Adherence to and effectiveness of Highly Active Antiretroviral Treatment for HIV infection: assessing the bidirectional relationship

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The cohort project was submitted and approved, according to French legal obligations, by the Ethical Committee of the Cochin Regional Hospital (Paris Region).

Abstract
It is well-established that high adherence to HAART is a major determinant of virological and immunological success. Furthermore, psycho-social research has identified a wide range of adherence factors. Our objective was to assess the bi-directional relationship between adherence and response to treatment among patients enrolled in the ANRS CO8 APROCO-COPILOTE study. An econometric approach was implemented through a bivariate two-equation simultaneous system, studying the factors associated with both adherence and undetectability of HIV plasma viral load. Our results highlight that good biological results induced by adherence reinforce continued adherence. This strengthens the argument that patients who do not experience rapid improvements in their immunological and clinical statuses after HAART initiation should be prioritized when developing adherence support interventions. Furthermore, it rules out the hypothesis that HAART leads to "false reassurance" among HIV infected patients.

INTRODUCTION

Since the introduction of highly active antiretroviral treatment (HAART), adherence to medication has become a major treatment issue for HIV-infected patients. Epidemiological and clinical research has established that high adherence to HAART is a prerequisite for clinical and biological treatment success at the individual level[1-3] and has a positive effect on public health, as non-adherence may facilitate the development of viral strains resistant to current therapies[4]. Furthermore, psycho-social research has identified a wide range of socio-economic, cognitive, attitudinal and behavioral factors -including patient beliefs about HAART effectiveness- which are significantly associated with adherence in various patient groups and cultural contexts[5].

Previous research has principally focused on methods which separately identify factors associated with either treatment effectiveness[1-3] or adherence[5]. However, such methods do not fully explore the true bi-directional relationship between both these phenomena, ignoring the fact that effectiveness may well be "endogenous" to adherence, i.e. that adherence behavior may itself be influenced by the impact of treatment benefits embodied in biological and/or clinical outcomes. Patients may be more motivated to adhere to treatment if they experience positive clinical and biological treatment results[6] and/or receive positive information about treatment effectiveness.

The econometric approach[7], using simultaneous multiple equations to control for potential endogeneity, may be more appropriate than current bio-statistical models for evaluating the

bi-directional relationship between adherence and HAART effectiveness, as it enables the identification of predictors of adherence and controls for the impact of adherence on treatment success.

The French ANRS CO8 APROCO-COPILOTE cohort study[8], which followed HIV-1 positive patients from HAART initiation, provided the opportunity to compare a "standard" statistical model (Generalized Estimated Equation -GEE-) with an econometric simultaneous two-equation model in a longitudinal study of adherence.

MATERIALS AND METHODS

The French ANRS CO8 APROCO-COPILOTE

The cohort was designed to study the clinical, immunological, virological, and socio-behavioral progression of disease in HIV-1 positive individuals who started a treatment regimen (enrollment=M0) including a protease inhibitor (PI)[1] in 47 centers throughout France between May 1997 and June 1999. Only PI-naive patients were included. Patients with acute HIV syndrome were excluded. Medical and socio-behavioral data were gathered at months 0 (i.e. M0), 1, 4, 12, 20, 28, 36, 44, 48, 52, 60, 72, 84, 96, 108, corresponding to patient visits. We analyzed data collected until December 2006.

Medical data. At each patient visit, the HIV care provider listed the antiretroviral regimen prescribed and completed a medical questionnaire which included clinical and laboratory data (CDC clinical stage, CD4 cell count, Viral Load -VL-). All VL levels were prospectively

[1] In 1997, the only triple therapy available was a PI based regimen. Therefore, this cohort corresponds to the first generation treated with HAART in France.

measured by the assay routinely available in each center. Three assays were approved in France at study initiation: RT-PCR (Amplicor, Roche), bDNA (Quantiplex, Chiron) and Nasba, with lower limits of detection of 200, 500 and 400 copies of HIV-1 RNA/ml respectively. VL titers were considered undetectable if they were lower than the threshold values specific to each center's assay. The medical questionnaire at enrollment collected retrospective data about each patient's HIV history: transmission category, time since diagnosis and antecedents of antiretroviral treatment.

Socio-behavioral data. At enrollment, a self-administered patient questionnaire collected social and demographic information including age, gender, education, marital status, employment status and housing conditions. It also collected information about depressive symptoms, alcohol consumption, HIV-related self-reported symptoms, and beliefs[9] regarding treatment effectiveness. This information was updated using identical questions at each follow-up visit.

Depression was measured using the French version of the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item scale[10] commonly used in studies involving HIV-infected patients. Although not a tool for clinically diagnosing depression, a CES-D score ≥16 is considered indicative of significant depressive symptoms.

Two questions examined alcohol consumption over the previous 7 days (frequency and quantity). Patients were considered daily drinkers if their average daily alcohol consumption was ≥1 units [11].

A French version of the 13-item HIV symptom index[12-15] collected information about self-reported symptoms. From month 1 (M1) onwards, patients reported any experience they had had in the previous 4 weeks of the following symptoms: diarrhea, nausea, stomach pain, headache, taste change, itching skin, muscle pain, heartburn, mouthsores, vomiting, fever, kidney stones or fatigue. The sum of all these self-reported symptoms was scored to quantitatively assess perceived side effects. The patient questionnaire also contained a separate list of nine symptoms related to possible manifestations of lipodystrophy[16].

From M1 onwards, patients rated HAART treatment as very effective, effective, somewhat effective and ineffective. As few patients (<5% at each interview) reported the latter two options, the variable was dichotomized (very effective *versus* other).

Five questions about treatment adherence were also included in all self-administered questionnaires, in accordance with the AIDS Clinical Trial Group[17] methodology. Patients were first asked to fill out a detailed table, writing down the number of pills they had actually taken during the previous four days, for each drug in their HAART regimen. Then, on a 4-point scale they indicated whether they had "totally", "almost totally", "partially" or "not at all" taken their prescribed doses of HAART. They were also asked if they had ever taken their full daily dose of prescribed drugs all at once during the same period and whether they had not followed their medication schedule on several occasions. Finally, they were asked whether they had skipped a dose during the previous weekend. As self-questionnaires tend to underestimate non-adherence due to memory bias, we used a dichotomous measure of adherence in order to have a robust measure of adherence for statistical analysis[18]. Patients were classified as "adherent" if they detailed that they had taken 100% of their prescribed doses. Among these patients, those who subsequently declared that they: a) had skipped a dose during the previous week-end b) had "almost totally" followed their HAART regimen, c)

did not follow their medication schedule on several occasions or d) took their full daily dose all at once on at least one occasion during the four days prior to the visit, were all reclassified as “non-adherent”. All other patients were classified as “non-adherent”.

Statistical analysis

GEE models

Two separate equations using adherence and treatment effectiveness respectively as the dependent variables and employing the dichotomized variables (“adherent” versus “non-adherent” and “undetectable” versus “detectable” VL respectively) were first estimated using GEE models[19,20]. GEE has been widely used in the biostatistical literature[21] as it takes into account intra-individual correlations between repeated observations in longitudinal settings. It is a semi-parametric approach using an extension of the quasi-maximum likelihood[22-24] method to longitudinal data. In our estimations, we used a probit link. In order to select a working correlation structure R, we first calculated the Quasi-likelihood Information Criterion (QIC)[25] for several popular working correlation structures including an independent ($R = I$), an exchangeable ($R_{jk} = \alpha, j \neq k$), and a first-order autoregressive ($R_{jk} = \alpha^{|j-k|}, j \neq k$) working correlation matrix. We chose to use the correlation structure with the smallest QIC for our analysis.

Econometric model

To capture the extent of bi-directional interaction between adherence and treatment effectiveness, we applied a simultaneous two-equation model to the same set of data. In this joint model, the longitudinal nature of data was taken into account through a random-effects

specification[26-28]. Hence, we estimated the following random-effects bivariate probit model:

$$\begin{cases} ADH_{it}^{*} = x_{1it}^{'}\beta_1 + \varepsilon_{1it} \\ EFF_{it}^{*} = x_{2it}^{'}\beta_2 + ADH_{it}\gamma_2 + \varepsilon_{2it} \end{cases} \quad (I)$$

$$ADH_{it} = 1 \text{ if } ADH_{it}^{*} > 0$$
$$EFF_{it} = 1 \text{ if } EFF_{it}^{*} > 0$$

$$\varepsilon_{it} = \begin{pmatrix} \varepsilon_{1it} \\ \varepsilon_{2it} \end{pmatrix} = \begin{pmatrix} v_{1i} \\ v_{2i} \end{pmatrix} + \begin{pmatrix} \eta_{1it} \\ \eta_{2it} \end{pmatrix} = v_i + \eta_{it}$$

$$\eta_{it} \mapsto N(0, \Sigma_\eta)$$

$$v_i \mapsto N(0, \Sigma_v)$$

$$\Sigma_\eta = \begin{pmatrix} \sigma_{\eta 1}^2 & \sigma_{\eta 12} \\ \sigma_{\eta 12} & \sigma_{\eta 2}^2 \end{pmatrix}$$

$$\Sigma_v = \begin{pmatrix} \sigma_{v1}^2 & \sigma_{v12} \\ \sigma_{v12} & \sigma_{v2}^2 \end{pmatrix}$$

where $ADH_{it} = 1$ if the individual *i* is highly adherent at time *t* ($ADH_{it} = 0$ if the individual *i* is not) and $EFF_{it} = 1$ if treatment effectiveness is high at *t* (i.e. if viral load is undetectable at *t*) ($EFF_{it} = 0$ if viral load is detectable at *t*). We assume that ADH_{it}^{*} is determined by a set of exogenous variables x_{1it}, and EFF_{it}^{*} is simultaneously determined by ADH_{it}^{*} and a set of exogenous variables x_{2it}. If adherence and treatment effectiveness interact bi-directionally, then correlated error terms are expected, i.e. some unobserved variables correlated with one another may explain both the patient's adherence behavior and his/her treatment response. For instance, patients who naturally tend to invest in healthcare may have a greater tendency to be

highly adherent and may show a better response to treatment. The random-effects specification implies that error terms are decomposed both in unobserved individual specific effects v_i and time-specific chance events η_{it}. Hence the correlation between residuals might be induced by either the correlation between patient-specific disturbances (e.g. a "structural propensity" for investment in one's own health) or between time-specific residuals (e.g. a change in treatment experience and/or illness between two time periods). Note that x_{1it} represents a set of instruments for ADH_{it}. In contrast to the two-equation model, a separate estimation of both the adherence and effectiveness equations would lead to asymptotically biased estimates if their disturbances were correlated.

It should be acknowledged that the recursive system (I) used in this simultaneous two-equation model (one dependent variable of one equation present on the right-hand side of the other equation) is logically consistent, in turn implying that a reduced form exists. Furthermore, it can be fully identified[7], i.e. there is a unique way to recover the structural form parameters from the reduced equation. As our model involved dichotomous dependent variables, for which standard instrumental techniques are inappropriate[7], we used a full information method of estimation. This estimation, performed using the "bivariate" command in LIMDEP version 9.0. , treats all equations and parameters jointly, thus ensuring that the most efficient estimates are obtained.

Empirical estimations

Estimations were performed over a 9-year period (M1 – M108).

In both the GEE and econometric models, patient, disease and treatment-related factors -all found to be significantly related to adherence in previous research- were initially introduced

into the adherence equation[21]. Patient variables included: age, educational level, employment status, housing conditions, marital status, being a migrant, depression status and finally, level of alcohol consumption. Disease-related variables included: HIV transmission mode, time since HIV diagnosis at inclusion and CDC clinical stage. Treatment-related factors included: whether the patient was HAART naive or not at inclusion, and, for each visit - a) the number of perceived toxicity-related symptoms and b) whether she/he was still receiving a regimen including a **PI**. In addition, patients' "subjective" beliefs regarding treatment effectiveness and "objective" measures of treatment success (i.e. increased CD4 cell counts since inclusion) were used. This latter measure referred to the most recent test results known to the patient before making a decision concerning drug intake at *t* and thus were indexed at *t-1*. As HIV-infected adults with a CD4 cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy have mortality rates similar to those of the general population[29], we also tested the variable $CD4_{t-1}$> 500-yes/no as an alternative to continuous CD4 cell count gains. Furthermore, we tested the interaction between "objective" and "subjective" treatment effectiveness measures.

In both models, the following variables, known to affect HAART effectiveness (i.e. whether VL was undetectable or not), were initially introduced in the treatment effectiveness equation: patient's age; VL and CD4 cell count at baseline; clinical stage at each assessment; being HAART naive at inclusion; whether the patient received a treatment including Invirase[2] at inclusion; time since initial HIV diagnosis at baseline; duration of exposure to HAART; variables related to co-morbidities and/or psychological health status (co-infection with Hepatitis C Virus, depression) during the course of treatment. Naturally, the adherence variable itself was also introduced into the treatment effectiveness equation.

[2]Unboosted saquinavir (Invirase) has been shown to be less effective than other PIs[30]

RESULTS

Descriptive Analysis

The study comprised 1,026 patients. Table 1 describes their baseline socio-demographic and clinical characteristics.

The proportion of patients treated with PIs declined over the full study period (M12=88%, M108=48%), despite all initiating HAART with regimens including at least one PI. At M1, 35% received a twice-daily regimen, the other 65% having a minimum of 3 daily doses. At M108, 32% were prescribed a once daily regimen, 67% twice-daily and only 1% more than 3 daily doses.

At M108, 73% had an undetectable plasma VL (Figure 1). Although the aggregated percentages of patients with this virological outcome stabilized at >60% after M12, analysis of individual patient paths revealed certain state changes (i.e. VL increases after periods where it had been controlled). Descriptive statistics (Figure 1) also suggest an evolution in the percentage of highly adherent patients over the study period: 65% at M0, 54% at M4 and then a progressive increase to peak at 67% by M28. Thereafter it stabilized at around 65% except during the last two observation periods (M96, M108) where percentages of highly adherent individuals had significantly increased (73%), due perhaps to the possibility that those still participating at M96 and M108 were better adherers than those who had dropped out. This point is explored in more detail in the discussion section.

Figure 2 shows that CD4 cell count after baseline increased quickly over the whole study population until M36, the median increase being 235 cells/mm^3. It then stabilized at around 270 cells/mm^3. Figure 2 also shows a significant positive relationship at most visits between

increased CD4 cell count after baseline and subjective patient beliefs about HAART effectiveness. Those deeming treatment to be very effective had, logically, higher CD4 gains.

Over the whole study period (M1 – M108), the median number of self-reported side-effects varied between 3.8 and 9.8. No side-effects were reported in only 6% of all assessments. A third of the respondents reported depressive symptoms at every visit.

Comparison of separate and joint multivariate estimations

Estimations were based on a total of 4,770 observations. Each patient attended an average of 5.6 visits during the study period. Table 2 presents both the separate estimations of adherence and virological success of HAART using GEE as well as the joint estimation of these same two variables, based on the simultaneous equation econometric model. Column (i) presents the specification where CD4 cell count gain was introduced separately. Column (ii) presents the specification containing the interaction between CD4 cell count gain and subjective beliefs about treatment effectiveness.

A number of variables previously found to be "determinants" of adherence were identified using the GEE model: older age[31], living in a stable relationship[32], HAART regimens with fewer daily drug intakes[21] and positive beliefs about the effectiveness of HAART[14] were all significantly associated with high adherence. Instead, depressive symptoms[33] and daily alcohol consumption[5] were associated with poor adherence. Table 2 shows that these same variables were also found to be significantly related to adherence in the joint econometric estimation. This latter model also highlighted certain additional *social* (e.g. poor housing

conditions), *clinical* (e.g. shorter time since initial HIV diagnosis, treatment with PI-containing HAART regimen, less advanced HIV clinical stage, HIV-infection through injecting drug use[33]) and *adverse event* (e.g. higher number of self-perceived side-effects[13]) variables significantly associated with poor adherence. Although immunological parameters did not reach the level of statistical significance (either directly or when crossed with patient beliefs about HAART effectiveness), in the GEE estimation of adherence, CD4 cell count gain after baseline as well as interaction between immunological status and patient beliefs about HAART effectiveness were both found to influence adherence in the joint estimation. After adjustment for all other factors, even those patients who had subjective doubts about HAART effectiveness tended to be more adherent when they were aware of their CD4 cell count gains. Similar results were obtained when substituting the continuous variable (CD4 cell count gain after baseline) with a CD4 cell count level higher than 500 (whether reached by patients or not).

Table 3 displays the Quasi-likelihood Information Criterion (QIC) for three different working correlation structures using both the adherence and effectiveness equations. Analysis of the table suggests that the "exchangeable" structure should be favored. In turn this result supports the use of the random-effects specification, which also assumes that the correlations between any two observations are stable. When patient heterogeneity is modeled explicitly through the random-effects specification, our results underline that unobserved patient characteristics significantly account for adherence behavior. It should also be stressed that in the simultaneous model, the co-variances between disturbances of both equations (Table 2) are significant, thus confirming the statistical appropriacy of taking the endogenous nature of adherence into account[3]. On the one hand, the correlation between patient-specific error terms

[3]Endogeneity is supported by a Hausman test, run on the corresponding linear probability model to examine whether adherence is an exogenous variable in the effectiveness equation. This test led to the exogeneity of adherence being rejected (significance level $p = 0.0004$). Specification (ii) (see Table 2) was used for the test.

is positive and significant, suggesting that intrinsic patient features result in some patients being both better adherents and respondents to treatment. On the other hand, the correlation between time-varying disturbances is positive and significant (Table 2), suggesting that unobserved time-varying factors inducing a positive change in health between any two time periods are correlated with unobserved factors having a positive impact on adherence behavior. This latter effect may indeed capture the indirect impact of improvements in health outcomes (EFF_{it} in (I)) on adherence behavior.

Both the separate GEE estimation and the effectiveness equation of the joint model confirm the positive impact of adherence on the probability of having an undetectable VL at any visit, after adjusting for other biological and clinical factors already known to be predictors of HAART success (i.e. lower viral load[34], no previous antiretroviral HIV drugs[35] and not receiving a regimen which included unboosted Invirase at HAART initiation[36]). Both also confirm that depressive symptoms are an independent predictor of a reduced likelihood of virological success with HAART. Advanced clinical HIV stage was not associated with treatment success in either estimation. Older age, found to be significantly associated with HAART effectiveness in the GEE model, was not significant in the joint model whereas Hepatitis C Virus co-infection and longer time between HIV diagnosis and HAART initiation were both associated with HAART effectiveness in the joint model only.

DISCUSSION

The diffusion of HAART to treat HIV infection in developed and developing countries has generated a huge body of research highlighting not only the importance of high adherence to

medical regimens for increased treatment effectiveness but also the complex array of socio-demographic, psycho-social and cultural factors affecting adherence behaviors. With a few exceptions in the study of Viral Load dynamics[37-39], the statistical methods commonly used in epidemiological and psychosocial research on adherence only permit separate estimations of the dependent variables, used as proxies of treatment effectiveness and of adherence, to be carried out.

Simultaneous-equation estimations have already been used in various fields of clinical research (e.g. studying the impact of smoking on birthweight[40]). However, to our knowledge, apart from one study showing that the probability of remaining in HIV clinical trials was associated with increased CD4 cell count[6], no previous research using such econometric methods has taken the hypothesis that positive biological and clinical HAART outcomes, as a result of high adherence, may themselves reinforce high adherence.

In this study, we compared the application of two estimation methods to the same set of longitudinal data from the APROCO-COPILOT cohort study of HIV-infected patients initiating a PI-containing HAART regimen. The comparison suggests that a joint estimation of adherence and treatment effectiveness, using a two-equation simultaneous econometric model controlling for endogeneity, may capture more determinants of adherence than do separate GEE estimations, which is the most common method found in the literature. There are two main modeling differences between separate GEE equations and joint random-effects models. First, the longitudinal nature of the data is modeled differently. The GEE approach treats correlations between repeated observations as measurement errors. In the random-effects approach, individual-specific disturbances are considered the sources of correlations between repeated observations. Second, unlike the separate GEE equations, the joint

estimation model takes into account a possible reciprocal relationship between adherence and treatment effectiveness. One could argue that for a comparison of separate and joint estimations it would have been more appropriate to use a random-effects probit model for both estimations. Indeed, we did investigate this method and it provided very similar results to those of the GEE model presented here. This is not surprising since the conditional mean functions are the same for both the GEE and random-effects models[41].

Certain studies in existing psycho-social literature describe contradictory findings about adherence determinants. For example some highlight the significant, negative impact of depression and alcohol consumption on adherence, whereas others, controlling for these same variables, do not[14]. This may be due to the limitations of statistically separate estimations of adherence which do not take into account the reciprocal effect of treatment outcomes on adherence behavior itself.

Furthermore, controlling for endogeneity provided more precise identification of factors associated with treatment success and adherence, as the genuine effect of variables can be separated from the role of unobserved factors, which explain both treatment success and high adherence behavior. This might explain why patient age was significant in our GEE model but not so in the joint one - if unobserved factors were partially captured by observed variables (such as age) in the separate estimation of the effectiveness equation, then the significance of observed variables might well be different in the joint model.

More importantly, only joint estimation identified a significant relationship between a positive HAART immunological outcome and high adherence, suggesting that treatment outcomes have a definite impact on adherence behaviors. Previous psycho-social research has already emphasized the role of perceived effectiveness of HAART (i.e. patients' beliefs about the benefits and risks of treatment[42] and their subjective experience with therapy during

treatment[12]) whose impact on adherence behavior is also confirmed in this study through the "time-varying beliefs" variable. However, only joint estimation was able to fully capture the longitudinal dynamic of interaction between objective improvements in immunological treatment outcomes and subjective perceptions about HAART effectiveness.

Another added value of applying a joint model to our data is that it not only highlights the direct impact of treatment outcomes on adherence through observed variables but also underlines the indirect impact of viral outcomes on adherence behavior through the correlation between time varying residuals η_{1it} and η_{2it}. This correlation was shown to be positive and significant (Table 2).

From a methodological point of view our results show that a two-equation approach (i.e. the joint estimation of adherence and effectiveness equations) may be the most appropriate **means** of capturing the relationship between adherence and treatment outcomes. The random-effects specification makes performing the joint estimation in a longitudinal framework possible. The joint study of two dependent variables requires a structural model: decomposing the error term into two parts makes it possible to specify the source of the relationship between the two phenomena. In this paper, correlation is assumed to arise from individual-specific error terms and from temporal disturbances. Note that our econometric modeling relies on the normality assumption of residuals. By contrast, the GEE method is not suited to handling simultaneity problems.

It should be acknowledged that the number of adherence observations in our analysis decreased over the study, with analysis at M4 and M108 based on 647 and 104 observations, respectively (Figure 1).

This decrease can be accounted for by three main phenomena: missed clinical visits, incomplete self-administered questionnaires and study drop-out (death or lost to follow-up). Consequently, checking for selection bias in our results is important: if poor adherers are responsible for missing data, our estimations may be biased. To control for this, we estimated

a trivariate probit model which included a selection equation (i.e. a missingness equation). Baseline fixed variables, last available CD4 cell count and viral load were all considered in order to identify the variables associated with missing data, for whatever reason, at any visit. We tested whether the correlation between the adherence and selection equations and the correlation between the effectiveness and selection equations were jointly equal to zero. With the test's p-value equaling 0.07, we concluded that our results were not affected by a selection bias. Note that the trivariate probit model was not estimated on panel data.

Our model of adherence behavior assumes that past experience of adherence has no effect on current adherence behavior. In order to evaluate this assumption, we tested whether ADH_{it-1} had an impact on ADH_{it}. We applied Wooldridge's [43] approach which led us to estimate the following model:

$$ADH_{it}^{*} = x_{1it}^{'}\beta_1 + ADH_{it-1}\alpha_1 + ADH_{i1}\alpha_2 + \overline{x_{1i}^{'}}\alpha_3 + a_{1i} + \eta_{1it}$$

where ADH_{i1} is the observation of adherence at date 1 (i.e. the initial observation) and $\overline{x_{1i}^{'}}$ the average of the explanatory variables over time.

We found that ADH_{i1} and ADH_{it-1} did not have a significant effect on ADH_{it}, as suggested both by the individual p-values and the Wald test evaluating whether the coefficients of ADH_{i1} and ADH_{it-1} were jointly equal to zero. Therefore we may conclude that being adherent in the past is not a key factor to current adherence behavior. Note however that we also found that time invariant patient inertia affected adherence behavior (i.e. some individuals had a greater tendency to be adherent at all assessments). Further research into the roles of state dependency and unobserved heterogeneities for adherence behaviors is required.

Beyond these methodological aspects, the demonstration of a bi-directional relationship between HAART adherence and effectiveness has two major implications for both clinical practice and psycho-social interventions aimed at reinforcing adherence behaviors. First, it strengthens the argument that patients not experiencing rapid improvements in their immunological and clinical statuses after HAART initiation should be prioritized when implementing adherence support interventions. Such interventions should start as soon as possible after treatment initiation and may be more cost-effective in that subgroup of patients,

as they would induce a “virtuous” circle between treatment adherence and effectiveness. This may also be particularly useful in low-resource settings faced with HAART delivery logistical issues. Second, this bi-directional relationship invalidates the hypothesis that HAART may lead to “false reassurance” among HIV-infected patients, i.e. that patients may become less adherent when they start experiencing good treatment outcomes. In reality, the opposite is true. This fact supports the argument for focusing interventions targeting the prevention of treatment failure, due to a lack of adherence, on those patients who do not experience the best improvements in their health status. Of course, our results come from analysis of data from a cohort of HIV individuals living in a developed country which provides a relatively high level of information and early access to HAART. Further research is required to verify whether our results hold for other HIV-positive populations. Our approach may also be useful for all chronic diseases where treatment effectiveness is dependent on long-term adherence to care and medication and where treatment benefits (including improved health status and quality of life) may in turn positively influence such adherence.

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Table 1: Population description at baseline (n = 1, 026) and Treatment characteristics at Month 1

Baseline characteristics	Mean (SD)	Median	%
Age (years)	37.5 (9.5)	36.0	
Male			77.5%
Born in an European Union country			72.0%
University degree			17.0%
Married or living with a partner			52.9%
Employed			54.0%
Depressed (CES-D score ≥ 16)			42.0%
Daily alcohol consumption			18.0%
Time since HIV seropositivity was detected *(months)*	56.6 (50.2)	47.0	
Co-infected with HCV**			23.1%
HIV transmission: drug injection			17.0%
HIV transmission: homosexual contact			41.0%
HIV transmission: heterosexual contact			32.0%
HIV transmission: other			10.0%
HAART*-naive at inclusion			44.0%
Clinical stage CDC: C			20.0%
CD4 cell count	298.0 (204.0)	279.0	
Log10 viral load	4.4 (1.0)	4.5	
Treatment characteristics at Month 1			
Number of drug intake each day *>2*			64.7%
Number of self-perceived side effects		4.5	

*Highly Active Antiretroviral Therapy
**Hepatitis C virus

Table 2: Estimations of the adherence and treatment equations (separate models and joint estimations)

(n = 4770)

	(i)				(ii)			
	Separate estimations using GEE[a]		**Joint model (random-effects bivariate probit model)**		**Separate estimations using GEE[a]**		**Joint model (random-effects bivariate probit model)**	
	coef	p	coef	p	*coef*	*p*	*coef*	*p*
ADHERENCE EQUATION (dependent variable adherent = 1)								
Age at *t*	0.03	<0.01	0.03	<0.01	0.03	<0.01	0.03	<0.01
Has a university diploma a *t*	-0.04	0.57	0.00	0.99	-0.04	0.60	0.00	0.99
Is employed at *t*	-0.01	0.77	0.04	0.32	0.02	0.75	0.04	0.33
Has good housing conditions at *t*	0.03	0.12	0.04	0.04	0.04	0.10	0.04	0.04
Married or living with a partner at *t*	0.13	<0.01	0.21	0.00	0.15	<0.01	0.21	<0.01
Born in a European Union country	0.04	0.91	0.06	0.28	0.04	0.95	0.06	0.28
HIV transmission: drug injection	-0.21	0.08	-0.12	0.05	-0.21	0.07	-0.12	0.05
HAART[c]-naive at inclusion	-0.02	0.78	-0.06	0.19	-0.02	0.78	-0.06	0.19
Time since HIV seropositivity was detected at baseline	0.00	0.48	0.00	0.03	0.00	0.49	0.00	0.03
Depressed at *t (CES-D score ≥ 16)*	-0.21	<0.01	-0.26	<0.01	-0.21	<0.01	-0.26	<0.01
Daily alcohol consumption at *t*	-0.13	0.05	-0.14	0.02	-0.12	0.05	-0.14	0.02
IP[d] in HAART[c] treatment at *t*	-0.08	0.08	-0.09	0.05	-0.08	0.09	-0.09	0.05
Number of drug intake each day at *t: >2*	-0.24	<0.01	-0.28	<0.01	-0.23	<0.01	-0.28	<0.01
Number of self-perceived side effects at *t*	-0.01	0.18	-0.01	0.01	-0.01	0.20	-0.01	0.01
Clinical stage CDC at *t*: C	0.15	0.06	0.18	<0.01	0.15	0.05	0.18	<0.01
CD4 > 200 at baseline	0.05	0.58	0.06	0.28	0.04	0.57	0.06	0.28
$(CD4_{t-1} - CD4t_0)/1000$	0.17	0.06	0.44	<0.01				
$(CD4_{t-1} - CD4t_0)/1000$ when HAART[c] is believed to be very effective					0.21	0.11	0.43	<0.01
$(CD4_{t-1} - CD4t_0)/1000$ when HAART[c] is believed to be effective/somewhat effective/ineffective					0.26	0.06	0.45	<0.01
Believes that HAART[c] treatment is very effective at *t*	0.10	0.09	0.15	<0.01	0.10	0.09	0.16	0.01
t	0.00	0.47	0.00	0.28	0.00	0.47	0.00	0.28
σ_{v1}			0.83[b]				0.83[b]	
EFFICACY EQUATION (dependent variable: undetectable VL = 1, detectable VL = 0)[e]								
Is adherent (versus non adherent) between(*t-1*) and *t*	0.13	<0.01	1.11	<0.01	0.14	<0.01	1.11	<0.01
Age at *t*	0.01	<0.01	0.00	0.71	0.01	0.01	0.00	0.71
Log10 viral load at baseline	-0.13	<0.01	-0.16	<0.01	-0.13	<0.01	-0.16	<0.01
CD4 > 200 at baseline	0.08	0.23	0.03	0.55	0.08	0.29	0.03	0.55
Clinical stage CDC at *t*: C	0.09	0.24	0.08	0.17	0.09	0.25	0.08	0.17
HAART[c] naive at inclusion	0.57	<0.01	0.72	<0.01	0.57	<0.01	0.72	<0.01
Has a treatment including Invirase at baseline	-0.23	<0.01	-0.26	<0.01	-0.22	0.02	-0.26	<0.01
Co-infected with HCV[f] at *t*	0.11	0.36	0.21	<0.01	0.11	0.21	0.21	<0.01
Depressed at *t* - 1 (CES-D score ≥ 16)	-0.15	<0.01	-0.15	<0.01	-0.14	<0.01	-0.15	<0.01
Time since HIV seropositivity was detected at baseline	0.00	0.21	0.00	0.04	0.00	0.21	0.00	0.04
t	0.00	<0.01	0.00	<0.01	0.00	<0.01	0.00	<0.01
σ_{v2}			0.92[b]				0.92[b]	
Covariance between individual effects			0.07	<0.01			0.07	<0.01
Covariance between error terms			0.10	<0.01			0.10	<0.01

[a]Generalized Estimated Equation (exchangeable correlation matrix)

[b]significant (likelihood ratio test)

[c]Highly Active Antiretroviral Therapy

[d]Protease Inhibitor

[e]<200, 400 or 500 copies of HIV-1 RNA /ml depending on the center

[f]Hepatitis C virus

In specification (i) the variable $(CD4_t - CD4t_0)$ is included as a plain covariate (i.e. not interacted with another covariate) in the adherence equation

In specification (ii) the interaction terms between the variable $(CD4_t - CD4t_0)$ and patient beliefs about treatment efficacy are introduced

We also excluded from the models those covariates which proved to be not statistically significant.

The results on the remaining significant variables were not qualitatively different for either the separate or joint estimations

Table 3: Quasi-likelihood Information Criterion (QIC) for various candidate working correlation structures

		Working correlation matrix		
		Independent	Exchangeable	First-order autoregressive
Adherence equation	QIC	6894	6888	6890
Efficacy equation	QIC	7657	7631	7674

Figure 1: Evolution of the percentage of highly adherent patients and of the percentage of patients with undetectable viral load from Month 1 (M1) to Month 108 (M108)

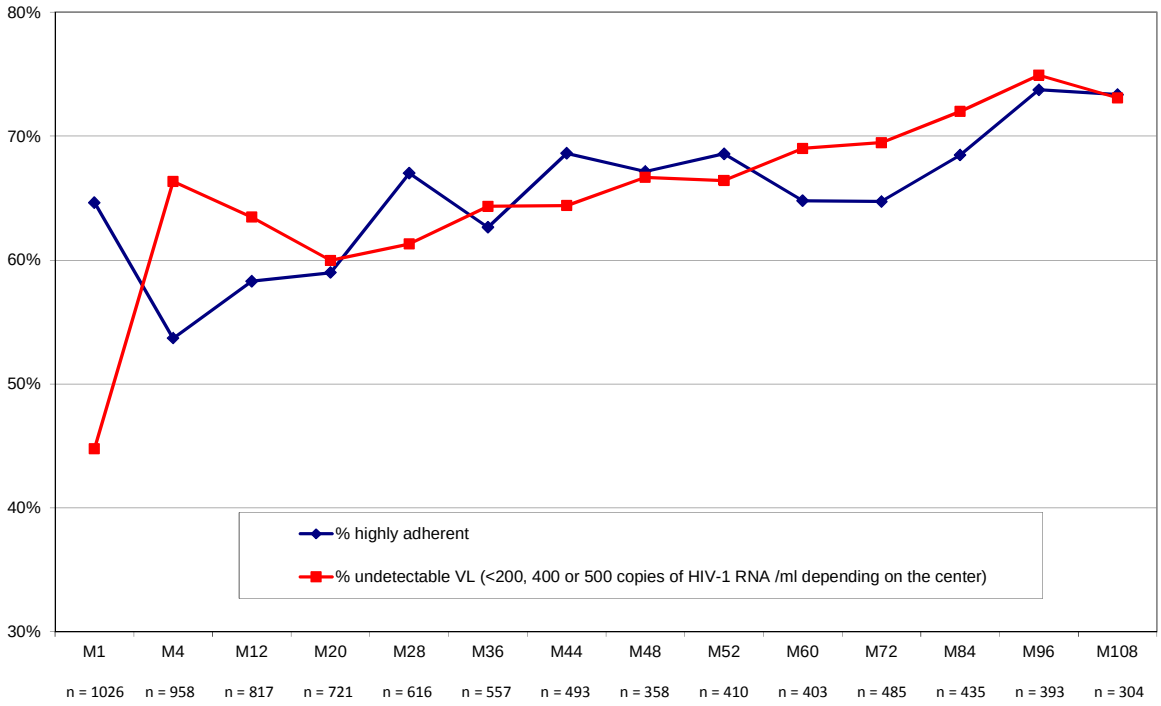
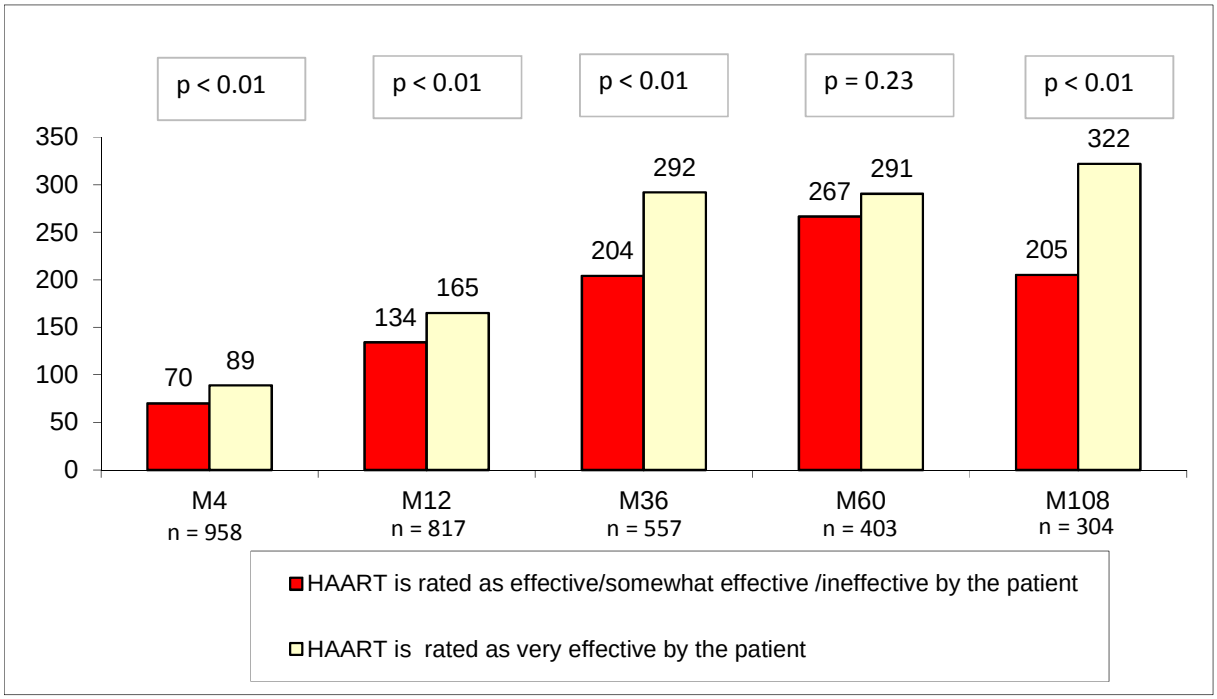


Figure 2: Median increase in CD4 cell count since Month 0 (M0) and p values of the Wilcoxon rank sum test comparing patients rating HAART as very effective and those rating HAART as effective/somewhat effective and ineffective



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