Longitudinal Analysis of Patterns and Predictors of Changes in Self-Reported Adherence to Antiretroviral Therapy: Swiss HIV Cohort Study

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Background: Adherence to combination antiretroviral therapy (cART) is a dynamic process, however, changes in adherence behavior over time are insufficiently understood.

Methods: Data on self-reported missed doses of cART was collected every 6 months in Swiss HIV Cohort Study participants. We identified behavioral groups associated with specific cART adherence patterns using trajectory analyses. Repeated measures logistic regression identified predictors of changes in adherence between consecutive visits.

Results: Six thousand seven hundred nine individuals completed 49,071 adherence questionnaires [median 8 (interquartile range: 5–10)] during a median follow-up time of 4.5 years (interquartile range: 2.4–5.1). Individuals were clustered into 4 adherence groups: good (51.8%), worsening (17.4%), improving (17.6%), and poor adherence (13.2%). Independent predictors of worsening adherence were younger age, basic education, loss of a roommate, starting intravenous drug use, increasing alcohol intake, depression, longer time with HIV, onset of lipodystrophy, and changing care provider. Independent predictors of improvements in adherence were regimen simplification, changing class of cART, less time on cART, and starting comedications.

Conclusions: Treatment, behavioral changes, and life events influence patterns of drug intake in HIV patients. Clinical care providers should routinely monitor factors related to worsening adherence and intervene early to reduce the risk of treatment failure and drug resistance.

Key Words: antiretroviral therapy, cohort study, latent trajectory analysis, medication adherence, patterns, repeated measures

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INTRODUCTION

Combination antiretroviral therapy (cART) has lead to dramatic reduction in hospitalization rates, opportunistic infections, and deaths associated with HIV infection.[1–4] Continuous and lasting suppression of viral replication is essential to allow for maximal CD4 cell recovery, the most important factors influencing long-term prognosis of HIV-infected individuals.[5,6] Adherence to cART is paramount to achieving these goals and nonadherence to therapy has been shown to be one of the strongest predictors of virological failure.[7,8] In addition, nonadherence has been linked to the emergence of drug resistance, often associated with cross resistance to other members of the same class, limiting future treatment options and possible transmission of multidrug-resistant virus.[9–11]

Factors associated with adherence have been well-documented.[12–15] Findings from our previous research have shown that younger age, lack of social support, increasing number of previous regimens, taking a protease inhibitor (PI), regimen complexity, and taking medication for opportunistic infections were significantly associated with nonadherence.[12]

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T.R.G. and H.C.B. designed the study and interpreted the results. T.R.G. did the statistical analysis. M.C., P.L.V., H.F., B.H., E.B., H.G., M.B., and H.C.B. were responsible for patient recruitment and clinical assessment, M.R. was involved in data management. The article was written by T.R.G. and reviewed by all other contributors.

The members of the Swiss HIV Cohort Study are listed in Appendix I.

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However, adherence is a dynamic process and only a few studies have addressed patterns and changes in adherence over time.[16–20] Most of these studies only considered special populations, such as men having sex with men (MSM)[16,18] or women.[16] In addition, all studies had methodological limitations, such as dichotomizing or summarizing adherence data leading to inefficient use of data [16,18,19] and short follow-up.[17–20]

To optimally design adherence intervention studies, there is a need for a detailed and sophisticated analysis of adherence patterns. The Swiss HIV Cohort Study (SHCS) provides a unique opportunity to achieve this with 6 years of follow-up in a large prospective cohort where women, heterosexuals, and intravenous drug users are well represented. The goals of this study were to identify clusters of individuals with unique patterns of adherence behavior and to assess factors, especially changes in factors, associated with changes in adherence over time.

METHODS

Design

This longitudinal study was based on prospectively collected data from individuals enrolled in the SHCS and followed at 1 of the 7 outpatient clinics (Basel, Berne, Geneva, Lausanne, Lugano, St Gallen, Zurich) or associated clinics and private urban practices (www.shcs.ch). At these routinely scheduled visits, patients' self-reported drug adherence and additional psychosocial clinical and laboratory data are collected. Eligible individuals were either treatment experienced or starting cART and responded to at least 2 adherence questionnaires between its introduction on January 1, 2003, and the end of study on January 1, 2009. Baseline was the date of the first completed adherence questionnaire.

Measure of Adherence

The simplified SHCS adherence questionnaire contains 2 questions addressing "taking adherence" and "drug holidays," 2 of the 4 dimensions of adherence to cART.[21] Taking adherence is defined as the number of missed doses in the last 4 weeks (daily, more than once a week, once a week, once every second week, once a month, never). Drug holidays are defined as missing 2 or more consecutive doses in the last 4 weeks (dummy variable).

Definition of Changes in Adherence Behavior

For the definition of change in adherence behavior, we formed consecutive visit pairs, which constitute the unit of analysis. For each consecutive visit pair, changes in adherence from one visit (V_i) to the next (V_{i+1}) is the outcome. We defined 3 possible groups: (1) individuals with no reported change in missed doses between 2 visits, (2) individuals who reported a change for the worse with more missed doses since the last visit, and (3) individuals who reported improvements in adherence with less missed doses than the previous visit.

Predictors of Changes in Adherence Behavior

To model behavior change in drug adherence, we included predictors from 5 dimensions identified by the World Health Organization as affecting adherence to cART[21]: sociodemographic-related, patient-related, health condition–related, treatment-related, and health system–related factors. For time-varying predictors, changes in a predictor from one visit (V_i) to the next (V_{i+1}) is modelled unless otherwise specified. The sociodemographic factors were age at baseline, gender, ethnicity (white vs. others), education (basic education vs. higher education), changes in stable partnership (loss of partner, gain of partner, no change), and living conditions (loss of roommate, gain of roommate, no change). Patient-related factors were collected via self-report at every follow-up visit and defined as follows. Changes in cigarette smoking (started smoking, quit smoking, no change), intravenous drug use (IDU) (started IDU, stopped IDU, no change), participation in drug substitution program (started drug program, stopped drug program, no change), and legal problems (developed legal problems, resolved legal problems, no change). Risky sex behavior was defined as unprotected sex (without condoms) with either an HIV-negative stable partners or occasional partners. Changes in sexual risk behavior were included (riskier behavior, less risky behavior, no change). Daily alcohol intake was translated into health risk categories developed by the World Health Organization (WHO)[22]: light ($<$20 g for women and $<$40 g for men), moderate (20–40 g for women and 40–60 g for men), and severe health risk ($>$40 g for women and $>$60 g for men) as done in a recent study.[23] Changes in categorization of alcohol risk were categorized as increased risk, decreased risk, or no change. Psychiatric treatment was defined as seeing a psychiatrist, diagnosis of depression, or taking antidepressants. Although most patients seeking psychiatric treatment were likely suffering from depression, specific information on depression was only collected as of July 2008. Changes in psychiatric treatment were classified as started treatment, stopped treatment, or no change. Health condition–related factors, collected via patient interview and hospital records, were hospitalization since the previous visit, comedication for opportunistic infections, cardiovascular disease prevention/treatment, hepatitis C or cancer (started co-medication, stopped co-medication, no change), and time since first HIV-1–positive test at baseline (in years). Treatment-related factors were number of previous cART regimens at baseline, time on cART at baseline, changes in regimen frequency (increase in frequency, decrease in frequency, no change), and changes in class of cART since the previous visit (yes, no). Class of cART is defined as nonnucleoside reverse transcriptase inhibitor (NNRTI), boosted PI, nonboosted PI, or triple nucleoside/other. Boosted PI regimens were defined as ritonavir with at least one other PI. Body fat changes, defined as peripheral lipoatrophy or central or nuchal body fat gain as diagnosed by the clinician and confirmed by the patient, were included (new report of body fat changes, resolution of body fat changes, no change). Health system–related factors were changes in the physician or center where the individual was being followed since the previous visit.

Statistical Analysis

Identification of Patterns in Adherence Behavior

Due to the infinite number of possible individual-specific adherence patterns, we used group-based trajectory

modeling for the identification of clusters of individuals with similar observed temporal patterns of adherence to cART.[24] Similar to latent class analysis,[25] this method assumes that the population is composed of a mixture of distinct groups defined by their behavioral trajectories. This procedure allows joint modeling of the probability of group membership and group-specific trajectories. The latter are modeled semiparametrically via flexible polynomial functions fitted to individual adherence responses over time. Given a specified number of groups, the model estimates membership probabilities in each group for every participant, based on the participant's observed patterns of adherence over time. Estimated variability in parameter estimates accounts for uncertainty in group membership and between-individual and within-individual variation in observed longitudinal responses. The modeling was performed for 2–6 groups with final selection of the optimal number of groups based on comparison of model fits using the Bayesian information criterion. Group assignments were based on posterior model-based probability calculations, with actual assignment based on the maximal group membership probability for each participant. Model results were summarized graphically with each groups predicted trajectories and their 95% confidence intervals (CIs). Baseline characteristics by group membership were summarized.

Changes in Adherence Behavior

To model changes in adherence behavior, we constructed 2 datasets, 1 for improvements in and 1 for worsening of adherence. All visit pairs with no reported changes in adherence (where the adherence on the initial visit pair was not perfect) and those with reported improvements in adherence at visit V_{i+1} were included in the model exploring the likelihood of an improvement in adherence since the previous visit. All visit pairs with no reported changes in adherence (where the adherence on the initial visit pair was not in the lowest possible category) and those with reported decreases in adherence at visit V_{i+1} were included in the model exploring the likelihood of a decrease in adherence since the previous visit. Both models included all preselected predictors from the 5 WHO dimensions. For time-independent factors (age, gender, ethnicity, education, time since HIV-1–positive test, number of previous cART regimens), the value of the predictor at visit V_i was included in the model. For time-dependent factors, their change from one visit (V_i) to the next (V_{i+1}) was modeled. We used generalized estimating equations to evaluate the repeated measures logistic regression models. This model adjusted for the correlation between visit pairs in the same individual. Results are presented with odds ratios and 95% CIs.

Sensitivity Analyses

To check the consistency of our results, we performed several sensitivity analyses. For the description of adherence behavior clusters, we repeated the trajectory analysis, stratifying the population by cART treatment naive or pretreated. For the identification of adherence patterns, we performed 3 sensitivity analyses. First, we stratified the analysis by gender to check if different factors affect changes in adherence for men and women. Second, we repeated the primary analysis stratifying by number of missed doses on the initial visit pair (V_i) to see if different factors influenced the likelihood of adherence changes depending on the initial adherence. Third, we removed changes in alcohol risk category from the multivariate model as this variable was only collected in the SHCS as of August 2005. Therefore, multivariate models including alcohol lose a lot of information, which might impact the results even though these values were missing by design (completely at random).

All analyses were done with SAS version 9.1 (SAS Institute Inc, Cary, NC) and Stata version 9 (StataCorp. College Station, TX).

RESULTS

A total of 7466 individuals completed 69,144 adherence questionnaires between January 1, 2003, and January 1, 2009. Of these, 19,238 were not completed during an official follow-up visit, and 105 were completed when an individual was not on cART; 654 individuals completed only 1 adherence questionnaire. The final analyses included 6709 individuals who completed 49,071 questionnaires and had 42,362 visit pairs during the 6-year study period. The median number of adherence questionnaires per individual was 8 [interquartile range (IQR): 5–10], and the median follow-up time was 4.5 years (IQR: 2.4–5.1). The population consisted largely of males (69.6%), whites (82.1%), those with suppressed HIV-1 RNA at baseline (64.8% with <50 copies/mL), 38.4% were heterosexuals, median age was 41 years, and individuals were diagnosed with HIV a median of 7.9 years ago (IQR: 3.0–13.5) (Table 1).

Missing 0 doses of cART was reported by patients on 78.1% of visits, missing 1 dose 13.1%, missing 2 doses 4.7%, and missing >2 doses 4.2% of visits. Missing more than 1 dose in a row was reported on 3.5% of visits. Overall, self-reported adherence was found to be improving over time, with 70% reporting missing 0 doses of cART at the beginning of the 6-year study period compared with 83% at the end (Fig. 1). In the subset of naive patients, this trend remained, but reports of missing 0 doses increased from 81% to 87% over time (data not shown).

Trajectory analysis was used to identify group patterns of adherence to cART. We considered groups of size 2–6 and selected a model of 4 groups as optimal based on fit (comparing the Bayesian Information Criterion between models), parsimony (comparing clusters in both naive and pretreated individuals), and interpretability. Group 1 (labelled "good adherence") was estimated at 51.8% and characterized by consistently high adherence (Fig. 2). Group 2 (labelled "worsening adherence") was estimated at 17.4% and included individuals with good adherence at baseline followed by steadily worsening adherence. Group 3 (labelled "improving adherence") was the opposite of group 2 characterized by reports of poor adherence at baseline followed by steadily improving adherence and had an estimated group membership of 17.6%. Group 4 (labelled "poor adherence") was estimated at 13.2% and characterized by consistent reports of poor adherence over time. There was very little overlap in the CIs of the groups indicating the trajectories are relatively distinct. The same 4 adherence patterns were identified in separate analyses of naive and pretreated patients, only the CIs widened

TABLE 1. Baseline Characteristics of Population by Membership in Adherence Pattern Group Identified by Trajectory Analysis

Variable	Overall	Group 1: Good Adherence	Group 2: Worsening Adherence	Group 3: Improving Adherence	Group 4: Poor Adherence
n (%)	6709	3837 (57.2)	927 (13.8)	1118 (16.7)	827 (12.3)
Age, median (IQR)	41 (36–47)	42 (36–49)	41 (35–46)	41 (36–46)	40 (36–45)
Male gender, %	69.6	71.3	66.7	68.4	65.7
White, %	82.1	82.5	81.9	81.3	81.4
Basic education, %*	26.7	23.3	29.4	30.9	34.1
Risk group for HIV infection, %					
MSM	37.5	41.8	32.9	33.7	27.6
Heterosexual	38.4	38.9	39.7	38.6	34.6
IDU	19.9	14.6	23.7	24.7	33.9
Other	4.2	4.7	3.7	3.0	4.0
Past or current IDU	22.3	16.6	27.1	27.3	36.6
Past or current psychiatric treatment	22.8	19.4	24.4	27.4	30.2
Past or current legal problems	9.9	6.9	13.2	11.6	17.7
Living alone	41.1	40.3	39.3	42.6	45.0
Stable partnership	57.3	58.9	55.5	54.9	54.9
Baseline viral load (copies/mL), %					
<50	64.8	66.1	64.7	63.1	61.3
50–399	15.4	15.9	14.9	15.5	13.7
≥400	19.8	18.0	20.4	21.5	25.0
Baseline CD4 cell count (μ/L), %					
<200	16.4	16.0	16.7	16.1	18.7
200–349	26.8	26.9	29.2	25.7	24.7
350–499	24.2	24.1	24.0	24.5	24.4
≥500	32.6	33.0	30.1	33.8	32.2
cART regimen at baseline					
NNRTI	35.5	38.7	33.8	33.8	25.2
PI boosted	14.6	12.5	16.6	16.1	20.0
PI non-boosted	37.0	36.7	40.1	34.9	37.8
Triple nucleoside/other	13.0	12.1	9.5	15.2	17.1
No. cART regimens, median (IQR)†	2 (1–5)	2 (1–4)	2 (1–4)	3 (1–5)	3 (2–6)
Time on cART, median (IQR) (yrs)‡	3.9 (0.6–6. 7)	3.1 (0.5–6.5)	4.0 (0.9–6.4)	4.7 (1.2–7.0)	5.4 (2.9–7.1)
Time since HIV diagnosis, median (IQR) (yrs)	7.9 (3.0–13.6)	6.9 (2.2–12.8)	7.9 (3.6–13.1)	9.5 (4.0–14.5)	10.6 (6.0–15.4)

*Nine years of mandatory schooling or less.
†Number of cART regimens at baseline, including the current one, taken while registered in the cohort.
‡For those cART taken while registered in the cohort.
NNRTI, nonnucleoside reverse transcriptase inhibitor.

and the predicted group membership changed. Compared with the model with all patients, naive patients were more likely to belong to the group with worsening adherence (27.0%) and less likely to belong to the poor adherence group (6.9%). Table 1 provides baseline characteristics by group membership from the analysis including all individuals. Individuals with consistently poor adherence, more often had only a basic education, were intravenous drug users (less often MSM), were under psychiatric treatment, had legal problems, on a NNRTI, on cART for longer, and living with HIV for a longer time.

Of the 42,362 visit pairs, no change in adherence was reported 76.2% of the time with 12.4% reported improvements and 11.4% reporting decrements in adherence. Different factors were found to be associated with worsening and improving adherence (Table 2). In multivariate models adjusted for adherence on the first visit of the pair, factors significantly associated with worsening adherence were younger age, basic education, loss of a roommate, starting IDU, increasing daily alcohol intake (resulting in categorization in a higher alcohol risk category), starting psychiatric treatment, longer time living with HIV, onset of lipodystrophy, and changes of the physician or center where the individual was followed. In multivariate models, factors significantly associated with improvements in adherence were starting comedications, changes in the class of cART, and regimen simplification (decreases in regimen frequency). Individuals with basic education and those on cART for a longer time at baseline were significantly less likely to improve their adherence.

Several sensitivity analyses were performed: (1) stratification by gender, (2) stratification by reported missed doses at the initial visit of the pair, and (3) removing alcohol from the

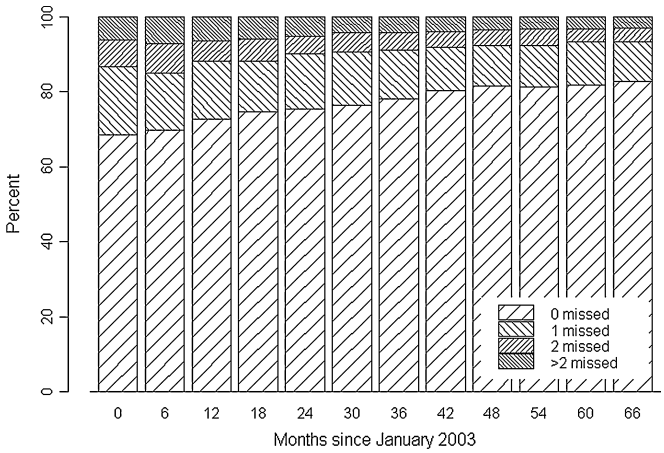

FIGURE 1. Self-reported missed doses of cART over time since introduction of the adherence questionnaire in January 2003.

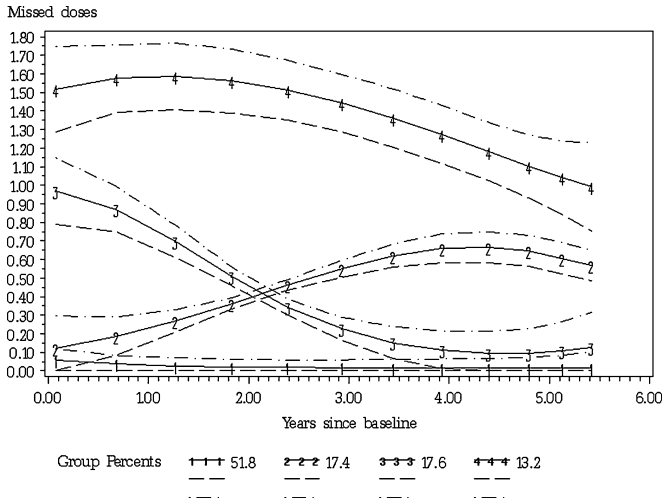

FIGURE 2. Trajectories with 95% CIs of adherence groups identified by clustering the number of missed doses over time: group 1 = consistently good adherence, group 2 = steadily worsening adherence, group 3 = steadily improving adherence, and group 4 = consistently poor adherence over time. The predicted probabilities of group membership are given.

model due to a large number of missing values (data collection began only in 2005). All models returned similar results demonstrating the robustness of our results (data not shown).

DISCUSSION

We did an in-depth and novel exploration of self-reported adherence to cART over time in individuals participating in the SHCS. Self-reported adherence was quite high with individuals reporting missing 0 doses of cART on almost 80% of visits. We identified 4 distinct adherence patterns based on almost 50,000 adherence questionnaires. We did a comprehensive and unique assessment of the effect of both time-independent and time-varying predictors on changes in adherence over the 6-year study period.

These same 4 adherence patterns (good, improving, worsening, and poor) observed in all patients were also detected in a population of only naive patients and pretreated patients. The pattern of consistently good adherence had the highest estimated group membership for all subpopulations, whereas naive patients were more likely to fall into the worsening adherence pattern than pretreated individuals. There were observed differences in group membership by several baseline factors, most notably that individuals with a history of psychiatric treatment or legal problems, were more often in the poor adherence group. In future work, we plan a validation of these adherence groups on clinical outcomes.

Our analysis of changes in adherence included factors from all 5 dimensions identified by the WHO as determinants of adherence.[21] Some of these variables, in particular the social support variables, comedication, and health system factors, have not been studied previously. In addition, no other study to our knowledge has included changes in factors as predictors of changes in adherence to explore potential triggers for periods of worsening adherence. We could confirm several factors found in other studies to be associated with worsening or improving adherence such as age,[18,20] education,[18] IDU,[16,18] alcohol intake,[16,18] depression,[18] taking a PI-based regimens,[16] and symptoms.[16,20] In addition to these variables, we found loss of a roommate, longer time since HIV diagnosis, and health system changes such as disruption of the continuity of care by the same physician or hospital were significantly more likely to be associated with reported worsening adherence. Newly identified factors significantly associated with improvements in adherence were changes in cART class, regimen simplification, and starting to take medication for opportunistic infections, cardiovascular disease, hepatitis C, or cancer.

Our results demonstrate that not only demographic factors such as age, gender, and education influence adherence, but also short-term *changes* in factors can impact changes in adherence as well. These changes can serve as signals to the clinicians to provide additional adherence support. Changes in a patient's living situation (such as loss of a roommate) or changes to their physician or center of care can signal a loss of social support and lead to lapses in medication taking. It may be the challenge of moving house or the difficulty in building a trusting relationship with a new physician that impacts adherence behavior. Changes to regimens with higher daily administration frequency or one with known side effects such as lipodystrophy—can all result in worsening adherence. These results suggest that clinicians need to anticipate the possibility of added stress during periods of change for patients and provide additional support during these times.

The SHCS is a long-standing and well-described prospective cohort that collects a variety of information longitudinally in a diverse population of heterosexuals and women, making the results generalizable. This study includes a large sample of HIV-infected individuals followed for up to 6 years. We have identified a number of new factors that affect adherence and thus impact drug failure. We conducted extensive sensitivity analyses to ensure the robustness of the results.

A limitation of this study is that our results are based on self-reported adherence provided in an interview with a clinician. These reports can be subject to recall bias or social

TABLE 2. Independent Predictors of Worsening or Improving in Adherence Using Repeated Measures Logistic Regression*

Predictor	Worsening Adherence OR (95% CI)	Improving Adherence OR (95% CI)
Sociodemographic-related factors		
Age (per 5 years)†	0.92 (0.89 to 0.95)	1.05 (0.99 to 1.10)
Male gender	0.91 (0.81 to 1.02)	0.86 (0.72 to 1.03)
White	0.98 (0.84 to 1.14)	0.82 (0.65 to 1.05)
Basic education*	1.16 (1.03 to 1.31)	0.82 (0.68 to 0.99)
Began living alone§	1.30 (1.06 to 1.60)	0.84 (0.61 to 1.15)
Ended a stable partnership§	1.06 (0.86 to 1.32)	0.98 (0.72 to 1.33)
Patient-related factors		
Started IDU§	1.89 (1.30 to 2.77)	1.11 (0.59 to 2.11)
Started drug maintenance program§	0.78 (0.47 to 1.29)	0.96 (0.49 to 1.86)
Increase in alcohol intake‡§	1.25 (1.10 to 1.43)	0.82 (0.67 to 1.01)
Started smoking§	1.11 (0.84 to 1.46)	1.07 (0.70 to 1.65)
Began riskier sex behavior§	1.09 (0.94 to 1.26)	1.13 (0.91 to 1.40)
Began psychiatric treatment§	1.26 (1.04 to 1.52)	1.08 (0.79 to 1.48)
Release from prison or resolution of legal issues§	1.24 (0.76 to 2.03)	0.74 (0.37 to 1.50)
Health condition–related factors		
Hospitalization§	1.12 (0.95 to 1.31)	0.85 (0.66 to 1.09)
Started comedication§	0.95 (0.73 to 1.23)	1.95 (1.29 to 2.94)
Time living with HIV (per 5 years)†	1.11 (1.05 to 1.17)	0.94 (0.87 to 1.02)
Treatment-related factors		
Change in class of cART§	0.90 (0.72 to 1.13)	1.48 (1.08 to 2.04)
Decrease in regimen frequency§	0.86 (0.70 to 1.05)	1.45 (1.08 to 1.94)
Time on cART (per year)†	0.99 (0.97 to 1.01)	0.95 (0.91 to 0.99)
Number of previous cART regimens†	1.02 (0.99 to 1.04)	1.02 (0.97 to 1.06)
Onset of lipodystrophy§	1.21 (1.00 to 1.47)	1.09 (0.81 to 1.46)
Health system–related factors		
Change of physician or center§	1.22 (1.10 to 1.36)	1.08 (0.91 to 1.27)

*Results are from 2 models, 1 for worsening of and 1 for improvements in adherence. Both models are adjusted for correlation between visit pairs from the same individuals. Adjusted for reported adherence on first visit (Vi) of the consecutive pair.

†At baseline.

‡Increase in daily alcohol consumption so that patient falls into a higher alcohol risk category (as defined by WHO[21]).

§Changes in the covariate between consecutive visit pairs or since the previous visit.

OR, odds ratio.

desirability bias, leading to underreporting of nonadherence behavior.[26,27] However, 2 systematic reviews including a large number of observational studies found a robust association between self-reported adherence and viral load over varying measures and recall periods[28] and indicated that self-reported adherence measures can distinguish between clinically meaningful patterns of medication-taking behavior.[29] Other information in the SHCS is also collected via self-report, such as sexual risk behavior, drug use, psychological, and legal problems, which could also result in reporting bias due to the sensitivity of these topics. Another limitation is the observational nature of the study, which can lead to biased results due to unmeasured confounding. In addition, there is likely confounding by indication with respect to the choice of cART, especially in groups at risk for adherence problems.

Adherence was found to be improving over time (Fig. 1), contrary to results from other studies[19,20] performed before 2001. A more recent study also detected a decreasing trend in adherence until 2003 and then adherence started to improve.[16] We can hypothesize that regimen simplification in recent years has facilitated improved adherence. It is also likely that introducing systematic adherence assessments resulted in increased attention in both patients and clinicians to the issue of adherence and therefore, led to improvements in adherence. Also, the SHCS is an open cohort and the population is changing over time—for example, the number of individuals from IDU risk group has decreased dramatically over time with a corresponding increase in MSM and heterosexuals, groups known to have better adherence. Therefore, our results provide unbiased measures of associations (but not causation) between covariates and outcome.

In conclusion, our results indicate that clinicians should routinely enquire about factors that may disrupt regular drug intake such as changes in substance and alcohol use, psychiatric treatment, and important lifestyle changes including loss of social support. In particular, clinicians should be sensitive to the risk of worsening drug adherence when changes in the patient care provider relationship are planned. Additional adherence counseling should be provided to patients experiencing potentially stressful situations so that they can learn the skills to cope with these changes without disruption in their drug intake. Future studies should

investigate whether simple patient focused interventions suitable to busy clinical practice, such as routine checking of risk factors for changes in regular drug intake identified by this study, may enhance drug adherence and reduce risk of treatment failure and drug resistance.

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APPENDIX I: MEMBERS OF THE SWISS HIV COHORT STUDY

The members of the Swiss HIV Cohort Study are Battegay M, Bernasconi E, Böni J, Bucher H. C, Bürgisser P, Calmy A, Cattacin S, Cavassini M, Dubs R, Egger M, Elzi L, Fischer M, Flepp M, Fontana A, Francioli P (President of the SHCS), Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard HF (Chairman of the Scientific Board), Hirsch HH, Hirschel B, Hösli I, Kahlert C, Kaiser L, Karrer U, Kind C, Klimkait T, Ledergerber B, Martinetti G, Müller N, Nadal D, Paccaud F, Pantaleo G, Rauch A, Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schmid P, Schultze D, Schüpbach J, Speck R, de Tejada B. M, Taffé P, Telenti A, Trkola A, Vernazza P, Weber R, and Yerly S.