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Rate and Predictors of Self-Chosen Drug Discontinuations in Highly Active Antiretroviral Therapy-Treated HIV-Positive Individuals

Rita Murri, M.D.,[1] Giovanni Guaraldi, M.D.,[2] Piergiorgio Lupoli, Ph.D.,[3] Raffaella Crisafulli, Ph.D.,[3] Simone Marcotullio, Ph.D.,[4] Filippo von Schloesser,[4] and Albert W. Wu, Ph.D.[5]

Abstract

Despite the clinical benefits of highly active antiretroviral therapy (HAART), sustained treatment remains a great challenge for HIV-infected people. The rate, consequences, and correlates of self-elected treatment interruptions (TI) are not known. The objectives of the study were to assess the rate of patient-elected TI in a cohort of HIV-infected people taking HAART, to evaluate whether patient-elected TI is correlated with suboptimal non-adherence, and to identify the predictors of self-chosen HAART interruptions. Using a Web-based cross-sectional survey beginning in January 2006 primary outcomes were: (1) reports of having asked their physician to interrupt the current regimen (AskDisc) and (2) reports of at least one interruption of a minimum of 1 day of any of the drugs included in the regimen (INTERR). Three hundred fifty-nine people were enrolled; 296 were taking HAART. Twenty-three percent self-reported suboptimal adherence, 45% reported AskDisc, and 25% INTERR. Forty percent of people reporting INTERR self-reported suboptimal adherence. As expected, AskDisc and INTERR were correlated with suboptimal adherence. The AskDisc group had higher CD4 cell counts and HIV RNA, more symptoms, and took more convenient regimens. The INTERR group had higher HIV RNA, were more likely to smoke, seek more information on HIV/AIDS, and less likely to take non-nucleoside reverse transcriptase inhibitors (NNRTIs). The rate of self-chosen TI was high and often related to suboptimal adherence. These findings may help clinicians to better monitor patients, and identify patients for targeted counseling.

Introduction

Despite important improvements in the convenience of antiretroviral regimens, long-term therapy is a major challenge for people living with HIV/AIDS (PLWHA). Highly active antiretroviral therapy (HAART) is now better tolerated; few daily pills and once-a-day regimens are common.[1,2] However, in the absence of alternative immunologic and vaccines strategies, HAART remains a life-long therapy and treatment fatigue is a key barrier to an optimal adherence to therapy.

Several studies have addressed the issue of treatment interruptions (TI) as a possible strategy to offset treatment fatigue and enhance quality of life, limit adverse events, reduce costs, and contain the emergence of multidrug-resistant virus. Results have been contradictory, but a recent large study suggests disadvantages to this strategy.[3] Particularly, an increased risk of cardiovascular diseases was observed during the TI period.[4] Similar results were confirmed in another large study even showing that the heightened risks linked to TI were not reversible after continuous treatment was resumed.[5]

Anecdotal evidence suggests that patients may undertake TI, sometimes referred to as drug holidays, and not discuss this decision with their physician. Few studies have examined the issue of self-elected TI.[5,6] The rate and predictors of patient-elected TI, particularly of when not agreed upon with the physician, are unknown.

The objectives of the present study were to assess the rate of self-chosen TI in a cohort of HIV-infected people taking HAART and identify the warning signs (i.e., predictors) of self-elected HAART interruptions.

[1]Catholic University of Rome, Rome, Italy.
[2]University of Modena and Reggio Emilia, Modena, Italy.
[3]Edge Consulting, Milan, Italy.
[4]Fondazione Nadir Onlus, Rome, Italy.
[5]Department of Health Policy and Management, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, Maryland.

Methods

This cross-sectional survey was conducted in conjunction with LONGIS (LONGitudinal Information Study), a prospective cohort study designed and supported by Nadir Onlus Foundation, a not-for-profit patient-based foundation, enrolling adults HIV-infected people via the Web. The aim of the cohort is to explore, using a patient-centered approach, preferences regarding antiretroviral therapy, belief in the efficacy of HAART, adherence to drugs, the role of the patient in choosing or switching the HAART regimens, cotherapies, and different aspects of the patient–physician relationship.

In the present study patients were recruited through a questionnaire posted on the Italian website of Nadir Onlus Foundation (www.nadironlus.org) between January and December 2006. No specific selection procedures were adopted. Visitors to the Nadir website were invited to participate in the survey; they could be directly linked to the questionnaire. No particular emphasis was placed on adherence to antiretrovirals or to satisfaction with therapy but only to patient preferences.

The following definitions of self-reported adherence were used: (1) patient rating report of accuracy of taking antiretroviral therapy; (2) report of missing doses in a fixed period (how many doses the patient missed in the previous week and how many in the previous month), (3) reported timing of therapy (how often the patient took pills 2 hours before or after the prescribed time), and (4) reporting at least one interruption of a minimum of 1 day of any of the drugs included in the regimen without having informed the physician either before or after ("Have you ever discontinued your current regimen for at least 1 day without informing your physician, before or after the fact?"). Suboptimal adherence was defined as answering "very bad," "bad," or "not well enough" to the question: "How do you think you are taking therapy?" or those reporting having missed at least one dose in the previous week.

We also included a question on the willingness to discontinue drugs ("Have you ever asked your physician to discontinue your current regimen for a period?" with possible options not or yes). This latter was considered the main outcome of the study.

The survey also included questions on health status ("How do you define your physical health?" and "How do you define your mental health?" with possible options "very bad," "bad," "not well enough," "good," or "excellent") and on self-reported symptoms (25 among the most experienced symptoms in HIV-infected people taking HAART with possible options from "not at all" to "very much"). A symptom score was calculated summing scores for any single symptom. Data on age, gender, mode of HIV transmission, educational attainment, smoking, drinking alcohol, coinfection with viral hepatitis, as well as on therapy characteristics (type of drugs, number of doses, number of previous antiretroviral schemes), most recent HIV-RNA level, and most recent CD4 cell count were collected.

Statistical Analysis

Bivariate analysis was performed to assess the correlation between the adherence dimensions and outcome and to identify other potential predictors (both subjective and objective) associated with asking to discontinue drugs. Backward stepwise logistic regression analysis was used to assess the independent effects of the significant ($p < 0.1$) explanatory variables on the outcome. Odds ratios (OR) and 95% confidence intervals (CI) were estimated. All analyses were done with SPSS version 13.0 (SPSS, Chicago, IL).

Results

Between January and December 2006, 359 patients were enrolled in the study (Table 1).

One hundred thirty-three subjects (44.9%) reported that they had asked their physician to discontinue therapy in the 4 weeks before the survey.

Of the 296 patients taking HAART, 68 (23%) self-reported suboptimal adherence in response to the question: "How do you think you are taking therapy?" and 13 patients (5.7%) reported that they missed at least one dose per week, even if

Table 1. Characteristics of the Three Hundred Fifty-Nine Enrolled people

Age, years, mean (± SD)	42 (± 6.6)
Females (%)	111 (30.9)
Taking HAART (months) (%)	296 (82.5)
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	122 (41.2%)
Protease inhibitors (PI)	138 (46.6%)
Experimental drugs	6 (2.0%)
Triple nucleoside reverse transcriptase inhibitors (NRTI)	30 (10.1%)
CD4 cell count, μL^{-1} (%)	
Less than 200	41 (11.4)
200–400	102 (28.4)
400–600	106 (29.5)
> 600	101 (28.1)
Missing	9 (2.5)
HIV RNA, copies/mL (%)	
< 500	265 (73.8)
500–5000	22 (6.1)
> 5000	42 (11.7)
Missing	30 (8.3)
HCV^+ or $HBsAg^+$ (%)	139 (38.7)
Injection drug users (%)	66 (18.4)
Men having sex with men (%)	167 (46.5)
Heterosexuals (%)	84 (23.4)
Not known (%)	42 (11.7)
Smokers[a] (%)	193 (53.8)
Daily[b] alcohol drinkers (%)	22 (6.1)
Education (%)	
Primary school	7 (1.9)
Secondary school	67 (18.7)
High college	190 (52.9)
University	92 (25.6)
Number of antiretroviral regimen (%)	
First	64 (21.8)
Second	48 (16.3)
Third	58 (19.7)
Fourth or more than fourth	124 (42.2)
Number of doses of antiretrovirals to be taken a day (%)	
Once a day	67 (22.7)
Twice a day	197 (66.8)
Thrice or more than thrice a day	31 (10.5)
Number of daily pills, mean (SD)	5.1 (± 2.6)

[a]Smokers were defined those reporting to smoke any number of cigarettes a day.

[b]Daily alcohol drinkers were defined those answering "yes, daily" at the question: "How often do you drink alcohol?"

HAART, highly active antiretroviral therapy; SD, standard deviation;

Table 2. Correlation of Different Adherence Definitions and of Drug Discontinuations with HIV RNA

	Adherence dimensions—Univariate OR (95%CI)				
	Taking therapy not so well or bad or very bad	*Having missed at least one dose in the last week*	*Not respecting prescribed timing*	*Asking to discontinue therapy*	*Having discontinued therapy for at least 1 day*
VL < 500 c/mL	1	1	1	1	1
VL > 500 c/mL	2.60 (1.22–5.57)[a]	1.80 (0.72–4.50)	1.14 (0.55–2.35)	3.39 (1.56–7.37)[a]	3.25 (1.56–6.78)[a]

[a] $p < 0.01$.
VL, viral load.

they reported optimal adherence. Seventy-three patients (24.7%) reported that they had discontinued therapy for at least 1 day without informing their physicians, either before or after the fact, and 40% self-reported suboptimal adherence. Only 49 patients of 133 (36.8%) who had asked their physician to discontinue therapy in the 4 weeks before the survey also reported having discontinued their current regimen. One hundred seven patients (36.1%) reported that they usually took their medications 2 hours before or after the prescribed time. Sixty-three percent of people had HIV RNA less than 50 copies per milliliter and 11% between 50 and 500 copies per milliliter. Only 2.5% and 8.3% of enrolled people did not report data on CD4 cell count or on HIV RNA, respectively. The risk of having an HIV RNA greater than 500 copies per milliliter was higher for those reporting suboptimal adherence as well as for people asking to discontinue therapy or having discontinued therapy for at least 1 day (Table 2).

Of note, nonadherence with the prescribed dosing time was more frequent for people who asked to discontinue drugs (OR 4.62 [95% CI 2.77–7.68] compared to people who did not ask to discontinue drugs) and for people who had discontinued drugs for at least 1 day (OR 3.56 [95% CI 2.06–6.16] compared to people not having discontinued drugs). Asking to discontinue drugs was significantly correlated with reports of having missed at least one dose in the previous week (OR 3.99 [95% CI 1.96–8.11] compared to people not asking to discontinue drugs).

In Table 3, bivariate and multivariable analyses of factors associated with asking to discontinue therapy or to having discontinued drugs are shown. People who asked to discontinue drugs had higher CD4 cell counts, higher HIV RNA, and more symptoms, took more convenient regimens, and self-reported suboptimal adherence. People who reported having discontinued drugs had higher HIV RNA, were more likely to smoke, have suboptimal adherence, seek more information on HIV/AIDS, and were less likely to take nonnucleoside reverse transcriptase inhibitors (NNRTIs).

Discussion

In the present study, nearly half of those surveyed reported having asked their physician to interrupt HAART, and nearly one quarter had interrupted HAART for at least 1 day without informing their physician. Reports of one of these behaviors was significantly associated with suboptimal adherence and virologic failure.

There have been few reports on patient treatment interruptions from traditional cohort studies of HIV-infected people taking HAART. In a French study, 27% of HIV-infected people reported a repeated drug holiday (defined as stopping the regimen entirely for more than 48 hours),[6] while in a Swiss cohort in which a drug holiday was defined as missing all the drugs for at least 24 hours, it was reported only in 5.8%.[7]

The results of this study also suggest that these behaviors are potential markers of suboptimal adherence. People who ask to discontinue therapy have a fourfold higher risk to miss at least one dose in the previous week. We believe that investigating multiple aspects of adherence behavior, including timing of therapy and willingness of discontinuation of drugs, may allow better identification of people who need a stronger or a more targeted support for maintaining an optimal adherence and to prevent future nonadherent behavior. For example, due to the long half-life of NNRTIs (namely efavirenz and nevirapine), discontinuing this class of drugs at the same time of NRTI may lead to a period of NNRTI monotherapy with dangerous consequences on the selection of drug-resistant viruses. It is also possible that increasing and supporting an optimal adherence could prevent unplanned and casual TI.[8,9] Appropriate counseling on the consequences of drug discontinuation, especially when not physician-driven and lasting for several days, could be crucial to motivate patients to adhere to therapy or even, if necessary, to educate the patient "to be nonadherent in a rational way."[10]

We also found that people taking NNRTIs were significantly less likely to have discontinued drugs. Possible explanations of this result are (1) a selection bias (more adherent people were prescribed NNRTI more frequently); (2) people taking NNRTI were more informed on the importance to avoid an uncontrolled discontinuation of the drug due to the long half-life; (3) NNRTI-containing regimens are better tolerated[11,12] leading to less treatment fatigue; (4) people taking NNRTI may have previously expressed concerns with prior, more complicated regimens resulting in a higher satisfaction with therapy with the current regimen.

It has been demonstrated that drug-related symptoms are related both to a higher rate of discontinuations[13,14] but also to a higher risk of suboptimal adherence.[15,16] Treatment fatigue may be an important reason for willingness to discontinue HAART in people reporting higher symptom scores. At the same time, people with better clinical status (higher CD4 cell count) or on more convenient regimens (with few daily doses and pills) were paradoxically more likely to discontinue drugs. This may be because patients who are perceived likely to have adherence problems may be prescribed simpler regimens. It is also likely that people with more complex regimens are those with less available therapeutic options and these individuals are more aware of the importance of maintaining the current regimen. Moreover, people on more convenient

Table 3. Correlates of Self-Chosen Discontinuations to Clinical and HAART-Related Parameters (n = 296)

Variables	*Asking to discontinue therapy*			*Having discontinued therapy for at least 1 day*		
	Univariate OR (95% CI)	*Multivariate OR (95% CI)*	p	*Univariate OR (95% CI)*	*Multivariate OR (95% CI)*	p
Age	0.98 (0.94–1.01)	—	—	1.00 (0.96–1.04)	—	—
Females	1.10 (0.79–1.53)	—	—	0.77 (0.50–1.18)	—	—
Education < 8 years	0.60 (0.34–1.07)[a]	0.60 (0.27–1.32)	0.20	1.22 (0.66–2.82)	—	—
Intravenous drug users	0.82 (0.44–1.52)	—	—	1.12 (0.56–2.26)	—	—
HCV^+ or $HbsAg^+$	0.90 (0.56–1.45)	—	—	1.59 (0.93–2.71)	—	—
Smokers	1.05 (0.66–1.66)	—	—	2.41 (1.36–4.26)[c]	2.00 (0.97–4.08)	0.06
CD4 cell count (for each 200 cells more)	1.26 (1.02–1.57)[b]	1.64 (1.18–2.28)	0.003	0.99 (0.77–1.26)	—	—
HIV RNA	3.39 (1.56–7.37)[c]	7.66 (2.53–23.15)	0.003	3.25 (1.56–6.78)[c]	2.88 (1.17–7.06)	0.02
Taking PIs	0.73 (0.45–1.17)	—	—	1.55 (0.90–2.66)	—	—
Taking NNRTIs	1.56 (0.97–2.51)[a]	1.18 (0.49–2.81)	0.71	0.26 (0.13–0.49)[c]	0.32 (0.15–0.67)	0.003
Number of daily doses of therapy (for each dose more)	0.62 (0.41–0.95)[b]	0.46 (0.25–0.84)	0.01	0.70 (0.44–1.13)	—	—
Third or more scheme	1.73 (1.07–2.8)[b]	1.26 (0.65–2.46)	0.49	1.55 (0.88–2.74)	—	—
Number of daily pills	0.59 (0.35–1.00)[b]	0.80 (0.70–0.92)	0.002	0.95 (0.86–1.06)	—	—
Missing at least one dose in the previous week	3.99 (1.96–8.11)[b]	7.46 (2.43–22.84)	0.004	3.94 (2.02–7.67)[c]	1.89 (0.76–4.65)	0.17
Self-reporting suboptimal adherence (Taking therapy not so well or bad)	1.41 (0.82–2.42)	—	—	3.11 (1.74–5.57)[c]	1.10 (0.43–2.78)	0.44
Uncorrect timing	4.62 (2.77–7.68)[c]	5.09 (2.58–10.02)	< 0.0001	3.56 (2.06-6.16)[c]	4.46 (2.23–8.91)	< 0.0001
Believing therapy has "nothing," "poor" or "enough efficacy"	1.33 (0.83–2.14)	—	—	1.75 (1.01–3.04)[b]	0.98 (0.46–2.11)	0.96
Seek for information on AIDS/HIV	1.11 (0.60–2.03)	—	—	2.60 (1.37–4.91)[c]	4.26 (1.87–9.71)	0.0006
Take homeopathic drugs	3.54 (1.73–7.26)[c]	1.43 (0.54–3.77)	0.47	2.83 (1.43–5.62)[c]	2.30 (0.85–6.20)	0.10
PHS (for each point more)	0.97 (0.55–1.70)	—	—	0.61 (0.30–1.25)	—	—
MHS (for each point more)	1.77 (1.03–3.06)[b]	0.77 (0.52–1.13)	0.18	1.02 (0.55–1.91)	—	—
Symptom score	4.62 (2.60–8.21)[c]	1.04 (1.02–1.06)	< 0.0001	1.01 (0.99–1.02)	—	—

[a] p = between 0.05 and 0.10.
[b] p = between 0.01 and 0.05.
[c] $p < 0.01$.
PIs, protease inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PHS, Physical Health Summary; MHS, Mental Health Summary.

regimens could underestimate the real complexity of the regimen they are taking and consequently believe that they are taking a less aggressive regimen or that they need less treatment. It would be important to investigate in further studies whether a simpler or simplified HAART regimen may be associated with being healthier and hence make patients more prone to missing doses or discontinuing them.

There are several limitations to this study. First, the cross-sectional design did not allow us to establish the direction of relationships among the variables in the study. Second, all variables were self-reported by patients, including clinical measures such as viroimmunologic parameters. This may increase the variability beyond that in which these data are measured objectively. However, it should be noted that the rate of missing data was very low and the population characteristics are similar to that of other cohorts of HIV-infected people. It can be also argued that self-report overestimates some outcomes such as adherence to therapy.[10] A self-reported web survey was chosen to avoid the bias of the presence of the physician in answering to the question on self-chosen TI and potentially reduce this overestimation, even though internet access may induce a bias in the sample.[17] Third, some of the measures used in the present survey were not previously validated. Fourth, genotypic data were not available in the case of virologic failure. Longitudinal studies are warranted to confirm the present findings.

In conclusion, the proportion of people asking for or undergoing self-elected TI appears to be high. TI can be considered a measure of suboptimal adherence. The willingness and desire of PLWHA on HIV therapy to undergo drug holidays due to treatment fatigue should be discussed in the context of the patient–physician relationship. Risks and uncertainties of monitored TI strategies may be different according to clinical status and to type of therapy and should be balanced with a higher risk of patient unilateral and dangerous decisions on discontinuation. Findings of the present study may help to better monitor patients in clinical practice, interpret viroimmunologic results, prevent the appearance of drug resistance or progression of HIV disease and, ultimately, identify patients who need targeted counseling.

Author Disclosure Statement

No competing financial interests exist.

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Address reprint requests to:
Rita Murri, M.D.
Department of Infectious Diseases
Catholic University of Rome
L.go A. Gemelli
8–00168 Rome
Italy

E-mail: ritamurri@libero.it