



A dynamic measure of self-reported adherence to ART predicts virologic failure: the Swiss HIV Cohort Study (SHCS)

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Background: Achieving and maintaining viral suppression is one of the primary goals of treatment for HIV patients. Few studies have explored the predictive value of longitudinal self-reported adherence data on viral rebound.

Methods: The SHCS is a prospective cohort study with continuing enrollment of HIV-infected individuals aged 16 years or older. At semi-annual visits, both lab data and information on adherence is collected. Individuals in the Swiss HIV Cohort Study (SHCS) on ART, with RNA < 50 copies/ml over the previous 3 months and who completed ≥ 1 adherence questionnaire prior to June 1, 2006 were included.

Adherence: At each cohort visit, individuals are asked about missed doses in the previous 4 weeks. Non-adherence was defined as missing ≥ 2 doses of ART in the previous 28 days.

Statistics: 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 viral rebound, which was defined as two consecutive RNA >500 copies/ml with the event date being the first of these dates. For individuals who did not experience an event, follow-up was censored on July 1, 2006, on the date when cART was stopped for ≥ 45 days, date of loss to follow-up or death. Covariates that were potential confounders of the relationship between adherence and viral rebound were considered for inclusion in the analysis.

Results: 2638 patients were followed for 13,217 visits over a 3-year period. Missing ≥ 1 dose was reported on 25.0% of visits, missing ≥ 2 doses on 9.9% and missing > 1 consecutive dose on 3.4% of visits. A total of 97 (3.7%) patients experienced viral rebound. After controlling for potential confounding variables, non-adherence was significantly associated with increased risk of viral rebound (hazard ratio (HR) 2.82, 95% confidence interval (CI): 1.76-4.50). Other variables significantly associated with increased risk of viral rebound were protease inhibitor intake, >5 previous cART regimens, seeing a less experienced physician, taking co-medication, and less time on cART (see Table).

Table: Association of baseline and time-varying covariates with the rate of occurrence of viral rebound (two consecutive RNA>500) using a Cox proportional hazards model

Variables	Adjusted model	
	Hazard ratio (95% CI)	p-value
IV drug use (current or past)	1.13 (0.72 – 1.79)	0.59
Increases in baseline CD4 of 100 (cells per 10 ⁹ /l)	1.07 (0.99 – 1.14)	0.07
PI regimen †	1.56 (1.04 – 2.34)	0.03
> 5 previous cART regimens at baseline	2.75 (1.65 – 4.61)	<0.001
Physician experience † (per 100 patients)	0.80 (0.68 – 0.95)	0.01
AIDS diagnosis	1.18 (0.77 – 1.82)	0.45
Co-medication ‡	2.42 (1.54 – 3.82)	<0.001
Time virally suppressed at baseline (per year)	0.91 (0.80 – 1.04)	0.18
Time on cART (per year)	0.91 (0.83 – 0.99)	0.04
Non-adherence: ≥ 2 missed doses *	2.82 (1.76 – 4.50)	<0.001

† Without any NNRTIs

‡ Number of patients treated by a physician at the time of patient's baseline visit

§ For cardiovascular problems, opportunistic infections, or hepatitis C

* In the previous 28 days

NA = non-adherence, PI=protease inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor

Sensitivity analyses:

In order to explore a potential threshold for non-adherence, we included non-adherence in the Cox model as number of missed doses in the previous 28 days (0, 1, 2, >2). In unadjusted analyses, there was no difference in the hazard of viral failure for individuals with perfect adherence compared to those with 1 missed dose in the previous 4 weeks, but for those with ≥ 2 missed doses the risk of failure increased significantly (1: HR 1.00, 95% CI: 0.69-1.44; 2: HR 1.89, 95% CI: 1.24-2.88; >2: HR 3.88, 95% CI: 2.75-5.48) (see Figure).

As an additional validation of the adherence measurement and to make our results comparable to other studies, non-adherence was calculated as taking <95% of doses. In an adjusted model, <95% adherence was significantly associated with increased hazard of viral rebound (HR 3.53, 95% CI: 2.02-6.20). The estimates for covariates were almost identical to the primary analysis.

Conclusions:

- A simple self-report adherence questionnaire measured repeatedly over time predicts viral rebound.
- Increasing number of self-reported missed doses of cART is associated with an increasing risk of virologic failure.
- The effect of co-medication has not been studied previously and our finding has important implications from the clinical and public health perspective for the current and future management of HIV-infected individuals.

Figure: Unadjusted hazard ratios (HR) and 95% confidence intervals for unadjusted Cox models of the effect of non-adherence on time to viral rebound.

