Correlates of Self-Reported Nonadherence to Antiretroviral Therapy in HIV-Infected Patients

The Swiss HIV Cohort Study

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Background: Adherence is one of the most crucial issues in the clinical management of HIV-infected patients receiving antiretroviral therapy (ART).

Methods: A 2-item adherence questionnaire was introduced into the Swiss HIV Cohort Study in July 2003. All 3607 eligible patients were on ART for ≥6 months and their current regimen for ≥1 month. Three definitions of nonadherence were considered: missing ≥1 dose, missing ≥2 doses, and taking <95% of doses in the past 4 weeks.

Results: Over 30% of patients reported missing ≥1 dose, 14.9% missed ≥2 doses, and 7.1% took <95% of doses in the previous 4 weeks. The rate of drug holidays was 5.8%. Whether using more or less conservative definitions of nonadherence, younger age, living alone, number of previous regimens, and boosted protease inhibitor regimens were independent factors associated with nonadherence. There was a significant association between optimal viral suppression and nonadherence as well as a significant linear trend in optimal viral suppression by missed doses.

Conclusions: Younger age, lack of social support, and complexity of therapy are important factors that are related to nonadherence with ART. Investment in behavioral dimensions of HIV is crucial to improve adherence in ART recipients.

Key Words: nonadherence, antiretroviral therapy, optimal viral suppression

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Antiretroviral therapy (ART) has led to a substantial reduction in HIV-associated morbidity and mortality and HIV infection has entered the stage of chronic disease management.[1–4] Lasting suppression of viral replication is the goal of ART and one of the most important factors influencing long-term prognosis of HIV infection.[5,6] Factors associated with the failure of viral suppression and progression to AIDS or death are low CD4 cell counts and viremia at the start of ART, nonnaiveté to ART, adverse drug reactions, and nonadherence to ART.[7–11]

Nonadherence increases the risk of viral mutations, which can result in cross-resistance to other medications[12–14] or transmission of multiresistant virus strains, and thus the risk for initial therapy failure in subsequently infected individuals.[15,16] Although preliminary evidence indicates that even high and sometimes complete adherence does not prevent accumulation of HIV drug resistance mutations, suboptimal adherence remains a critical issue in the development of resistance.[13,17] Adherence is imperative to guarantee the effectiveness of ART.[18–20]

The medication event monitoring system is the most reliable and sensitive method of assessing adherence,[18] but it is not feasible in a large HIV-infected population such as the Swiss HIV Cohort Study (SHCS) largely due to cost. Patient self-report has the advantage of low cost, simplicity, and feasibility and correlates reasonably well with viral load and suppression,[21] but it can overestimate adherence rates due to recall bias and social desirability.[22]

The goals of this study were to determine the prevalence of self-reported adherence to ART in the SHCS and to explore relationships between socioeconomic-, patient-, condition-, therapy-, and system-related factors and self-reported adherence to ART.

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METHODS

Patients

The SHCS is a prospective cohort study with continuing enrollment of HIV-infected individuals aged 16 years or older. Beginning in July 2003, an adherence questionnaire was introduced into the cohort follow-up. Visits take place every 6 months at 7 outpatient clinics from participating HIV centers, associated hospitals, or specialized private practices. Eligible individuals were actively enrolled in the SHCS and on potent ART for at least 6 months and their current regimen for at least 1 month at the time of their first cohort visit after July 2003. Potent ART was defined as any 2-class regimen from a protease inhibitor (PI), nucleoside reverse transcriptase inhibitor (NRTI), nonnucleoside reverse transcriptase inhibitor (NNRTI), or fusion inhibitor class, or a triple-NRTI regimen. A treatment interruption of <4 weeks was allowed except in the 4 weeks immediately prior to the date the questionnaire was completed.

Outcome Definition

Four dimensions of adherence merit consideration when focusing on the behavioral dimension of adherence to ART: taking adherence (the extent to which a patient is taking a prescribed drug regimen), timing adherence (the extent a patient is adhering to the prescribed schedule for the drug intake), drug holidays (the extent a patient is missing several doses in a row), and food restrictions (the extent a patient is adhering to drug intake in relation to food restrictions). Due to feasibility constraints, the SHCS adherence questionnaire includes only 2 questions: taking adherence ("How often did you miss a dose in the last 4 weeks: daily, more than once a week, once a week, once every second week, once a month, never?") and drug holidays ("Did you have a period of no drug intake for >24 hours in the last 4 weeks? Yes, no"). As there is no standard definition of nonadherence, we considered 3 definitions, each increasingly less conservative: missing ≥1 dose of medication; missing ≥2 doses of medication; and taking <95% of prescribed doses of ART in the past 4 weeks.

Covariate Definitions

At each cohort visit, laboratory measurements are taken and information on cardiovascular risk factors and social support is collected. In addition, any changes in treatment, such as dose, drugs, toxicity, and reasons for switching drugs, are recorded. Using the new taxonomy of the World Health Organization,[23] correlates of nonadherence can be categorized as socioeconomic-related factors, patient-related factors, condition-related factors, treatment-related factors, and system-related factors. We considered the following socioeconomic-related factors: gender, age, ethnicity, education level (completed 9 years of mandatory schooling or less vs. higher), having a stable partner in the previous 6 months, and currently living alone. Patient-related factors were current intravenous drug use or being in an intravenous drug maintenance program and seeking psychiatric treatment in the past 6 months. Condition-related factors included progression to AIDS, time on current ART, and time on ART. Treatment-related factors were number of previous ART regimens, daily pill burden, dose frequency (once daily, twice daily, ≥3 times daily), drug class of current regimen (NNRTI, boosted PI, nonboosted PI, triple nucleoside), ART toxicity since the year 2000, fat loss or fat gain in the past 12 months, and current use of comedications (opportunistic infections, hepatitis C, risk factors of cardiovascular disease). The system-related factor was the center where the patient had their last visit.

Definitions of Surrogate Markers for HIV Infection

Optimal viral suppression was defined as having plasma HIV RNA (viral load) <50 copies/mL allowing for nonconsecutive blips (50 ≤HIV RNA ≤400 copies/mL) over the previous 6 months. Two consecutive blips or a viral load >400 copies/mL was considered nonoptimal viral suppression. Increases in CD4 cell count were defined as any increase of >50 or >100 $\times$ 10^9/L in the previous 12 months.

Statistical Methods

For each of the 3 outcomes, univariate and multivariate logistic regression models were used to assess the association between the outcome and covariates. Initially, univariate models were fit and factors associated with nonadherence (P <0.10) were entered into multivariate models. Some factors were excluded from the multivariate model due to multicolinearity. To adjust for potential correlation in adherence behavior within patients at the same center, a multilevel mixed model was fit to the data with center as a random effect. Likelihood ratio tests were used to determine significant associations between covariates and nonadherence. Odds ratios (ORs) and 95% CIs were estimated. The association between surrogate markers of HIV infection and the outcomes was assessed in sensitivity analyses. Linear trends in the data were assessed using the Cochran–Armitage trend test. All analyses were done with Stata 8.0 (StataCorp LP, College Station, TX) and SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

Sample Population and Nonresponders

In total, 5861 individuals were registered in the SHCS and had not dropped out prior to July 1, 2003. Of these, 1458 were not on treatment and 128 did not complete an adherence questionnaire. In addition, 668 did not meet the treatment criteria: 619 had not been on potent ART for at least 6 months and 49 had not been on their current regimen for at least 4 weeks. A total of 3607 individuals were included in the analysis.

The 668 patients who did not meet eligibility criteria were more likely to be female (33.7% vs. 28.6%), have a basic education (30.9% vs. 25.7%), not be in a stable partnership (48.8% vs. 40.8%), use intravenous drugs (15.0% vs. 10.3%), and have been HIV positive for a shorter period (8 vs. 10 years) compared with the analysis population.

Self-Reported Nonadherence

Self-reported nonadherence over the previous 4 weeks was as follows: 31.1% of patients reported missing ≥1 dose

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(range across centers: 26.1%–41.5%); 14.9% reported missing ≥2 doses (range across centers: 11.0%–22.3%); and 7.1% of patients took <95% of prescribed ART doses (range across centers: 4.3%–12.3%). Almost 6% reported having taken a drug holiday (no drug intake in >24 hours) in the previous 4 weeks (Table 1).

Adherence rates by potential correlates (Table 2A) and surrogate markers of HIV infection (Table 2B) are provided. The more nonadherent individuals become, the worse the HIV infection profile. More than 78% of all patients had optimal viral suppression during the previous 6 months; this percentage dropped to 72.1% in those who had missed ≥1 dose of medication, 64.0% in those who had missed ≥2 doses, and 58.4% in those with <95% adherence. The percentage of individuals with increases in CD4 count of >50 cell per 10^9/L in the previous year decreased from 57.1% to 49.8% with diminishing adherence. Of those who reported taking a drug holiday, only 52.8% had optimal viral suppression compared with 80.4% of those who did not report taking a drug holiday. A strong linear relationship was found between the number of missed doses and optimal viral suppression (Fig. 1) and the test for linear trend was highly significant (P <0.0001).

Univariate Results

Across all 3 definitions of adherence, univariate models showed that individuals of younger age, female gender, basic education, living alone, currently using intravenous drugs, with higher number of previous ART regimens, higher daily pill burden, and not on an NNRTI-based regimen were more likely to nonadhere to therapy (Table 3). Pill burden was not included in the multivariate models due to high correlation with drug regimen.

Multivariate Results

Table 3 provides the results of the multivariate models. For all 3 definitions of adherence, individuals of younger age, living alone, having a higher number of previous ART regimens, and those on a boosted PI regimen were significantly more likely to nonadhere to therapy in the previous 4 weeks. Odds ratios and confidence intervals were similar for all models although the effect strengthened as the definition of adherence became less conservative. In all models, there was a significant amount of variation in nonadherence explained by the center where the patient had their follow-up visit even after adjusting for all other variables in the model.

In each of the 3 final models, additional variables were significantly associated with nonadherence in the multivariate model. For nonadherence defined as missing ≥1 dose, individuals on their current regimen for a longer time (OR 1.08, 95% CI: 1.02 to 1.13) were more likely to nonadhere to therapy, whereas individuals taking comedication for opportunistic infections (OR 0.65, 95% CI: 0.43 to 0.98) were less likely to nonadhere to therapy. For nonadherence defined as missing ≥2 doses, individuals on a nonboosted PI regimen (OR 1.53, 95% CI: 1.15 to 2.04) were more likely to nonadhere to therapy, whereas individuals with reported fat loss (OR 0.76, 95% CI: 0.60 to 0.95) were less likely to nonadhere to therapy. For nonadherence defined as taking <95% of doses, individuals with a basic education (OR 1.42, 95% CI: 1.04 to 1.94), current intravenous drug users (OR 1.67, 95% CI: 1.12 to 2.51), and those on a nonboosted PI regimen (OR 1.70, 95% CI: 1.12 to 2.57) or a triple-nucleoside regimen (OR 2.03, 95% CI: 1.33 to 3.11) were more likely to nonadhere to therapy, whereas individuals of white race (OR 0.66, 95% CI: 0.46 to 0.95) and with reported fat loss (OR 0.63, 95% CI: 0.45 to 0.88) were less likely to nonadhere to therapy.

TABLE 1. Self-Reported Nonadherence to Potent ART in the SHCS

Total patients, n	3607
How often a dose was missed in past 4 weeks, %	
Never	68.9
Once a month	17.3
Once every 2 weeks	6.7
Once a week	3.1
More than once a week	3.1
Every day	1.0
Drug holidays, %	
No drug intake >24 hours	5.8
Percent adherence in the past 4 weeks	
≥95%	92.9
90%–95%	6.0
<90%	1.1
Nonadherence in the past 4 weeks	
Missed ≥1 dose	31.1
Missed ≥2 doses	14.9

Sensitivity Analyses

As a sensitivity analysis, surrogates of HIV infection (optimal viral suppression and increases in CD4 count of >50 cells) were added to the final multivariate models. Individuals who had optimal viral suppression over the previous 6 months were significantly less likely to nonadhere (P <0.001) in all 3 multivariate models (≥1 dose: OR 0.62, 95% CI: 0.51 to 0.75; ≥2 doses: OR 0.49, 95% CI: 0.39 to 0.62; <95% adherence: OR 0.44, 95% CI: 0.32 to 0.60). Individuals with increases in CD4 cell count of >50 cells × 10/L were significantly less likely to nonadhere only as the definition of nonadherence became less conservative (≥2 missed doses: OR 0.73, 95% CI: 0.59 to 0.91, P = 0.004; <95% adherence: OR 0.69, 95% CI: 0.51 to 0.93, P = 0.02).

With all 3 adherence outcomes, most ORs for original covariates remained very similar, with slightly wider CIs but with no resulting change in significance. Exceptions were that once daily became significant (OR 0.48, 95% CI: 0.25 to 0.92) for missing ≥2 doses, and age, basic education, and nonboosted PI regimen became nonsignificant (P >0.05) for <95% adherence.

DISCUSSION

To our knowledge, this is the largest study so far to look at correlates of self-reported nonadherence in HIV-infected individuals. The analysis population includes individuals

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TABLE 2A. Adherence Rates by Potential Correlates and Surrogate Markers of HIV Infection

	Factors by Self-Reported Nonadherence*			
	All Patients	**Missed ≥ 1 Dose**	**Missed ≥ 2 Doses**	**< 95% Doses Taken**
Total, n (%)	3607 (100)	1123 (31.1)	537 (14.9)	258 (7.2)
Age in years				
Mean (SD)	43.5 (9.7)	42.5 (9.1)	42.2 (9.0)	41.4 (8.3)
Gender, %				
Male	71.4	68.6	67.2	65.5
Race, %				
White	82.7	81.0	79.0	75.2
Black	9.6	10.3	11.0	13.2
Hispanic American	1.8	2.1	2.4	2.7
Asian	3.2	2.9	3.9	4.7
Other/unknown	2.6	3.6	3.7	4.3
Education, %				
Basic	25.7	29.2	31.3	37.7
Stable partnership, %	59.2	59.3	56.8	56.0
Living alone, %	41.5	44.6	45.4	48.0
Current IV drug use or drug treatment program, %†	10.3	13.1	13.8	18.3
Psychiatric treatment, %†	7.1	8.6	8.6	8.9
AIDS, %	30.1	28.9	29.8	31.4
Years on ART, mean (SD)				
Current ART	2.2 (1.7)	2.3 (1.7)	2.2 (1.8)	2.1 (1.6)
All previous ART	4.6 (2.8)	4.6 (2.8)	4.5 (2.9)	4.1 (2.8)
Years since first positive HIV test				
Mean (SD)	10.1 (5.5)	11.1 (5.3)	11.2 (5.2)	11.0 (5.2)
Number of previous regimens				
Mean (SD)	4.3 (3.3)	4.6 (3.4)	4.9 (3.6)	4.9 (3.6)
Median	3	4	4	4
Daily pill burden, %				
Mean (SD)	7.6 (5.1)	8.0 (5.3)	8.3 (5.2)	8.1 (5.5)
Median	6	8	8	8
<7	50.1	46.7	42.6	44.4
7–11	22.7	24.3	27.1	25.7
≥12	27.3	29.0	30.3	30.0
ART Toxicity, %‡				
Major toxicity	26.1	26.1	27.2	28.7
Other toxicity	19.2	19.8	23.3	24.8
None	54.8	54.1	49.5	46.5
Lipodystrophy, %				
Any fat loss	30.6	29.8	28.0	25.2
Any fat gain	28.9	28.5	28.6	28.0
Dose frequency, %				
Once daily	5.2	3.8	3.4	5.8
Twice daily	91.8	92.7	92.7	93.0
≥3 times daily	3.1	3.5	3.9	1.2
Current drug regimen, %				
NNRTI	32.2	27.8	24.8	21.7
PI boosted	25.9	26.7	27.8	24.0
PI nonboosted	25.0	27.3	29.8	31.8
Triple nucleoside	16.9	18.3	17.7	22.5
Current comedication, %				
Cardiovascular risk factors	2.6	2.9	2.8	2.3
Hepatitis C	0.9	0.6	0.6	0.8
Opportunistic infections	4.1	2.9	3.5	5.0

*Nonadherence in the previous 4 weeks.
†In the 6-month period prior to the adherence questionnaire.
‡Any ART toxicity since the year 2000. Major toxicities were abnormal fat distribution, hypersensitivity reaction, abdominal/gastrointestinal tract, nervous system, and hematologic toxicity.
IV indicates intravenous.

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TABLE 2B. Adherence Rates by Potential Correlates and Surrogate Markers of HIV Infection

	Surrogates for HIV Infection by Self-Reported Nonadherence*			
	All Patients	**Missed ≥ 1 Dose**	**Missed ≥ 2 Doses**	**< 95% Doses Taken**
Total, n (%)	3607 (100)	1123 (31.1)	537 (14.9)	258 (7.2)
Optimal viral suppression†	78.9	72.1	64.0	59.2
HIV RNA viral load (copies/mL), %‡				
Mean (SD) of log copies/mL	1.8 (3.0)	2.4 (3.4)	3.1 (3.8)	3.7 (4.1)
< 50	79.5	72.5	64.2	58.4
50–399	9.0	9.7	10.7	11.0
≥400	11.5	17.8	25.1	30.6
CD4 increase (cells per 10^9/L), %§				
>50	57.1	54.7	50.9	49.8
>100	34.4	33.5	31.9	33.0
CD4 count (cells per 10^9/L), %‡				
Mean (SD)	492.6 (279)	488.5 (268)	463.4 (268)	452.6 (263)
<200	11.0	10.8	12.9	14.6
200–349	22.8	21.7	23.9	23.7
350–499	24.7	26.9	26.5	26.1
≥500	41.6	40.7	36.7	35.6

*Nonadherence in the previous 4 weeks.
†In the 6-month period prior to the adherence questionnaire. For definition see "Methods" section.
‡Closest to the date of the adherence questionnaire.
§In the 12-month period prior to the adherence questionnaire.

receiving ART for at least 6 months and has large proportions of women and patients from different ages and HIV transmission groups.

A clinically meaningful definition of the level of adherence below which patients with HIV are at risk for poor virologic outcome has yet to be determined. For this reason, we chose relatively conservative definitions of nonadherence because even minimal deviations in dosing are known to affect outcome[18] and self-report is associated with underreporting of nonadherence.[23,24] With the most conservative definition of nonadherence, we found 31.1% of patients missing ≥1 dose of ART, which is lower than nonadherence rates between 40% and 80% that have been found by others in both clinical trials and clinical practice settings. These differences may depend in part on operational definitions, case finding, or measurement methods for nonadherence.[23]

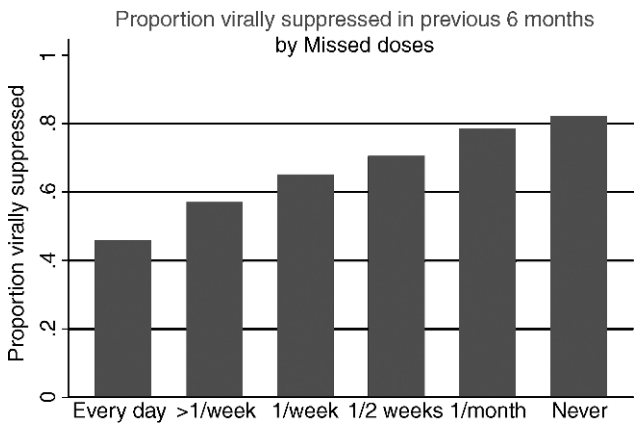

FIGURE 1. Proportion virally suppressed in previous 6 months by the number of doses missed during the previous 4 weeks.

We were unable to detect a significant association between nonadherence and gender, and the significance of ethnicity and education depended on the definition of nonadherence, which could explain the conflicting results found in previous studies.[18,19,25,26] We included an indicator of those seeking psychiatric treatment in the previous 6 months, as this may capture those who have anxiety or depression, known correlates of nonadherence.[18,27,28] However, we did not have sufficient power to detect an association. We did not detect an association between nonadherence and reported ART toxicity, which was defined as the reason an individual stopped a particular drug since the year 2000. This definition might not accurately measure symptom distress due to side effects, which was found to significantly correlate with nonadherence.[29,30]

Using more liberal definitions of nonadherence strengthened several trends found with the most conservative definition with respect to race, education, intravenous drug use, triple-nucleoside therapy, and fat loss. Individuals on a nonboosted PI regimen were just as likely to miss ≥1 dose but were more likely to miss ≥2 doses or to take <95% of ART doses when compared with those on an NNRTI-based regimen. This could be due to the higher pill burden and dosing frequency for PI-based regimens.

It is increasingly recognized that system factors are an understudied but important set of determinants of compliance.[31] This study found that for definitions of nonadherence, compliance rates differed between centers even after controlling for a range of other factors. This is an important finding as these center differences might be a proxy of differences in clinical and behavioral management of patients among centers, such as continuous compliance assessment,

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TABLE 3. Correlates of Self-Reported Non-Adherence to Potent ART in the Last 4 Weeks

	Missed ≥ 1 Dose			Missed ≥ 2 Doses			< 95% of Drugs Taken		
Factor Dimensions	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**	***P* value**	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**	***P* value**	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**	***P* value**
Socioeconomic-related									
Age (in years)	0.98 (0.98 to 0.99)	0.98 (0.97 to 0.99)	< 0.001	0.98 (0.97 to 0.99)	0.98 (0.97 to 0.99)	0.002	0.97 (0.96 to 0.99)	0.98 (0.96 to 1.00)	0.02
Male Gender	0.83 (0.71 to 0.97)	0.88 (0.74 to 1.05)	0.16	0.81 (0.67 to 0.99)	0.90 (0.72 to 1.13)	0.36	0.78 (0.59 to 1.02)	0.98 (0.72 to 1.35)	0.92
Caucasian race	0.88 (0.73 to 1.07)			0.79 (0.63 to 0.99)	0.88 (0.67 to 1.16)	0.37	0.67 (0.49 to 0.90)	0.66 (0.46 to 0.95)	0.03
Basic Education	1.25 (1.06 to 1.49)	1.11 (0.93 to 1.33)	0.23	1.37 (1.11 to 1.69)	1.15 (0.91 to 1.45)	0.23	1.76 (1.33 to 2.32)	1.42 (1.04 to 1.94)	0.03
Stable Partnership	1.01 (0.87 to 1.17)			0.89 (0.74 to 1.08)			0.87 (0.67 to 1.13)		
Living Alone	1.19 (1.03 to 1.37)	1.26 (1.08 to 1.47)	0.003	1.18 (0.98 to 1.42)	1.27 (1.04 to 1.56)	0.02	1.30 (1.00 to 1.68)	1.55 (1.17 to 2.05)	0.002
Patient and condition-related									
Current IV drug use or in drug treatment program	1.47 (1.18 to 1.84)	1.18 (0.92 to 1.52)	0.19	1.50 (1.14 to 1.98)	1.22 (0.89 to 1.68)	0.22	2.05 (1.46 to 2.88)	1.67 (1.12 to 2.51)	0.01
Psychiatric treatment	1.42 (1.09 to 1.85)	1.26 (0.92 to 1.52)	0.12	1.32 (0.95 to 1.85)	1.14 (0.78 to 1.65)	0.50	1.37 (0.87 to 2.15)		
AIDS	0.92 (0.78 to 1.07)			1.00 (0.81 to 1.22)			1.09 (0.83 to 1.43)		
Time on current ART (years)†	1.06 (1.02 to 1.11)	1.08 (1.02 to 1.13)	0.004	1.03 (0.97 to 1.08)			1.00 (1.00 to 1.00)		
Time on ART (years)†	1.00 (0.98 to 1.03)			0.99 (0.95 to 1.02)			0.94 (0.89 to 0.98)	0.96 (0.91 to 1.01)	0.12
Treatment-related									
Number of previous regimens	1.04 (1.01 to 1.06)	1.05 (1.02 to 1.07)	< 0.001	1.05 (1.02 to 1.08)	1.06 (1.03 to 1.10)	< 0.001	1.04 (1.00 to 1.07)	1.08 (1.03 to 1.12)	0.001
Daily pill burden									
<7	1.0			1.0			1.0		
7–11	1.31 (1.09 to 1.57)			1.76 (1.39 to 2.22)			1.52 (1.10 to 2.10)		
≥ 12	1.34 (1.13 to 1.59)			1.72 (1.37 to 2.16)			1.64 (1.20 to 2.24)		
ART toxicity†‡									
Major toxicity	1.0			1.0			1.0		
Other toxicity	0.99 (0.83 to 1.17)			0.88 (0.71 to 1.10)			0.79 (0.58 to 1.08)		
None	1.02 (0.82 to 1.26)			1.19 (0.92 to 1.56)			1.18 (0.83 to 1.68)		
Lipodystrophy in previous year									
Any fat loss	0.91 (0.78 to 1.06)			0.82 (0.67 to 1.01)	0.76 (0.60 to 0.95)	0.02	0.70 (0.52 to 0.94)	0.63 (0.45 to 0.88)	0.008
Any fat gain	0.92 (0.78 to 1.07)			0.93 (0.75 to 1.15)			0.89 (0.66 to 1.18)		
Dose frequency									
Once daily	0.62 (0.43 to 0.88)	0.69 (0.46 to 1.03)	0.07	0.58 (0.35 to 0.95)	0.56 (0.31 to 1.01)	0.06	1.06 (0.61 to 1.83)		
Twice daily	1.0	1.0	–	1.0	1.0	–	1.0		
Three times or more daily	1.26 (0.85 to 1.89)	1.16 (0.75 to 1.78)	0.51	1.52 (0.93 to 2.49)	1.31 (0.77 to 2.22)	0.31	0.41 (0.13 to 1.31)		
Current drug regimen									
NNRTI	1.0	1.0	–	1.0	1.0	–	1.0	1.0	
PI–non-boosted	1.48 (1.21 to 1.81)	1.19 (0.95 to 1.48)	0.13	1.80 (1.39 to 2.34)	1.53 (1.15 to 2.04)	0.004	1.76 (1.20 to 2.59)	1.70 (1.12 to 2.57)	0.01
PI–boosted	1.52 (1.25 to 1.86)	1.37 (1.10 to 1.69)	0.004	1.89 (146 to 2.44)	1.53 (1.15 to 2.03)	0.003	2.23 (1.56 to 3.19)	1.98 (1.32 to 2.92)	0.001
Triple nucleoside	1.31 (1.05 to 1.62)	1.19 (0.95 to 1.50)	0.13	1.31 (0.98 to 1.75)	1.24 (0.91 to 1.69)	0.18	1.95 (1.32 to 2.87)	2.03 (1.33 to 3.11)	0.001
Co-medication									
Cardiovascular	1.16 (0.74 to 1.80)			1.11 (0.63 to 1.96)			0.92 (0.40 to 2.14)		
Hepatitis C	0.65 (0.28 to 1.53)			0.68 (0.20 to 2.26)			1.05 (0.25 to 4.47)		
Opportunistic infections	0.61 (0.41 to 0.91)	0.65 (0.43 to 0.98)	0.04	0.89 (0.54 to 1.46)			1.37 (0.76 to 2.47)		

†ART indicates antiretroviral therapy.
‡Any ART toxicity since the year 2000. Major toxicities were abnormal fat distribution, hypersensitivity reaction, abdominal/GI tract, nervous system, and hematologic toxicity.

support provided in patients' self-management, and quality of relationship between patient and health care provider.

In a sensitivity analysis, we found a statistically significant association between nonadherence and optimal viral suppression that strengthened as the definition of nonadherence became less conservative. Our results add to evidence from previous studies that have demonstrated acceptable correlation between self-reported drug adherence and HIV-1 plasma viral load,[12,17,21,32–34] thus providing clinical validation of self-reported drug intake in HIV-infected individuals taking ART. Previously, conflicting results were found between CD4 cell counts and nonadherence.[19,30] In this analysis, we found a significant association between nonadherence and increases in CD4 cell count only with the 2 least conservative definitions of nonadherence.

This study has several strengths. We defined adherence in 3 different ways using 2 simple questions that are easy to understand and clinically relevant. We have detailed data on treatment from a large cohort of HIV-infected individuals and our analysis had the power to verify suspected trends in adherence. In addition, detailed treatment information is collected on individuals in the SHCS, allowing us to explore a large range of treatment-related variables. We controlled for

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variations in nonadherence across centers, providing a more accurate picture of trends in the data.

This study also has several limitations. The analysis is based on cross-sectional, not prospective, data and therefore no causal conclusions can be drawn. In addition, we did not have information on food restrictions or alcohol abuse, variables known to be correlated with nonadherence.[18,27,28]

Adherence has become one of the most crucial issues in the clinical management of HIV-infected patients receiving ART to achieve sustained long-term suppression of HIV replication and to avoid resistance to antiretroviral drugs. These results confirm the importance of understanding the necessary level of nonadherence as it relates to patient outcomes. Health care providers need to provide the foundation and support for the behavioral dimension of long-term disease management and recognize that younger patients and those without social support are at increased risk for nonadherence. Preliminary evidence from our study suggests that patients on NNRTI regimens, especially when compared with those on PI regimens, may be at lower risk for nonadherence.

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APPENDIX

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