Original article

Self-reported non-adherence to antiretroviral therapy repeatedly assessed by two questions predicts treatment failure in virologically suppressed patients

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Background: The aim of this study was to explore the predictive value of longitudinal self-reported adherence data on viral rebound.

Methods: Individuals in the Swiss HIV Cohort Study on combined antiretroviral therapy (cART) with RNA <50 copies/ml over the previous 3 months and who were interviewed about adherence at least once prior to 1 March 2007 were eligible. Adherence was defined in terms of missed doses of cART (0, 1, 2 or >2) in the previous 28 days. Viral rebound was defined as RNA >500 copies/ml. Cox regression models with time-independent and -dependent covariates were used to evaluate time to viral rebound.

Results: A total of 2,664 individuals and 15,530 visits were included. Across all visits, missing doses were reported as follows: 1 dose 14.7%, 2 doses 5.1%, >2 doses 3.8%, taking <95% of doses 4.5% and missing ≥2 consecutive doses 3.2%. In total, 308 (11.6%) patients experienced viral rebound. After controlling for confounding variables, self-reported non-adherence remained significantly associated with the rate of occurrence of viral rebound (compared with zero missed doses: 1 dose, hazard ratio [HR] 1.03, 95% confidence interval [CI] 0.72–1.48; 2 doses, HR 2.17, 95% CI 1.46–3.25; >2 doses, HR 3.66, 95% CI 2.50–5.34). Several variables significantly associated with an increased risk of viral rebound irrespective of adherence were identified: being on a protease inhibitor or triple nucleoside regimen (compared with a non-nucleoside reverse transcriptase inhibitor), >5 previous cART regimens, seeing a less-experienced physician, taking co-medication, and a shorter time virally suppressed.

Conclusions: A simple self-report adherence questionnaire repeatedly administered provides a sensitive measure of non-adherence that predicts viral rebound.

Introduction

Adherence to combined antiretroviral therapy (cART) is fundamental to achieving and maintaining viral suppression, preventing drug resistance and improving survival in HIV-infected individuals [1–3]. However, there remains no definitive approach to adherence assessment [4,5] and no standard definition of non-adherence. Many studies have indicated that high levels of adherence to cART are necessary to achieve optimal suppression of HIV-1 RNA [6,7], but the exact level of adherence necessary is unknown and likely to vary by cART regimen [8,9].

The ongoing debate over the best way to measure and utilize adherence data is being fueled by the need for

simple and accurate methods for measuring adherence to cART in routine clinical practice. Standardized measurement tools are needed because physicians experience difficulties in assessing patient adherence to cART accurately [10,11]. Self-report of drug adherence offers the primary advantages of ease of administration, flexibility and low cost. However, self-report is subject to recall bias. Patients' reporting of non-adherence has been found to be credible [12,13] but their estimate of the degree of adherence is often inaccurate [14], overestimating adherence by 10–20% compared with electronic monitoring (EM) [15,16]. Despite these disadvantages, two recent systematic reviews both including a large number of observational studies found a robust association between self-reported adherence and viral load over varying measures and recall periods [5], and indicated that self-reported adherence measures can distinguish between clinically meaningful patterns of medication-taking behaviour [17].

Although other methods such as pill count and prescription refill have been used successfully to measure adherence, these methods are not practical over the long term, suffer from implementation problems and do not provide detailed information such as drug holidays. Although EM provides an accurate, detailed measure of adherence, it is not practical for routine use and would be better used to educate naive individuals starting therapy or as an aid for individuals with known adherence problems.

Most observational studies – independent from the measurement method for adherence – suffer from additional shortcomings. The majority of studies are of cross-sectional design, precluding the opportunity to make causal inferences. Longitudinal studies with multiple adherence measurements in the same patient often summarize adherence behaviour over the whole study period leading to a loss of efficiency and information; this approach also ignores the important dynamic of adherence changes over time [18,19].

In a previous cross-sectional analysis of the Swiss HIV Cohort Study (SHCS) we showed a strong linear relationship between self-reported non-adherence by interview over the previous 28 days and optimal viral suppression [20]. The goal of this study of HIV-infected individuals with complete viral suppression on cART was to use all the information from repeatedly applied questionnaires in a time-updated analysis to test whether the two-item questionnaire of the SHCS predicts viral rebound.

Methods

Patients

The SHCS is a prospective cohort study with continuing enrollment of HIV-infected individuals aged 16 years or older. Visits take place every 6 months at seven outpatient clinics in participating HIV centres, associated hospitals or specialized private practices. Eligible individuals were: actively enrolled in the SHCS, on cART, virally suppressed (HIV-1 RNA ≤50 copies/ml) for at least 3 months prior to baseline and had at least one follow-up HIV-1 viral load measurement. Baseline is taken as the official cohort visit prior to completion of their first adherence questionnaire.

Outcome definition

The primary endpoint of the study was time to virological rebound defined as time to HIV-1 RNA >500 copies/ml. Confirmed viral rebound (two consecutive RNA >500 copies/ml) was also considered as an outcome. The majority of recent treatment guidelines suggest that intermittent viraemia (isolated HIV-1 RNA levels between 50 and 500 copies/ml) are often of no clinical consequence, but consecutive rebounds of HIV-1 RNA >500 copies/ml can be associated with virological failure [21].

Adherence definitions

An adherence questionnaire was introduced into the follow-up of the SHCS in July 2003 and has been previously described [20]. Individuals were asked two questions by their clinician: (i) How often did you miss a dose of your medication in the last 4 weeks? Daily, more than once a week, once a week, once every two weeks, once a month, never; and (ii) Did you miss more than one dose in a row? Yes, no. The questionnaire has been validated in a study that compared the European HIV treatment questionnaire, a visual analogue scale (VAS) and EM (AE Deschamps *et al.* unpublished data). Using virological failure as the gold standard, the SHCS adherence questionnaire in the validation study performed slightly better than either EM or a combination of the adherence questionnaire and a VAS with a sensitivity of 88% and a specificity of 79%. In this study, non-adherence was categorized into the number of missed doses: 0, 1, 2 and >2. Several methods for handling missing adherence data were considered: missing data were excluded from the analysis, the last non-missing observation was carried forward (LOCF), 'missing' was added as a category of missed doses, and 'missing data' was replaced by an indicator of non-adherence (missing two doses).

Covariate definitions

Covariates that were potential confounders of the relationship between adherence and viral rebound were considered for inclusion in the analysis. The following time-independent covariates were measured at baseline: gender, age, prior intravenous drug use, $CD4^+$ T-cell count (cells per 10^9/l), duration of viral

suppression, prior AIDS diagnosis, number of previous cART regimens (≤5 or >5), physician experience (defined as the number of HIV-infected patients in the SHCS previously treated by a physician at the time of the patient's baseline visit), and time on cART. The following time-dependent (that is, time-varying) covariates were measured at each follow-up visit: (i) having a stable partner, (ii) taking co-medication (for risk factors for cardiovascular disease [dyslipidaemia, diabetes or hypertension], opportunistic infections [OI], hepatitis C or cancer), (iii) hospitalization, and (iv) current cART (non-nucleoside reverse transcriptase inhibitor [NNRTI], non-boosted protease inhibitor [PI], boosted PI, triple nucleoside). An interaction between adherence and cART regimen and dosing frequency was tested for inclusion in the model.

Statistical methods

A time-to-event analysis was performed using a Cox proportional hazards model to study the effects of both time-independent and time-dependent explanatory variables on the event incidence. Events were defined as the first date where HIV-1 RNA was >500 copies/ml. For individuals who did not experience an event, follow-up was censored on 1 March 2007, on the date when cART was stopped for ≥45 days, the date of loss to follow-up or death. The association between explanatory variables and viral rebound was assessed by using hazard ratios (HRs) and 95% confidence intervals (CIs); HRs >1 indicate a covariate is positively associated with the event probability. Variables known to be confounders were automatically considered for inclusion in the final adjusted model while all other previously untested variables were included only if there was some evidence of an association ($P<0.25$) in unadjusted models. Following the fit of the multivariate model, the importance of the variable as a confounder (as measured by its effect on the HR of the other variables) was verified or the variable was eliminated from the final model. All analyses were carried out with SAS v9.1 (SAS Institute Inc., Cary, NC, USA). The manuscript was written to comply with STROBE guidelines for observational studies [22].

Sensitivity analyses

As an additional validation of the adherence measurement, several additional measures of non-adherence were calculated. To explore the effect of previous reports of non-adherence, we constructed an indicator of the highest number of reported missed doses (0, 1, 2 or >2) at each time point for all follow-up visits including the current visit. To make our results comparable with other studies, non-adherence was calculated as taking <95% of doses. However, as we do not collect adherence information as a percentage of doses taken, this definition had to be approximated based on the number of missed doses in the previous 28 days and the dosing frequency of the current cART regimen. For example, an individual on a once daily regimen who missed two doses in the previous 28 days was calculated to have taken <95% of doses (26/28=92.8%). In addition, we tested whether missing at least two consecutive doses of cART was an independent predictor of virological failure.

Results

In total, 7,539 patients were actively registered in the SHCS between 1 July 2003 and 1 March 2007. Of these, 5,368 had at least one follow-up visit within 1 year of the baseline visit where they completed an adherence questionnaire and had corresponding laboratory data recorded. Of these, 2,704 were excluded for several reasons: not virally suppressed (HIV-1 RNA ≥50 copies/ml) for a minimum of 3 months (n=2,689), off treatment at baseline visit (n=10), cART-naive (n=2), no follow-up HIV-1 RNA values (n=2), and stopped treatment 1 day after baseline (n=1). A total of 2,664 patients with 15,530 visits were included in the analysis. The total prospective follow-up until the event date or until the censoring date for those without an event was 7,693 person-years, with a median individual follow-up time of 3.3 years (interquartile range [IQR] 2.5–3.6). The median number of follow-up visits after baseline was six (range 1–8). A total of 308 (11.6%) patients experienced viral rebound during the study period, with a median time to viral rebound of 16 months (IQR 9.5–29).

Baseline characteristics of the analysis population are displayed in Table 1. Over all visits in the study period, missing doses were reported as follows: 1 dose 14.7%, 2 doses 5.1%, >2 doses 3.8%, taking <95% of doses 4.5%, and missing ≥2 consecutive doses 3.2%. A total of 49% of patients reported a change in the number of missed doses over the study period. Individuals were mostly on twice daily regimens (87.1%) with only marginal numbers on either once daily (10.7%) or three times daily regimens (2.2%); however, the number of individuals on once daily regimens was increasing over the study period with a corresponding decrease in both those on twice daily and three times daily regimens.

Adherence data were missing for 452 (3.3%) visits and the rate of missed doses steadily increased over time (1.3% to 5.3%). All four methods of replacing missing data were explored in unadjusted Cox models. The methods yielded similar results and only the HR for missing >2 doses was slightly lower but still highly significant with LOCF, known to be a conservative method for handling missing data. In addition, when

missing adherence information was included as a category of non-adherence, individuals with missing adherence data were significantly more likely to experience viral rebound than individuals with no reported missed doses with an estimate similar to that of missing two doses (HR 2.39, 95% CI 1.62–3.51). Although there is some indication that missing information is informative, individuals with missing adherence data were excluded from the final analysis as the overall percentage of missing data was very small.

The proportion of individuals experiencing viral rebound increased with increasing number of missed doses. In addition, with two or more reported missed doses, there were differences in the rate of viral rebound by class of ART (Figure 1).

The results of the Cox proportional hazards models of the association between time-updated non-adherence and virological rebound are provided in Table 2.

Table 1. Baseline characteristics of individuals included in the analysis

Characteristic	
Total *n* (%)	2,664 (100)
Median age, years (IQR)	42 (37–48)
Male gender, %	70.8
Past or present intravenous drug use, %	22.9
Smoker*, %	46.4
Stable partnership*, %	60.8
Living alone*, %	39.9
Previous AIDS diagnosis, %	28.6
Hospitalization*, %	7.7
Experience of physician†, median (IQR)	170 (102–294)
$CD4^+$ T-cell count, cells per 10^9/l	
Median (IQR)	478 (331–677)
<200, %	8.6
200–349, %	19.0
350–499, %	25.1
≥500, %	47.3
Current cART regimen, %	
NNRTI	34.8
Non-boosted PI	21.9
PI boosted	24.5
Triple nucleoside and other	18.8
Number of previous cART regimens	
Median (IQR)	3 (2–5)
Time on cART, years	
Median (IQR)	5.7 (3.4–7.3)
Mean (SD)	5.6 (2.7)
Time optimally virally suppressed, years	
Median (IQR)	2.4 (1.1–4.3)
Mean (SD)	2.7 (1.8)

*In the previous 6 months. †Number of HIV-infected patients treated by a physician at the time of the patient's baseline visit. cART, combined antiretroviral therapy; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

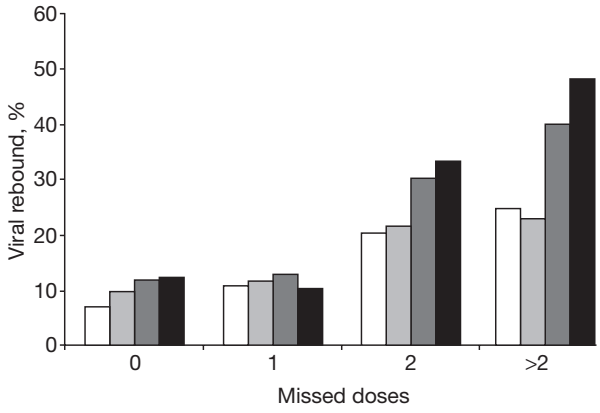
In unadjusted models, two or more missed doses were significantly associated with the risk of viral rebound when compared with perfect adherence (1 dose, HR 1.11, 95% CI 0.78–1.57; 2 doses, HR 2.34, 95% CI 1.57–3.50; >2 doses, HR 4.04, 95% CI 2.78–5.87). After controlling for potential confounding variables, self-reported non-adherence remained significantly associated with the rate of occurrence of viral rebound (compared with zero missed doses: 1 dose, HR 1.03, 95% CI 0.72–1.48; 2 doses, HR 2.17, 95% CI 1.46–3.25; >2 doses, HR 3.66, 95% CI 2.50–5.34). Five variables significantly associated with an increased risk of viral rebound irrespective of adherence were identified: (i) being on a PI or triple nucleoside regimen (compared with an NNRTI regimen), (ii) having experienced >5 previous cART regimens, (iii) seeing a physician with less experience, (iv) taking co-medication, and (v) less time with viral suppression at baseline. Age, gender, stable partnership, AIDS diagnosis and hospitalization were not significantly associated with viral rebound in adjusted models and exhibited no evidence of confounding and therefore were excluded from the final analysis.

To further explore the effect of co-medication, the indicator of taking any co-medication was replaced in turn in the final adjusted model by an indicator of taking co-medication for each indication separately. Only medication taken for risk factors for cardiovascular disease showed no evidence of effect on treatment failure. Receiving treatment for OI, hepatitis C and cancer were all independently associated with an increased hazard for treatment failure, although hepatitis C was only marginally significant. When all four indicators of taking specific co-medication were entered simultaneously into the adjusted model, the results remained the same (Table 3).

There is evidence to suggest that missing doses of medication has different implications for treatment failure depending on both the class of ART regimen and the dosing frequency of the regimen [23–26]. The interaction between missed doses and class of ART regimen was non-significant and therefore not included in the final model. With regards to dosing frequency, interaction variables for both consecutive missed doses and missed doses were constructed. However, due to low numbers of individuals on once and three times daily regimens, the HRs were not estimable for most categories. The only additional comparisons produced from this analysis were between those reporting perfect adherence (over all dosing frequencies) and those who reported missing one dose on a once daily regimen (HR 2.82, 95% CI 1.32–6.01) and missing one dose on a twice daily regimen (HR 0.91, 95% CI 0.60–1.36).

When the outcome was time to confirmed viral rebound (two consecutive RNA >500 copies/ml), the

Figure 1. Percentage of patients with viral rebound (RNA >500 copies/ml) by self-reported missed doses and current class of cART regimen



714	100	34	20
305	67	23	26
240	46	23	20
564	114	27	29

NNRTI
Triple nucleoside
PI non-boosted
PI boosted

cART, combined antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2. Association of baseline and time-varying covariates with the rate of occurrence of viral rebound, RNA >500 copies/ml (both unconfirmed and confirmed), using a Cox proportional hazards model

	Adjusted model VR = RNA >500 copies/ml (*n*=308 events)		Adjusted model VR = two consecutive RNA >500 copies/ml (*n*=102 events)	
Variables	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Intravenous drug use (current or past)	1.20 (0.92–1.57)	0.19	1.15 (0.71–1.86)	0.573
Increases in baseline CD4$^+$ T-cell count of 100, cells per 10^9/l	1.02 (0.98–1.07)	0.39	1.02 (0.95–1.04)	0.60
cART regimen				
NNRTI	Reference		Reference	
Non-boosted PI	1.50 (1.04–2.17)	0.03	1.23 (0.61–2.49)	0.56
Boosted PI	1.53 (1.13–2.09)	0.007	1.67 (0.96–2.91)	0.07
Triple nucleoside/other	1.63 (1.13–2.35)	0.01	1.62 (0.82–3.23)	0.17
>5 Previous cART regimens at baseline	1.44 (1.09–1.89)	0.009	1.96 (1.23–3.11)	0.005
Physician experience* per 100 patients	0.83 (0.76–0.92)	<0.001	0.84 (0.71–0.99)	0.04
Co-medication†	1.44 (1.06–1.96)	0.02	2.42 (1.50–3.90)	<0.001
Time virally suppressed at baseline per year	0.77 (0.71–0.83)	<0.001	0.82 (0.72–0.94)	0.005
Non-adherence (missed doses)‡				
0	Reference		Reference	
1	1.03 (0.72–1.48)	0.86	1.25 (0.68–2.30)	0.48
2	2.17 (1.46–3.25)	<0.001	1.24 (0.50–3.12)	0.64
>2	3.66 (2.50–5.34)	<0.001	4.51 (2.47–8.24)	<0.001

*Number of HIV-infected patients treated by a physician at the time of the patient's baseline visit. †For cardiovascular problems, opportunistic infections, hepatitis C or cancer. ‡In the previous 28 days. cART, combined antiretroviral therapy; CI, confidence interval; HR, hazard ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VR, viral rebound.

adjusted Cox model yielded very similar results to the model with unconfirmed viral rebound (Table 2). CIs were generally wider and some variables were no longer significant probably due to having only one-third of the number of events (102 versus 308).

In sensitivity analyses, we explored whether these results could be validated when different levels of non-adherence were considered. The time-varying indicator of the highest number of missed doses up to the point of the current follow-up visit provided similar results to the primary analysis although the HRs were lower (one dose: HR 0.73, 95% CI 0.53–1.02; two doses: HR 1.51, 95% CI 1.08–2.11; >2 doses: HR 2.44, 95% CI 1.78–3.34). Taking <95% of doses of cART in the previous 4 weeks was significantly associated with viral rebound as a time-updated predictor in an adjusted model (HR 3.18, 95% CI 2.20–4.60). The estimates for covariates were almost identical to the primary analysis (data not shown). Missing two or more consecutive doses of cART in the previous 4 weeks was found to be an independent predictor of time to viral rebound in an adjusted model (HR 3.53, 95% CI 2.42–5.15). Effect estimates and CIs for covariates were also almost identical to those in the primary analyses (data not shown).

Discussion

This study demonstrates that in HIV-infected individuals on cART with prior viral suppression, self-reported missed doses are associated with a higher risk of virological failure. Increasing number of missed doses in the previous 4 weeks was associated with an increasing hazard of virological failure. Missing two or more consecutive doses of cART was reported on fewer than 4% of visits but was associated with 3.5 times increased risk of viral failure.

Although several other studies have collected longitudinal self-reported adherence information [1,27–29], we know of no other study that has used time-updated measurements of self-reported adherence to predict viral rebound. With this approach, we avoid the loss of information inherent in analyses that summarize adherence information over time. In addition, an individual's adherence pattern is allowed to vary in a dynamic way, which is a better reflection of reality and is supported by the finding that almost 50% of individuals reported a change in the number of missed doses over the study period. This approach gave a precise and sensitive estimate of the risk of viral rebound by missed doses after adjusting for a comprehensive list of potential confounders. Also important to note was that we considered several additional definitions of non-adherence in sensitivity analyses and our results were highly consistent, with similar effect estimates for all confounders.

The simplification of regimens will certainly have a positive effect on adherence and treatment outcomes [25,30], but the introduction of an increasing number of once daily regimens will not eliminate concerns about adherence to ART. We found evidence that individuals missing only one dose of ART on a once daily regimen are at 2.8 times increased risk of treatment failure, whereas those missing one dose on a twice daily regimen showed no increased risk. Although there were not sufficient numbers on either once daily or three times daily regimens to fully explore the effect of an interaction between missed doses and dosing frequency, these findings should be explored further and incorporated into future adherence definitions.

This study considered a large number of important confounders: clinical factors (including the previously unstudied effect of co-medication) as well as psychosocial factors such as stable partnership and health system factors such as physician experience. Independent of reported adherence to cART, several factors were significantly associated with an increased hazard of viral rebound. Individuals on NNRTI regimens were at a decreased risk of virological failure compared

Table 3. Exploring the association of use of any co-medication as well as co-medication use by individual indication with the rate of occurrence of viral rebound (unconfirmed RNA >500 copies/ml) using Cox proportional hazards models

Variables	Unadjusted model		Adjusted model*	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All co-medication†	1.52 (1.14–2.03)	0.004	1.44 (1.06–1.96)	0.02
Co-medication by indication‡				
Risk factors for cardiovascular disease§	1.07 (0.70–1.63)	0.75	1.01 (0.64–1.59)	0.97
Opportunistic infections	2.17 (1.50–3.14)	<0.001	1.80 (1.20–2.69)	0.004
Hepatitis C	1.69 (0.90–3.17)	0.10	1.73 (0.91–3.29)	0.09
Cancer	4.13 (1.32–12.88)	0.01	3.20 (1.01–10.17)	0.05

*Adjusted for intravenous drug use, baseline CD4$^+$ T-cell count, antiretroviral therapy (ART) regimen, number of previous ART regimens, physician experience, time virally suppressed at baseline and non-adherence (see Table 2). †For risk factors for cardiovascular disease, opportunistic infections, hepatitis C or cancer. ‡The indicator for taking any co-medication was replaced in the adjusted model by the four separate indicators of taking co-medication for the individual indication. §For dyslipidaemia, hypertension or diabetes.

with individuals on all other regimens, although previous studies have shown varied results [1,9,31]. Similar to other studies where suboptimal HIV management was associated with physicians who care for only a few HIV-infected patients [32–34], we found a significant association between lower physician experience and higher incidence of virological failure, although a recent study did not confirm these findings [31]. Individuals taking any co-medication for the treatment of risk factors for cardiovascular disease, OI, hepatitis C or cancer had a 1.4 times higher risk of viral rebound (see Table 3). Additional analyses suggested that this effect is largely driven by the taking of medication for OI, hepatitis C and cancer. Treatment for some OI, hepatitis C and cancer may result in side effects, drug interactions and potential treatment interruption and thus risk of virological failure.

The lack of an effect from co-medication taken for cardiovascular risk factors is encouraging news as an increasing number of treated individuals will probably be at risk for ART-induced metabolic disorders [35]. Our findings suggest that the condition of the co-morbidity and its treatment and not necessarily the additional pill burden of co-medication, are related to treatment failure. The effect of co-medication has not been studied previously and our findings have important implications for the management of an ageing HIV-infected population in need of both drug treatment for HIV and other chronic conditions.

Our data confirm recent evidence suggesting that different classes of cART regimens can require varying levels of adherence to maintain viral suppression [4,9]. However, previous studies did not include individuals on either boosted PI regimens or triple nucleoside regimens. Individuals on NNRTIs and triple nucleosides had lower rates of viral rebound than those on PI regimens with similar levels of self-reported adherence (Figure 1). It has been suggested that boosted PI regimens may provide forgiveability as well [36,37], however we did not find evidence to support this. This could be related to a selection bias with individuals with more treatment experience and greater adherence problems placed on boosted PIs due to higher resistance barriers or because of concerns related to drug interactions, for example, with methadone.

The rate of missing adherence information increased in proportion to the length of time the patients were under follow-up. As the adherence questionnaire is administered by interview with the clinician, this is suggestive of several potential problems. It is possible that the clinician has assumed to know the adherence of an individual from past information, although we know from our data and others that adherence is a dynamic process. Another issue could be that with the focus of health care on acute illnesses and with only short consultation times, physicians might only have time to discuss clinical aspects of a patient's care and therefore behavioural aspects, such as adherence, might be given a lower priority. Regardless of the reasons behind this finding, it is extremely important that clinicians find a way to address the adherence of their patients as part of their regular follow-up.

Our data have several limitations. As discussed above, patients are asked about their adherence by their clinician, and therefore may be reluctant to admit non-adherence. However, previous studies have failed to find a relationship between self-report and social desirability bias [15,16] and one study even found that anonymous surveys increased individuals' reluctance to disclose non-adherence [17]. We cannot, however, rule out the possibility that changing the mode of administration of the questionnaire would minimize potential social desirability bias and provide more accurate responses. Second, missing adherence information was excluded from the analysis leading to a loss of information. However, several other methods of handling missing data provided consistent results. An in-depth study into adherence patterns may reveal a more meaningful way to impute adherence information for these patients, but it is beyond the scope of this study. Third, our results are limited to virally suppressed individuals on cART and therefore the effect of adherence on viral load for those who are not suppressed is unknown.

In conclusion, our simple two-item questionnaire, which is easy to implement in routine clinical practice, is an independent predictor for future viral failure in individuals with well-suppressed viral loads. Even though self-report is known to overestimate adherence and suffers from a ceiling effect [14,16,38], the questionnaire was sensitive enough to detect both the increased risk of missing one dose of ART on a once daily regimen and some level of forgiveness in twice daily regimens. Adherence should be monitored continuously and systematically in all HIV-infected individuals on cART. Self-report provides the most practical approach and, our instrument, with only two questions, provides a sensitive indicator of future virological failure. These results warrant further investigation in other populations and cultural settings.

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Disclosure statement

The authors declare no competing interests.

Additional file

The additional file 'Members of the Swiss HIV Cohort Study' can be accessed via the Volume 13 Issue 1 contents page for *Antiviral Therapy*, which can be found at www.intmedpress.com (by clicking on 'Antiviral Therapy' and then 'Journal PDFs').

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