 (10)
Care setting	
Public	290 (53)
Private	103 (19)
Public–private	159 (29)
HAART Regimen (at study enrollment)	
3TC + D4T + NVP	188 (34)
3TC + AZT + NVP	273 (49)
Other NVP-based	3 (1)
3TC + D4T + EFV	33 (6)
3TC + AZT + EFV	42 (8)
TDF + FTC + EFV	8 (1)
Protease inhibitor-based	4 (1)
NRTI only	1 (0)
Median (IQR) CD4 cells/ml at study enrollment ^a	318 (195–460)
Median (range) duration on HAART, in months	18 (1–175)

SD, standard deviation; IQR, inter-quartile range.

^aBased on *n* = 551.

Table 2

Correlates of treatment interruption (TI, defined as interrupting therapy for >8 hours) among 552 patients on HAART, Bangalore, India (2007).

Odds of treatment interruption ^a	OR [CI]
Unmarried vs. married	1.9 [1.2–3.1]
Private clinic vs. public clinic	2.7 [1.6–4.6]
Private clinic vs. public–private clinic	4.1 [1.9–9.0]
Efavirenz-based therapy vs. nonefavirenz based therapy	2.0 [1.1–3.6]

^aAfter controlling for time on HAART.

Table 3

Treatment interruption (TI, defined as interrupting therapy for >48 hours) among 552 patients on HAART, Bangalore, India (2007).

	<i>N (%)</i>
1 Treatment interruption	110 (20)
<i>For those with 1 TI (n = 110)</i>	
Number of TI	
1	74 (67)
2–4	25 (23)
5	11 (10)
Median (range) length of TI (number of days)	
For longest TI ^a	15 (2–1095)
For latest TI ^b	10 (2–1095)
<i>Reasons for TI: N (%)</i>	
Financial	
Cost	24 (22)
Structural	
Pharmacy stock out/closed	6 (5)
MD visit for new Rx delayed	7 (6)
Clinical	
Side effects	28 (25)
Doctor told me to	9 (8)
Immune reconstitution syndrome	2 (2)
Felt sick	6 (5)
Felt depressed	9 (8)
Felt healthy	1 (1)
Away from home	13 (12)
Busy with other things	4 (4)
Did not understand regimen	3 (3)
Consuming alcohol	2 (2)
Switched to traditional medicines	3 (3)
Other reason	9 (8)

^aBased on *n* = 108.

^bBased on *n* = 107.