



**HAL**  
open science

## Therapeutic non adherence: a rational behavior revealing patient preferences ?

Karine Lamiraud, Pierre-Yves Geoffard

► **To cite this version:**

Karine Lamiraud, Pierre-Yves Geoffard. Therapeutic non adherence: a rational behavior revealing patient preferences ?. 2006. halshs-00589121

**HAL Id: halshs-00589121**

**<https://shs.hal.science/halshs-00589121>**

Preprint submitted on 27 Apr 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



## PARIS-JOURDAN SCIENCES ECONOMIQUES

48, Bd JOURDAN – E.N.S. – 75014 PARIS  
TEL. : 33(0) 1 43 13 63 00 – FAX : 33 (0) 1 43 13 63 10  
www.pse.ens.fr

**WORKING PAPER N° 2006 - 48**

### **Therapeutic non adherence: a rational behavior revealing patient preferences ?**

**Karine Lamiraud**

**Pierre-Yves Geoffard**

**JEL Codes : C33, C35, C81, D12, D61, I12**

**Keywords : Drug valuation method, revealed preferences,  
endogenous adherence behavior, panel bivariate probit  
estimation, HIV**

Therapeutic non adherence: a rational behavior  
revealing patient preferences ?

Karine Lamiraud and Pierre-Yves Geoffard

November 2, 2006

### Authors

Karine Lamiraud, Institute of Health Economics and Management (IEMS), University of Lausanne, Switzerland, and Pse (Paris-Jourdan)

Pierre-Yves Geoffard, Pse (Paris-Jourdan), Institute of Health Economics and Management (IEMS), and CEPR.

**Corresponding author:** Karine Lamiraud, Institute of Health Economics and Management (IEMS), DEEP-HEC, University of Lausanne, Extranef, 1015 Lausanne - Dorigny. Phone.:00 41 21 692 34 36; Fax: 00 41 21 692 36 55 ; E-mail: [karine.lamiraud@unil.ch](mailto:karine.lamiraud@unil.ch)

This paper was presented at the 13th European Workshop on Econometrics and Health Economics in Venafro.

## **Therapeutic non adherence: a rational behavior revealing patient preferences?**

### **Abstract**

This paper offers an indirect measure of patient welfare based on whether patients comply with the prescription they receive. Adherence behavior is supposed to reveal patients' subjective valuations of particular therapies. We write a simple theoretical model of patient adherence behavior, that reflects the trade-off between perceived costs and observed regimen efficacy. A discrete choice framework is then used for the estimation, ie the comparison of the incremental benefit of drug intake between two regimens. Consequently, the empirical analysis is based on the identification of patient and drug characteristics associated with adherence. The econometric approach is implemented through a bivariate panel two-equation simultaneous system studying jointly the factors associated with adherence and response to treatment. The data come from a randomized clinical trial conducted in France between 1999 and 2001 and comparing the efficacy of 2 tritherapy strategies in HIV disease.

Both the theoretical and empirical results suggest that, for comparable clinical efficacy and toxicity levels, a higher adherence level is associated with higher patient welfare, thus adding valuable information to conclusions drawn by a mere biostatistical analysis. Therefore, from the perspective of the patient, the adherence-enhancing drug must be favored. Our results based on panel data also stress that unobserved patient characteristics account substantially for drug valuation and that the assessment evolves during the course of the treatment. Furthermore, we provide a new framework for the analysis of adherence data. The microeconomic framework highlights that non adherence is an endogenous behavior, thus suggesting new ways for improving adherence.

**KEYWORDS:** drug valuation method, revealed preferences, endogenous adherence behavior, panel bivariate probit estimation, HIV

## 1 Introduction

Whereas the valuation of health care strategies is usually based on stated preferences toward hypothetical choices presented in questionnaires, this paper aims at offering an indirect measure of patient welfare based on observed individual behaviors in real choice situations. The key assumption is that observed choices reveal individual subjective preferences, and may be used to assess consumer welfare. Our proposed estimator for comparing patient well-being between various therapies depends on whether patients adhere to (respect) the treatment they receive.

Adherence is usually defined as “the extent to which a person’s behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice ”(Haynes, 1979). In this paper, we will lay the emphasis upon adherence to medication regimens, especially drug regimens in HIV disease. Since the introduction of highly active antiretroviral treatment (HAART) including the powerful but demanding protease inhibitors (PI), adherence has become a major issue in the treatment of HIV patients. In particular, numerous studies show that medication failure rates increase sharply with decreasing levels of adherence (Haubrich et al., 1999; Bangsberg et al., 2000; Nieuwkerk et al., 2001). Traditionally, health care researchers have regarded non-adherence as the result of irrational or at best misinformed behavior. We argue that patient compliance is a true choice made by the patient and that consequently compliance rates reflect patient valuations of particular therapies. As a result, adherence behavior may provide information that is useful in the evaluation of the treatment.

Within a rational choice microeconomic framework, we begin by modeling the adherence behavior as the patient trade-off between perceived costs and observed regimen efficacy before providing an econometric pattern for the estimation. Relying on a discrete choice model, the empirical analysis will focus on identifying patient and drug characteristics associated with non adherence while controlling for the impact of adherence on health outcome. The econometric approach is then implemented through a panel two equation system studying jointly the factors associated with adherence and response to treatment. Finally, we present the results of our estimations: we lay the emphasis upon the major implications of our study as far as the comparative assessment of health strategies is concerned; furthermore, we underline to what extent our framework which takes adherence endogeneity into account makes it possible to renew the understanding of medication compliance and overcome some major methodological shortcomings of the

large body of literature dealing with adherence data.

## 2 A rational choice framework

### 2.1 Valuation methods: indirect versus direct approaches

First it should be stressed that the proposed valuation method is based on indirect inference through observed choice behavior, as opposed to traditional evaluation methods (Drummond, 1997) aimed at revealing individual preferences toward alternative health outcomes by using direct questionnaires presenting hypothetical situations (for example, "imagine that you will have to spend 4 months in one of the following health conditions. Please rank them in order of preference", or "how much would you be willing to pay for..."). The limitations of such hypothetical preference evaluation methods to produce empirical values for QALYs (used in the cost-utility analysis) or Willingness to Pay (used in the cost-benefit analysis) are well-known. There is no clear incentive for the patient or the doctor to express their true preference, the level and type of information provided in the scenarios may affect answers (Berwick and Weinstein, 1985) and respondents may find it difficult to answer quite complex questions. Furthermore, patients are likely to behave in a different way from their declarations. In contrast, the suggested approach based on direct observation of adherence does not suffer from these limitations as it uses a genuine behavior choice encountered by the patient, thus being in line with a growing literature aiming at acknowledging the information value inherent in patient decision-making (Philipson and Posner, 1993 ; Meltzer, 1999). Note that indirect valuation methods have been rarely applied to value health care. When there exist indirect monetary costs (eg transportation) associated with treatment intake, it is possible to derive indirectly monetary measures of Willingness-to-Pay (Johansson, 1997). The most common example of this approach is provided by the transport cost method previously used for the evaluation of national parks and in the health care field for the valuation of preferences toward mammography screening for breast cancer (Clarke, 1998 ; Sandstrom, 1999). When there is no direct nor indirect money cost associated with treatment intake as may be the case within a clinical trial, it is not possible to implement the method suggested by Johansson (1997) and monetary measures of WTP cannot be derived. This article offers a framework to infer welfare in such a situation.

## 2.2 Another look at adherence

This approach makes us study adherence from the perspective of the patient behaving as an active agent in his/her treatment regimen. Up to now most health researchers have taken it for granted that non-adherence is induced by an irrational behavior or a lack of information. Poor adherence has generally been viewed as either a deviance (Parsons, 1951), a statistical bias (Scharfstein et al., 1999) or a cost-driving issue (Cleemput et al., 2002; Hughes et al., 2001) that should be prevented or controlled for. Very few approaches are patient-targeted and what is missing from most adherence analyses is a discussion of patient welfare. However, some authors point out that compliance could be the result of a rational trade-off operated by the patient. Before capturing the patient's weighing process in a simple theoretical model, we will briefly review the articles supporting some form of rational non adherence.

A couple of empirical studies actually suggest that patients are responding to perceived costs and benefits, when choosing whether or not to comply. In particular, patients' diaries (Johnston-Roberts and Mann, 2003) relate intentional nonadherence and unveil that patients are weighing the costs with the benefits of non-adherence. For example, poor adherent patients report that they skip medications in order to get rid of unbearable adverse events despite awareness of the severe health risks associated with imperfect drug intake. Above all, the idea of a rational non-adherence behavior was conceptualized by such socio-behavioral models as the "health belief model". The health-belief model (Rosenstock, 1974; Becker and Maiman, 1975) suggests that patients are more likely to comply with doctors' orders when they feel susceptibility to illness, believe the illness to have potential serious consequences for health or daily functioning, feel benefits on health and do not anticipate major obstacles, such as side effects or costs. Becker (1976) found general support for a relationship between compliance and patients' beliefs about susceptibility, severity, benefits and costs. However, note that the whole notion of "compliance" still suggests here a medically centered orientation. The assumption is the doctor gives the orders; patients are expected to comply. It is based on a consensual model of doctor-patient relations, in line with Parsons's perspective (1951), where noncompliance is a form of deviance in need of explanation. A patient-centered perspective has been developed by Conrad (1985). Conrad focuses on the meanings of medication in people's everyday lives and looks at why people take their medications as well as why they do not. He argues that from a patient's perspective, the issue is more one of self-regulation than compliance. This patient-centered



perspective regards patients as active agents in their treatment rather than as “passive and obedient recipients of medical instructions”.

To the extent that patients choose not to comply with prescribed therapies, a gulf may arise between physician prescribing patterns and realized patient welfare, which turns out to be confirmed by numerous studies. The degree of observed patient noncompliance is truly surprising. Several studies put overall patient noncompliance at around 50 % (Sackett and Snow, 1979). Among HAART-treated patients, cross-sectional studies in Europe and North America, have indicated that 20% to 40% do not fully take their regimens as prescribed at any point in time (Chesney, Morin, Sherr, 2000). This may indicate a sizeable difference between the benefits perceived by physician and patient. In other words, from the patient point of view, the optimal level of adherence may be lower than 100%, which is regarded as the ideal to be reached for the medication to be fully active.

In sum, the evidence clearly indicates that patient compliance is an important empirical phenomenon, with far reaching economic consequences.

However, in the microeconomic field, very few studies have developed a microeconomic analysis of adherence behaviors. Philipson and DeSimone (1997), Philipson and Hedges (1998), Chan and Hamilton (2005) have laid the emphasis on attrition. They argue that dropout behavior provides information that is useful in the evaluation of the treatment. In particular, it is outlined that dropout behaviour provides insight not only into the direct efficacy of the treatment but also potential side effects that may not be easily measured or are privately observed by the subject. However, attrition is only a special case of non-adherence. In particular, dropout occurs only once while medication non-compliance varies over time and can be regarded as a reversible state. To our knowledge, only Ellickson, Stern and Trajtenberg (1999) endeavor to develop an economic analysis of the medication adherence behavior. Their proposed estimator of patient welfare depends both on whether patients comply with the prescriptions and on the selection of patients into drugs by their physicians. The authors focus on building an econometric framework for the evaluation of benefits within discrete choice models. However no estimation is provided due to the lack of relevant data.

In this paper, we will concentrate on the patient adherence behavior, thus trying to understand the underlying mechanisms involving individual preferences.

### 2.3 A simple model

Relying on the studies mentioned above, we assume that the individual adherence behavior is the result of some trade-off between the immediate and noticeable side effects that affect negatively her quality of life related to treatment intake, denoted by  $q$ , and the treatment effects on her health, denoted by  $h$ . More precisely  $h$  refers to the clinical and biological markers of the treated disease (ie either viral load or CD4 cell counts in HIV disease) whereas  $q$  refers to the lack of treatment-related adverse events or in other words to the tolerance of the treatment in daily life. To take the trade off into account, we assume that individual preferences are represented by a utility function  $u(h, q)$ , with standard assumptions ( $u_h > 0$ ,  $u_q > 0$ ,  $u_{hh} < 0$ ,  $u_{qq} < 0$ , and  $u_{hq} \geq 0$ ). A simple specification could be  $u(h, q) = \pi(h)v(q)$ , where  $\pi(h)$  is the survival probability associated with health state  $h$ , and  $v(q)$  the subjective value of quality of life, which may be interpreted in terms of QALY. We abstract from monetary cost considerations since, as far as individuals are concerned, treatments are delivered free of charge in the course of a clinical trial. As already mentioned, this rules out the estimation of money measures of welfare. However it is possible to measure a compensating variation in terms of the amount of extra health that would be required to compensate for a reduction in quality of life. Moreover, we limit this first approach to a static decision set-up, that illustrates the basic trade off.

We denote the adherence level by  $\theta$  and the health state without treatment by  $h$ . In line with the econometric specification (see next section), we assume that the individual faces a discrete choice problem: either to be perfectly adherent ( $\theta = 1$ ) or not adherent at all ( $\theta = 0$ ). If the individual is adherent, then her health state is equal to  $h' = h + k$ ;  $k$  denotes the treatment effect on health. Similarly, quality of life is given by:  $q' = q - c\theta$ ;  $c$  denotes the subjective costs associated to the treatment, i.e. the magnitude of the negative side effects. To sum up, the utility level is given by  $u(h + k, q - c)$  if  $\theta = 1$ , and  $u(h, q)$  if  $\theta = 0$ . The following proposition characterises the optimal behavior.

**Proposition 1** *For any level  $c$ , there exists a threshold level  $k(c; h, q)$  such that:*

$$u(h + k, q - c) > u(h, q) \text{ if and only if } k > k(c; h, q).$$

*Moreover,  $k$  is increasing with  $c$  or  $h$ , and decreasing with  $q$ .*

PROOF:

The patient's initial condition is  $(h, q)$ . For any given  $c$ ,  $k(c; h, q)$  is implicitly determined by the equation  $\Delta(k, c; h, q) \equiv u(h+k, q-c) - u(h, q) = 0$ . Under the above assumptions on  $u$ , we have that  $\Delta_k = u_h(h+k, q-c) > 0$ . Set  $c > 0$ . For  $k = 0$ , since  $u_q > 0$ , we have that  $\Delta < 0$ . For very large values of  $k$ , either  $\Delta(k, c) \leq 0$  or  $\Delta(k, c) > 0$ . In the first case, we set  $k(c) = +\infty$ : the side effects are so bad that the individual is never adherent, whatever the health benefit. In the second case, there exists a threshold value  $k(c; h, q)$  such that the individual is adherent if and only if  $k \geq k(c; h, q)$ . Notice that, since  $\Delta_c = -u_q < 0$ , the implicit function theorem gives that  $k_c = -\frac{\Delta_c}{\Delta_k} = \frac{u_q}{u_k} > 0$ . Moreover, we have that:  $\Delta_q = u_q(h+k, q-c) - u_q(h, q) \geq u_q(h, q-c) - u_q(h, q)$  (since  $u_{hq} \geq 0$ ), and  $u_q(h, q-c) - u_q(h, q) > 0$  (since  $u_{qq} < 0$ ), and thus  $\Delta_q > 0$ . Similarly,  $\Delta_h < 0$  (since  $u_{hq} \geq 0$  and  $u_{hh} < 0$ ). Therefore, again by the implicit function theorem, the threshold value  $k$  is increasing with  $h$  and decreasing with  $q$ . ■

The interpretation of  $k(c; h, q)$  is straightforward. Indeed, the quantity  $k - k(c; h, q)$  may be interpreted as an analogue of the compensating variation in applied welfare economics: it measures the additional gain, *expressed in health units*, obtained by an individual whose quality of life is  $q$  and health is  $h$  who consumes a drug that has side effects (it deteriorates quality of life by  $c$  units), but improves health by  $k$  units. Of course, if  $k - k(c; h, q)$  is negative, the individual's optimal behaviour is to not take the drug. That  $k$  increases with  $c$  simply reflects the fact that, in order to be adherent, the individual is more demanding in terms of health benefits when the drug has very negative side effects. Moreover, a good health state increases the requirement set upon the drug; finally, a poor quality of life makes additional losses  $c$  very costly (again when the cost is expressed in health units). In other words, this simple model predicts two main effects. First, for small values of  $h$ , the marginal utility of health  $u_h$  is large and an increase in  $h$  induced by perfect adherence may lead to a substantial utility gain. Second, for small values of  $q$ , the marginal utility of quality of life is high, negative side effects are very costly, and therefore the optimal behavior tends to favor  $\theta = 0$ .

To fix the ideas, under a QALY-type specification  $u(h, q) = \pi(h)v(q)$ , straightforward computations show that the threshold function  $k(c)$  is equal to:

$$k(c; h, q) = -h + \pi^{-1} \left[ \pi(h) \frac{v(q)}{v(q-c)} \right],$$

which for small values of  $c$  may be approximated by  $k(c; h, q) \simeq c \frac{\pi(h)}{\pi'(h)} \frac{v'(q)}{v(q)}$ . In particular, under the Cobb-Douglas specification  $u(h, q) = h^{1-\alpha} q^\alpha$ , we have that the threshold function  $k(c)$  is approximated by:  $k(c) \simeq \left(\frac{\alpha}{1-\alpha}\right) \frac{ch}{q}$ . In that case, the adherence decision is determined by the simple rule:

$$\frac{k}{c} \geq \left(\frac{\alpha}{1-\alpha}\right) \frac{h}{q}.$$

In other words, the benefit-cost ratio  $k/c$  must be large enough. Notice that an increase in  $h$  or a decrease in  $q$  increases the slope of the threshold function  $k(c)$ ; therefore, not surprisingly, it reduces the propensity to choose  $\theta = 1$ . Also,  $\frac{\alpha}{1-\alpha}$  measures the relative weight the patient puts on quality of life (with respect to health). The following figure summarises this issue.

INSERT HERE FIGURE 1

Notice that the patient's decision is based upon her own subjective evaluation of  $(k, c)$ . Hence, observation of adherence behaviour will provide information about the subjective values of  $(k, c)$ .

### 2.3.1 Empirical implications

The population is split in two sub-populations  $i \in A, B$ , depending on the treatment they receive ( $A$  or  $B$ ). For individual  $i$ , the treatment effect on health is denoted by  $k^i$ , and on quality of life by  $c^i$ . Assume that we observe that the proportion of adherent individuals is smaller in group  $A$  than in group  $B$ :

$$P(\theta^i = 1 | i \in A) < P(\theta^i = 1 | i \in B). \quad (1)$$

Hence, observing (1) implies that  $P(k^i \geq k(c^i; h^i, q^i) | i \in A) > P(k^i \geq k(c^i; h^i, q^i) | i \in B)$ . Under the linear approximation above,  $(\theta^i = 1)$  is equivalent to  $\frac{k^i}{c^i} \geq \frac{\pi(h^i)}{\pi'(h^i)} \frac{v'(q^i)}{v(q^i)}$ . If the two groups have been determined by an adequate randomisation procedure, the distribution of  $(h, q)$  is identical across the two groups, and is also independent of the distribution of the treatment effects  $(k, c)$ . Hence, if we denote by  $\tau \equiv E\left[\frac{\pi(h^i)}{\pi'(h^i)} \frac{v'(q^i)}{v(q^i)}\right]$ , we have that:

$$P\left(\frac{k^i}{c^i} \geq \tau \mid i \in A\right) < P\left(\frac{k^i}{c^i} \geq \tau \mid i \in B\right).$$

In short, a lower adherence level reveals that the benefit cost ratio is smaller. If, in addition, the trial proves that treatment  $A$  is at least as efficient on health, i.e. that  $k^A \geq k^B$ , this immediately reveals that  $c^A > c^B$ .

### 3 Econometric Implementation

This section presents the econometric method used to estimate the economic model described in the previous section and to infer patient welfare from adherence behavior. The simple model above gives that  $(\theta^i = 1)$  is equivalent to  $k^i - k(c^i; h^i, q^i) \geq 0$  or  $u(h^i + k^i, q^i - c^i) - u(h^i, q^i) > 0$ . We want to estimate  $\Delta(h^i, q^i) \equiv u(h^i + k^i, q^i - c^i) - u(h^i, q^i)$ , ie the incremental benefit provided by treatment intake (full adherence) over the alternative of no drug at all.

#### 3.1 A discrete choice framework

We assume that consumer welfare can be measured by the “revealed preferences” of consumers through their observed choices. Extending previous studies of the welfare benefits from innovation or product differentiation (Berry, 1994; Bresnahan, 1986; Hausman, 1997; Stern and Trajtenberg, 1998; Trajtenberg, 1989; Trajtenberg, 1990), we develop a discrete choice framework. The basic notions in these models is that competing products in a given market can be thought of as consisting of different vectors of characteristics (or performance dimensions), selling for different prices. The utility of consumer  $i$  for product  $j$  depends on the characteristics of the product and the consumer. Consumers choose their preferred product by comparing the various options available on the market in terms of the overall utility that different products provide. The estimate of the value that consumers place on attributes can be used to compute the incremental surplus associated with the introduction of new products incorporating superior characteristics.

In our framework, patients choose whether or not to consume the prescribed drug at date  $t$ , ie whether or not to comply at date  $t$ . Let us consider  $\theta_{it}$  the dichotomous compliance variable defined above:  $\theta_{it} = 1$  (respectively,  $\theta_{it} = 0$ ) when the patient  $i$  is adherent (resp., non adherent) at time  $t$ . The discrete choice approach requires us to identify the various factors influencing the patient’s adherence behavior. We assume that each patient maximizes the utility derived from drug consumption. Let us note  $U_{it}(1, X_{1it}, \varepsilon_{1it})$  the utility level associated with being adherent at time  $t$  and  $U_{it}(0, X_{1it}, \varepsilon_{1it})$  the utility level associated with not being adherent at time  $t$ .  $X_{1it}$  is a vector of baseline or time-dependent covariates influencing adherence behaviors, including observed outcomes before drug intake ( $h$ ) and side effects before drug intake ( $q$ ) as suggested by the trade off model.  $\varepsilon_{1it}$  is a vector of unobserved (by the econometrician) patient and regimen characteristics. The patient  $i$  is adherent at time  $t$  if

$U_{it}(1, X_{1it}, \varepsilon_{1it}) \geq U_{it}(0, X_{1it}, \varepsilon_{1it})$ . The econometric estimation is founded on the latent variable  $\theta_{it}^*$ , which can be interpreted as the difference between the utility levels presented above  $U_{it}(1, X_{1it}, \varepsilon_{1it}) - U_{it}(0, X_{1it}, \varepsilon_{1it})$  (i.e.  $\Delta(h, q) \equiv u(h + k, q - c) - u(h, q)$ ).

Let us assume that the population is randomly split into two groups  $A$  and  $B$ . The binary choice model could help us estimate a compensating variation in terms of the amount of additional treatment efficacy that would be required to compensate for an increase in side effects. Indeed, let us assume that the treatment group (new treatment versus reference treatment) and side effects (whether the patient experiences side effects or not) are used as covariates in the adherence equation and that the estimated coefficients are respectively  $a$  and  $b$  on these covariates. Let us also suppose that treatments are completely similar except for efficacy level and that all side effects are observable. Coefficient  $a$  tells about the patient's response to all the things that are different about the two treatments. Coefficient  $b$  tells about the response to side effects. Then the ratio  $-a/b$  gives the rate at which the patient would be willing to substitute better efficacy for side effects at constant utility.

Furthermore, the binary choice framework makes it possible to rank two treatments in terms of welfare. The quantity  $[U_{it}^A(1, X_{1it}, \varepsilon_{1it}) - U_{it}^A(0, X_{1it}, \varepsilon_{1it})] - [U_{it}^B(1, X_{1it}, \varepsilon_{1it}) - U_{it}^B(0, X_{1it}, \varepsilon_{1it})]$  can be interpreted as the incremental benefit allowed by the consumption of treatment  $A$  (over the benefit allowed by the consumption of treatment  $B$ ). The estimation of the adherence equation with the randomization group as a covariate enables us to assess whether the benefit associated with drug consumption differs significantly between both groups. The randomization guaranties that the groups are the same except for the treatment received and that hence the observed adherence behaviors do reflect different preferences regarding the treatment.

Up to now, we have developed to what extent patient compliance represents an economic choice which should allow for identification of the incremental benefits of a given drug. We have suggested to perform the estimation within a discrete choice framework based on the estimation of an adherence equation. The next step consists in specifying the econometric model.

### 3.2 Model specification

Our proposed method to estimate factors associated with compliance must account for the impact of adherence on health status, as specified in the theoretical model. As a result, we study both the predictors of adherence

and treatment efficacy simultaneously. The therapeutic outcome will be observed as a continuous variable and handled as a dichotomous variable, which is relevant in HIV disease. Unobserved heterogeneity between patients will be taken into account through a random effects specification using panel data (Butler and Moffitt, 1982 ; Guilkey and Murphy, 1993 ; Greene, 2003).

Finally, our method results in the estimation of the following system:

$$\begin{cases} \theta_{it}^* = x_{1it}\beta_1 + \varepsilon_{1it} \\ h_{it}^* = x_{2it}\beta_2 + \theta_{it}\gamma + \varepsilon_{2it} \end{cases}$$

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

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

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

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

$$\Sigma_v = \begin{pmatrix} \sigma_{v 1}^2 & \sigma_{v 12} \\ \sigma_{v 12} & \sigma_{v 2}^2 \end{pmatrix}$$

where  $h_{it} = 1$  if health status is good (undetectable viral load) at  $t$  ( $= 0$  if health status is bad). We assume that  $\theta_{it}^*$  is determined by a set of exogenous variables, denoted by  $x_{1it}$ , and  $h_{it}^*$  is simultaneously determined by  $\theta_{it}$  and a set of exogenous variables  $x_{2it}$ . Self-selection into a high adherence behavior is captured through omitted variables. The error component structure implies that error terms are decomposed in unobserved individual specific effects  $v_i$  and time-specific chance events  $\eta_{it}$ . Therefore endogeneity is induced by either the correlation between patient-specific disturbances or by the correlation between residuals. Note that  $x_{1it}$  represents a set of instruments for  $\theta_{it}$ . It should also be noted that the recursive framework (one endogenous variable present on the right-hand side of the other equation) implies that  $h_{it}$  may have an indirect impact on adherence through omitted variables.

### 3.3 Model estimation

Finally, we estimate a panel non linear simultaneous two-equation system. This recursive system is logically consistent (Maddala, 1983) which implies

the existence of a reduced form. Furthermore, it can be fully identified (Maddala, 1983), i.e. there is a unique way to recover the structural form parameters from the reduced equation. Two main difficulties must be dealt with. First, we are faced with dichotomous dependent variables, for which standard instrumental techniques are inappropriate. Second, the panel data structure makes the problem a bit worse.

We use a full information method of estimation. The estimation treats all equations and all parameters jointly, thus ensuring that the most efficient estimates are obtained. It takes into account the possible correlation between the individual unobserved specific terms and the disturbances in the two equations. A maximum-likelihood method involving the numerical evaluation of exact log-likelihood (Lazard-Holly and Holly, 2003) and the BHHH algorithm (Berndt, Hall, Hall, Hausman 1974) is used. It is implemented through a specific programming on gauss software (Huguenin, 2004). Though a similar bivariate specification was first used on panel data for the joint study of health status and employment decision of the elderly (Sickles and Taubman, 1986), it has not been much used since then and still requires heavy programming.

We wish to emphasize that this way of analyzing compliance data through a two-equation system composed of an adherence and an outcome equation addresses some limitations of most current methods used in medical and epidemiological studies. First, most medical studies treat adherence as an exogenous variable, thus solving the outcome equation. Second, if the biostatistical literature dealing with the correction of the selection bias induced by partial adherence (Angrist et al., 1996) takes into account the endogenous nature of adherence, the most common strategy has been based on the use of the randomization group as an instrument. Hence, we claim that other instruments (included in  $x_{1it}$  and detailed in the following sections) must be used when the experiment compares two active treatments. Third, there is usually no relationship between medical studies regarding compliance as an explanatory variable contributing to clinical or biological endpoints and social sciences considering adherence as a dependent variable to be explained in order to implement compliance-enhancing interventions. Knowing that the collection of adherence data is common in medical studies, the lack of any standard method for the analysis of adherence data may seem astonishing. The structural approach that we suggest provides a unified framework.

Before coming to the results, we shortly present the data used for the analysis.



## 4 The Data

### 4.1 The CNAF 3007 trial

Data were obtained from the so-called CNAF3007 multicenter, comparative, open label, randomized Phase IIIB trial which evaluated and compared the safety and efficacy of two different HAART therapies in HIV-1 infected patients. It should be reminded that the main objectives of HAART therapies are to induce immunologic (rise in CD4 cell counts) and virologic (decline in plasma HIV viral load to unquantifiable levels such as 400 copies/ml) responses.

In this trial, the overall strategy was to judge the utility of a “protease inhibitor (PI)-saving regimen” for first line antiretroviral treatment. Patients were sequentially randomized into two groups: one received a new combination of three reverse transcriptase inhibitors (one Combivir® tablet (lamivudine/zidovudine) twice a day, plus one Ziagen® (abacavir) tablet, twice a day) whereas the other received the standard therapy including a protease inhibitor and a combination of two reverse transcriptase inhibitors (Viracept® (nelfinavir) three capsules q8h) plus one Combivir® tablet twice a day, plus ). The simplified 4-pill daily regimen or two-intake regimen will be referred to as CBV/ ABC and the 11-pill daily or 3-intake regimen will be referred to as CBV/ NFV. To briefly summarize inclusion criteria, patients (male and female) were 18 years of age or over, had viral plasma HIV-1 RNA loads in the range 1000 - 500 000 copies/ml at the time of the screening visit and were naive of any antiretroviral therapies.

The study was conducted from November 1998 to July 2001 at 60 centers throughout France. A total of 195 screened patients were randomized and underwent 48 weeks of treatment. Protocol visits were scheduled at baseline, week 4, week 8, week 16, week 24, week 36, week 40 and week 48. The study’s principal objective was the evaluation of the treatments’ efficacy after 48 weeks of treatment, in terms of the proportion of patients in each group whose plasma viral load had decreased to an undetectable level. Health status (Viral Load, CD4 cell counts, occurrence of opportunistic diseases), toxicity (occurrence of treatment-related side effects) and adherence were evaluated at each visit.

### 4.2 Clinical Trial Results

For the purpose of our analysis, all results will be reported for the per protocol (PP) population, which only included patients who generated data

while on the originally randomized therapy. For the type of pathology studied here, it is not uncommon for patients to terminate one treatment during the study period (usually for tolerance reasons) and switch to the other study treatment. In such a case, compliance data would no longer reflect adherence to the originally randomized therapy. Hence, the PP population included only those patients not having modified their initial treatment, i.e. those who discontinued or switched antiviral therapy were not included in the PP beyond the last dose of originally-designated treatment.

#### 4.2.1 Comparable Efficacy and Toxicity

We first checked that subjects were initially comparable in both groups in terms of demographic and health status characteristics (Table 1).

As far as efficacy results were concerned, it turned out that the simplified regimen showed similar antiretroviral activity to that of a PI containing regimen. Indeed 89% (95%CI = [81%,97%]) subjects in the CBV/ABC group versus 90% (95%CI = [80%,96%]) in the CBV/NFV group had plasma HIV-1 RNA < 400 copies/ml at week 48 (Table 2). Though the aggregated percentages of patients with good virologic outcomes became stable after week 8, the analysis of individual paths revealed some state changes (ie viral load increases after controlled periods) in 51 patients. Furthermore, during the course of the treatment, the median rise in CD4 cell counts was linear and also comparable between both groups (+124 cells/mm<sup>3</sup> and +130 cells/mm<sup>3</sup> respectively in the CBV/ABC and CBV/NFV regimen) over the 48 weeks of treatment.

As far as toxicity results were concerned, both treatment regimens were generally well tolerated. 12 patients (13%) in the PI-free regimen and 11 patients (12%) in the PI-containing regimen underwent both at least one treatment-related digestive inconvenient episode and one clinical sign of lipodystrophy. Note that side effects popped up and vanished during the course of the medication.

Further information on the trial protocol and results are available elsewhere (Descamps et al., 2001; Matheron et al., 2003; Lamiraud, 2004).

#### 4.2.2 Differences in Adherence behaviors

Adherence was recorded at each visit through two commonly used measurement methods: the pill count and a patient self-administered questionnaire. Tablet count was based on an inventory of study drugs supplied to the patient and subsequently returned to the investigational site. As part of

their taking part in the trial, patients committed themselves to bringing all used or unused material back. Furthermore, an adherence questionnaire was completed by patients at each visit. All questions addressed the 4 weeks preceding the visit. In particular, the patient was asked to estimate the frequency of lapses in taking medication.

Neither of these methods can be regarded as gold-standard methods. However, we decided to discard the self-questionnaire for our analyses for two main reasons. First, recent research has defined validity criteria for self-questionnaires including the use of short recall periods (inferior to 7 days) (Miller and Hays, 2000). The 4-week recall period used in our study totally violates these recommendations. Second, it turned out that as many as 32% of patients declaring not to have missed any single dose were indeed overstating their actual adherence level because they brought unused pills back. To the contrary, some arguments in favor of the pill count included the fact that it was an objective indicator ; besides it succeeded in detecting as poor adherers those reporting skipped doses (the specificity of the pill count in comparison with the self-questionnaire amounted to 95%), thus excluding the possibility that some truly non adherent patients might have disposed of extra medication in order to appear more adherent (Cramer, 1991); indeed patients admitting non adherence must be trusted and can be regarded as non adherers unambiguously(Farmer, 1999).

The pill count measure made it possible to compute an adherence rate as defined by the percentage of pills taken out of those supposed to be taken. Based on this continuous measure, the mean adherence level amounted to 87.7 % and the median to 95%. The asymmetric distribution of the variable revealed two groups of patients, adherent and non adherent ones. Compliance was then summarized by a dichotomous variable. A patient was adherent if the adherence rate was higher than 95%. This threshold is in line with the medical literature showing that it is necessary to take more than 95% of the prescribed medicines to maintain suppression of viral replication (Paterson et al., 2000). Note that both the asymmetric distribution of the adherence variable and the medical knowledge suggesting that what really matters in HIV disease is the ability to reach a perfect adherence support the use of a binary adherence variable. It could be checked whether this choice might have induced some loss of information concerning the factors associated with adherence.

Descriptive statistics showed that compliance tended to decrease over time though not linearly. Another interesting feature stressed by the descriptive analysis was a certain stability of the decision whether to comply or not. Individual adherence paths revealed that most patients could be

classified as either good or poor adherers. Some patients remained in the same state all over the trial. 30 patients remained perfect adherers and 24 patients remained poor adherers. For the others, some rare deviations occurred in adherent and non adherent paths without any consistency across patients. We assume that these brief state changes might result from individual events related to the experience of the treatment. Our estimation on longitudinal data should be able to distinguish between the impacts of permanent heterogeneity and the effects of time-varying events on adherence behaviors. Furthermore, the percentage of compliant patients turned out to be higher in CBV/ ABC group (simplified arm), with significant differences (at a 10% level) at weeks 6, 7, 8 and 9 according to the Khi2 statistics (Table 3). Our estimations will enable us to assess to what extent the distributions of adherence may inform us upon the valuation of the treatment.

### 4.3 An original and rich database

It should be stressed that exploiting the clinical dataset of adherence from a patient’s perspective is both innovative and very informative. In particular, the trial framework bears three main advantages. First, it controls for co-factors related to the patient-physician relationship. Indeed, all components of the patient-physician relationship (framing of the questions, ...) are defined by the protocol and should be quite homogenous across patients. Second, the randomization procedure ensures that observable and unobservable individual attributes are independent of the treatment group. Third, it provides us with extensive individual longitudinal information. Consequently, three dimensions of factors will be included in  $X_{1it}$  in accordance with the large body of literature dealing with the determinants of compliance (Meichenbaum and Turk, 1987): patient-related, treatment-related (side effects, intake of concomitant treatments), disease-related factors. All variables that were found to be significantly associated with adherence behavior (at a 10% level) in univariate analyses were incorporated in  $X_{1it}$ . The variables that might be expected to affect the subject-level treatment impact on  $h_{it}$  (ie whether the viral load is undetectable or not) (Girard, Katlama and Pialoux, 2003) will be included in  $X_{2it}$ : demographic variables (age and gender) ; variables measuring the extent of disease at baseline (Viral load and CD4 cell counts); the duration of exposure to therapy (time variable). Summary statistics of all endogenous and exogenous covariates used in the final estimations are provided in Table 4.

Of course, we cannot avoid shortcomings inherent in any experimental studies, in particular the fact that some specific groups of patients with

general problems of non-adherence to regular medical follow-up may be underrepresented in this sample. Furthermore, the clinical trial did not collect such socio-economic variables as education level, income, professional activity which might have an impact on the adherence level though most studies have been inconsistent in this respect (Meichenbaum and Turk, 1987).

## 5 Major findings and discussion

Separate equation results (performed with a probit random effects model) and non linear panel simultaneous estimations are presented in Table 5.

First, we wish to comment on welfare results, which have been our main focus of interest. Then we will discuss the factors associated with adherence and the findings of the simultaneous system.

### 5.1 Welfare inference

As explained, the discrete choice framework allows us to interpret the latent variable of the adherence equation as the incremental benefit provided by treatment consumption (full adherence) over no drug intake (nonadherence). Table 6 shows that patients are significantly more adherent to the simplified combination than to the reference therapy after other covariates have been controlled for. It means that the utility level associated with treatment consumption is significantly higher in the PI free regimen (CBV/ ABC) than in the PI containing regimen, whereas both regimen were found to have comparable antiviral activity. This implies that a welfare approach based on compliance may add valuable information to conclusions drawn by a mere biostatistical analysis. In particular, we are able to interpret in a new manner the situation when there is no significant difference between both arms as far as efficacy and toxicity criteria are concerned, though patients are significantly more adherent in one group than in the other one. In terms of well being, the compliance-enhancing drug must be favored. To the contrary, the clinicians of the trial were tempted to support the treatment in which the adherence level was smaller, based on the rationale that a higher adherence would have pushed the efficacy to upper levels in that group. Furthermore, it is important to mention that a traditional cost-effectiveness study performed over the same data set also proved unable to highlight any differences between both regimens.

In line with section 3.1, we could interpret the ratio 0.52/0.82 as the rate at which patients would be willing to substitute the new treatment for more side effects. However note that the coefficient on the randomization

group variable tells about the patient’s response to all the things that are different about the two treatments (in particular intake frequency and not only efficacy) and that some unobserved side effects may not be captured in the observed variable.

## 5.2 Factors associated with adherence

Furthermore, our estimations make us identify a couple of factors associated with adherence. We show that the probability of being adherent at  $t$  decreases when side effects are experienced at  $t - 1$  and when the patient observes positive outcomes at  $t - 1$  (as measured by a positive CD4 response), i.e. before making decision concerning drug intake at  $t$ . Once the CD4 cell counts have increased by a minimal threshold (50 cells), the marginal welfare of taking medication may not be large enough for the patient to be adherent, i.e. the private costs associated with adherence may outweigh the benefits. These effects are consistent with the predictions of the theoretical models as expressed by the impacts of  $h$  and  $q$  to the extent that the observed change in CD4 counts can be regarded as a proxy of the direct impact of the observed health status on compliance. The indirect impact of  $h_{it}$  on adherence are captured through disturbances (see next section). Note that in preliminary estimates (results not shown) of the adherence equation, patients were found to respond to their CD4 cell counts and not to any viral load measure, which might be explained by the fact that the CD4 cell count is the measure that describes the natural evolution of HIV disease. Other factors independently associated with high adherence include a simplified regimen (as mentioned above), the lack of consumption of concomitant drugs, a less advanced virological and immunological stage of the disease before treatment initiation.

Our findings confirm a couple of factors that have been emphasized upon in previous works. In particular, studies conducted in HIV disease have found that nonadherence tends to be higher when medical regimens are more complex (Stone et al., 2001 ; Trotta et al., 2002) or more precisely when the pill burden is higher (Bartlett, DeMasi and Quinn, 2001); when there are several troublesome drug side effects (Heath et al., 2001; Duran et al., 2001). However, we do not confirm findings suggesting that non-compliance tends to be higher when the initial clinical or immunological stage of the disease is less advanced (Gordillo et al., 1999 ; Ostrop, Hallet and Gill, 2000). More importantly, as opposed to previous studies (Weiss, 2000; Spire et al., 2002) we find that patients’s beliefs about the capacity of the treatment to restore the biological markers are not associated with

the adherence behavior after other covariates have been controlled for. The microeconomic analysis suggests other possible mechanisms leading to non adherence, even in the context of proper information, based on an individual patient's rational outweighing process. This result points out intrinsic limitations of popular behavioral models such as the Health Belief Model: in these models, false or improper beliefs about the effectiveness of HAART have been highlighted as major explanatory factors of non adherence. The microeconomic framework has the advantage of implying that, even in optimal conditions, in which the patients interpret their biological markers properly and have good knowledge of disease progression (which is quite a reasonable assumption in HIV disease), they might still rationally choose not to take their medicines.

Note that the occurrence of side effects, the intake of concomitant drugs and the achievement of immunologic success are the variables that we used as instruments. We have made sure that they do satisfy the properties of instruments. We have checked that these variables are not correlated with  $v_{1i}$  (Mundlak, 1978) and with  $\eta_{1it}$  conditional on  $v_{1i}$  (Woolridge, 2002). Furthermore it is reasonable to admit that these three variables are not eligible covariates of the outcome equation and thus are not included in  $\varepsilon_{2i}$ . Indeed, within the clinical trial, concomitant treatments must be chosen not to interfere with the antiviral activity of tritherapies. Furthermore, there is no reason why side effects should have a direct impact on outcome; the expected impact is indirect via compliance. Finally, in line with some medical research (Katlama et al., 2003), we admit that the recovery of CD4 cell counts is not predictive of virological success.

### 5.3 The panel data and simultaneous equation approach

Our results based on panel data also stress that unobserved patient characteristics account significantly for adherence behavior. These unobserved individual terms may capture a part of the pain or discomfort that the patient feels when taking the treatment medication, as well as a natural propensity to invest in health.

Furthermore, the covariances between disturbances of both equations are significant, thus confirming that it is appropriate to take the endogenous nature of adherence into account in a two-equation system. In our data, two contradictory effects play a significant role. On the one hand, the correlation between time-varying residuals turns out to be negative. It suggests that unobserved factors inducing a change in health between two time periods (from bad to good health) may have a negative impact on adherence. This

effect captures the indirect impact of health status on adherence behavior. On the other hand, the correlation between patient-specific error terms is positive. It means that patients who are structurally high compliers tend to be healthier to begin with or are more prone to engage in healthier behaviors.

Thus, we show that there exist unobservable factors that are correlated with one another and that impact simultaneously the adherence to HAART and the virologic response to the treatment. This interesting and new result confirms the need to promote an empathic approach to adherence (Spire et al., 2002). In particular, it is necessary to better investigate the usually unobserved factors that may have a positive impact both on adherence level and treatment success and may have to deal with patients' experience in their daily lives with the disease and its current long term chronic treatment by HAART.

Most regression results performed on the efficacy variable were to be expected. We confirm that it takes a couple of weeks to reach an undetectable viral load and that there is still no difference between treatment arms after controlling for covariates. The baseline immunological status becoming a significant predictor of treatment success once the endogeneity of compliance has been taken into account. However, note that adherence was significantly associated with treatment success in the single efficacy equation. After controlling for endogeneity, the adherence variable is no longer associated with the completion of an undetectable viral load. This astonishing result is likely to be attributable to the correlation between the adherence variable and the disturbances. As a result, the effect of adherence is overstated in the separate equation approach when endogeneity is overlooked. Conditional on unobserved heterogeneity, the remaining variability is so small that the adherence variable is no longer significant in the efficacy equation. Other possible explanations may be related to the clinical setting which reduces adherence variability and to the instrument variables which might carry too little information in this dataset. Another phenomenon could account for the adherence variable no longer being significant in the two-equation system, namely a selection bias due to attrition.

At this point, it is worth checking whether our results suffer from an attrition bias. In fact, 49 patients withdrew from the trial or switched to another treatment during the follow-up period (respectively 25 and 24 patients in the CBV/ABC and CBV/NFV arms). If attriters are also bad adherers, our estimations could be biased. However, we checked (tables 6 and 7) that patients having completed the trial under the randomization regimen ( $n = 128$ ) do not differ from randomized patients ( $n = 195$ ). Furthermore, the characteristics of patients did not significantly differ between treatment



groups at week 48. These descriptive results suggest that dropouts may be randomly distributed. In order to control for a possible attrition, we further estimated a hazard function and proposed to solve a trivariate probit model. Attrition is described by a hazard of the form  $S_{it} = 1(S_{it}^* = x'_{3it}\beta_3 + \varepsilon_{3it})$  where  $S_{it}$  indicates non attrition, that is :  $\Pr(\text{observed in } t \setminus \text{observed in } t - 1, x_{3it})$ . The estimated model is the following :

$$\varepsilon_{it} = \begin{pmatrix} \varepsilon_{1it} \\ \varepsilon_{2it} \\ \varepsilon_{3it} \end{pmatrix}$$

$$\varepsilon_{it} \hookrightarrow N(0, \Sigma_\varepsilon)$$

$$\Sigma_\varepsilon = \begin{pmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} \\ \sigma_{12} & \sigma_2^2 & \sigma_{23} \\ \sigma_{13} & \sigma_{23} & \sigma_3^2 \end{pmatrix}$$

The system is estimated by maximum likelihood and the results are provided in table 8. Both  $\rho_{13}$  (correlation between adherence and attrition equation) and  $\rho_{23}$  (correlation between efficacy and attrition equations) proved to be non significant. We can conclude that our results are not affected by an attrition bias. Note that the trivariate probit model is not estimated on panel data. As a result, the estimated coefficients are not to be directly compared with those of the panel bivariate probit system.

## 5.4 Conclusions

This paper proposed a theoretical framework in which welfare may be inferred from observed behavior. Within a structural and econometric framework, we show that patient compliance behavior relies on a trade-off between benefits and costs associated with treatment intake. This allows for the estimation of two elements: (1) the rate at which the patient is willing to substitute better treatment for worse side effects; (2) the incremental benefits of a drug consumption over the alternative of no drug intake. Such an empirical strategy might be useful for the comparison of two alternative treatments. To the extent that compliance is increasing in simplified formulations, a revealed preference perspective suggests that there may be substantial incremental welfare gains associated with such "patient-friendly" therapies. Our method both complements usual efficacy and toxicity analyses performed in clinical trials and traditional economic evaluations. This approach may be usefully applied to other areas in the economics of health

care where similar problems occur, namely examining those specific margins where patients do exercise choice. For example, evaluating the welfare benefits from invasive health care technologies such as colonoscopy could focus around such decision making as whether to accept such a procedure or not. It is worth pointing out that the welfare measure associated with adherence in a trial context is going to be a non money measure of welfare. It could be possible to use adherence to derive money measures of welfare if the person were paying for health, which would be possible in an observational setting.

In terms of valuation methods, our results based on panel data have also the advantage of controlling for patient heterogeneity. Indeed, two patients with similar observable characteristics may value the same drug differently because they may respond differently to doses or react in a different fashion to prices. We also show that the assessment evolves during the course of the treatment according to the occurrence of side effects, suggesting that traditional point estimates may be misleading.

Furthermore, our results put some new light on the momentous issue of medication non adherence. An economic approach pointing out that non adherence may often be a "rational" choice from the patient's point of view would suggest new ways for improving adherence. Patient-targeted interventions will have to cope with the involvement of the active patient who may find the marginal utility of taking medication too low. However we must recognize that our results may be closely tied to the specific field of HIV disease, characterized by highly informed and involved patients. Nevertheless, the framework could be easily extended to other chronic diseases. Another important result of the paper as for the understanding of adherence is the necessity to handle adherence endogeneity, which we did by estimating a panel bivariate probit model. This represents a real advance in comparison with current methods, though it must be admitted that our econometric modelling relies on the normality assumption of residuals and let the endogeneity go through omitted variables.

## 6 Acknowledgments

We wish to thank JN. Bail, C. Thiaux and A. Goetschel who, working with GlaxoSmithkline, enabled us to follow the implementation of the CNAF3007 clinical trial and to have access to the clinical trial data base in the context of a partnership between GSK, Pse and ANRT. Remaining errors are ours.

We are much grateful to the anonymous referee for very valuable suggestions.

## References

- [1] Angrist JD, Imbens GW, Rubin DB. Identification of causal effects using instrumental variables. *Journal of the American Statistical Association* 1996; 91: 444-472.
- [2] Bangsberg DR, Hecht FM, Charlebois ED, Zolopa AR, Holodiniy M, Sheiner L et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS* 2000; 14: 357-366.
- [3] Bartlett JA, DeMasi R, Quinn J et al. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS* 2001; 15: 1369 - 77.
- [4] Becker MH and Maiman LA. Sociobehavioral determinants of compliance with health and medical care recommendations. *Med. Care* 1975; 13: 10 - 24.
- [5] Becker MH. Sociobehavioral determinants of compliance. In *Compliance With Therapeutic Regimens*, Sackett D.L., Haynes R.B. (eds.). Baltimore, Johns Hopkins University Press: Baltimore, 1976; 40-50.
- [6] Berndt E, Hall B, Hall R, Hausman J. Estimation and inference in non-linear structural models. *Annals of Economic and Social Measurement* 1974; 3: 653 - 665.
- [7] Berry S. Estimating Discrete Choice Models of Product Differentiation. *Rand Journal of Economics* 1994; 25 (2): 24-62.
- [8] Berwick DM, Weinstein MC. What do patients value? Willingness to pay for ultrasound in normal pregnancy. *Medical Care* 1985; 23: 881 - 893.
- [9] Bresnahan T. Measuring the Spillovers from Technical Advance : Mainframe Computers in Financial Services. *American Economic Review* 1986; 76 (4): 742-55.
- [10] Butler J, Moffitt R. A computationally efficient quadrature procedure for the one-factor multinomial probit model. *Econometrica* 1982; 50 (3): 761-764.
- [11] Chan TY, Hamilton BH. Learning, private information and the economic evaluation of randomized experiments. Working paper 2005.

- [12] Chesney MA, Morin M, Sherr L. Adherence to HIV combination therapy. *Social Science and Medicine* 2000; 50 (11): 1599 - 1605.
- [13] Clarke PM. Cost-benefit analysis and mammographic screening: a travel cost approach. *Journal of Health Economics* 1998; 17: 767 - 787.
- [14] Cleemput I, Kesteloot K, and DeGeest S. A review of the literature on the economics of non compliance: room for methodological improvement. *Health Policy* 2002; 59: 65-94.
- [15] Conrad P. The meaning of medications: another look at compliance. *Soc. Sci. Med.* 1985; 20: 29-37.
- [16] Cramer JA, Spilker B. *Patient Compliance in Medical Practice and Clinical Trials*. Ravens Press: New York, NY, 1991.
- [17] Descamps D, Brun-Vzinet F, Izopet J, Vabret A, Boue F, 2001. Genotypic and phenotypic resistance and virological failure in HIV-1-infected antiretroviral therapy-naive adults: an open label comparative study (CNAF 3007). *Antivir Ther* 2001; 6(1): 76-76.
- [18] Drummond MF, O'Brien B, Stoddard GL, Torrance GW. *Methods for the Economics Evaluation of Health Care Programmes*. Oxford University Press, Oxford, 1997.
- [19] Duran S, Spire B, Raffi F, Walter V, Bouhour D, Journot V et al. Self-reported symptoms after initiation of protease inhibitor in HIV-infected patients and their impact on adherence to HAART. *HCT* 2001; 2: 38 - 45.
- [20] Ellickson P, Stern S, Trajtenberg M. *Patient Welfare and Patient Compliance: an empirical framework for measuring the benefits from pharmaceutical innovation*. NBER Working Paper 1999; 6890
- [21] Farmer CK. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clinical Therapeutics* 1999; 21(6): 1074-90.
- [22] Girard PM, Katlama C, Pialoux G. *VIH* 2004. Doin, 2003.
- [23] Gordillo V, Del Amo J, Soriano et al. Socio-demographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS* 1999; 13: 1763 - 176.

- [24] Greene W. *Econometric Analysis*. Prentice Hall International, 2003.
- [25] Guilkey DK, Murphy JL. Estimation and Testing in the Random Effects Probit Model. *Journal of Econometrics* 1993; 59 (3): 201 - 318.
- [26] Haubrich RH, Little SJ, Currier JS, Forthal DN, Kemper CA, Beall GN et al. The value of patient reported-adherence to antiretroviral therapy in predicting virologic and immunologic response. *AIDS* 1999; 13: 1099-1107.
- [27] Hausman J, 1997. Valuation of New Goods Under Perfect and Imperfect Competition. In: *The Economics of New Products*, Bresnahan T and Gordon R (eds). University of Chicago Press, Chicago, 1997.
- [28] Haynes RB. Determinants of compliance: the disease and the mechanics of treatment. In *Compliance in Health Care*, Haynes RB, Taylor DW, Sackett DL (eds). The John Hopkins University Press: Baltimore, 1979; 49-62.
- [29] Heath KV, Hogg RS, Chan KJ, Harris M, Montessori V, O'Shaughnessy MV, Montanera JS. Lipodystrophy-associated morphological, cholesterol and triglyceride abnormalities in a population-based HIV/ AIDS treatment database. *AIDS* 2001; 15: 231-239.
- [30] Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. *Health Economics* 2001; 10: 601 - 615.
- [31] Huguenin J. The multivariate normal distribution and multivariate probit analysis. PhD Thesis, University of Lausanne, 2004.
- [32] Johansson P. On the use of market prices to evaluate medical treatments. *Journal of Health Economics* 1997; 16: 609 - 615.
- [33] Johnston-Roberts K, Mann T. Adherence to antiretroviral medications in HIV/AIDS care: a narrative exploration of one woman's foray into intentional nonadherence. *Health Care for Women International* 2003; 24: 552-564.
- [34] Lamiraud K. Evaluation methods of patient utility: an economic and econometric analysis of adherence behavior within a clinical trial. PhD Thesis, EHESS, Paris and University of Lausanne, 2004.

- [35] Lazard-Holly H, Holly A. Computation of the probability of a d-dimensional normal variable belongs to a polyhedral cone with arbitrary vertex. Mimeo, 2003.
- [36] Maddala G. Limited Dependent and Qualitative Variables in Econometrics. Cambridge University Press: New York, 1983.
- [37] Matheron S, Descamps D, Bou F, Livrozet JM, Lafeuillade A, Aquilina C, Troisvallets D, Goetschel A, Brun-Vzinet F, Mamet JP, Thiaux C, on behalf of CNAF3007 study group. Triple nucleoside combination zidovudine/ lamivudine/ abacavir versus zidovudine/ lamivudine/ nevirapine as first-line therapy in HIV-1 infected adults: a randomized trial. *Antiviral Therapy* 2003; 8: 163 - 171.
- [38] Meltzer D. Theoretical Foundations of Medical Cost Effectiveness Analysis: Implications for the Measurement of Benefits and Costs of Medical Care Output and Productivity. NBER/ CRIM Conference Volume, 1999.
- [39] Miller GL, Hays DR. Adherence to combination antiretroviral therapy: synthesis of the literature and clinical implications. *AIDS Reader* 2000; 10: 177-85.
- [40] Mundlak Y. On the pooling of time series and cross section data. *Econometrica* 1978; 46 (1): 69-85.
- [41] Nieuwkerk P, Gisolf E, Sprangers M, Danner S. Adherence over 48 weeks in an antiretroviral clinical trial: variable within patients, affected by toxicities and independently predictive of virological response. *Antiviral Therapy* 2001; 6: 97-103.
- [42] Ostrop NJ, Hallet KA, Gill MJ. Long-term patient adherence to antiretroviral therapy. *Annals of Pharmacotherapy* 2000; 34 (6): 703 - 709.
- [43] Parsons T. The Social System. Free Press: Glencoe, 1951.
- [44] Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, Wagener M, Singh N. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine* 2000; 133 (1): 21 - 30.
- [45] Philipson T, Posner R. Private choices and Public Health: The AIDS Epidemic. Harvard University Press: Cambridge, 1993.

- [46] Philipson T, DeSimone J. Experiments and Subject Sampling. *Biometrika* 1997; 84: 619-631.
- [47] Philipson T, Hedges L. Subject Evaluation in Social Experiments. *Econometrica* 1998; 66: 381-408.
- [48] Rosenstock IM. The Health Belief Model and Preventative Health Behavior. *Health Education Monographs* 1974; 2: 35 - 86.
- [49] Sandstrom, Phd Thesis, 1999. Evaluating the benefits and effectiveness of public policy. <http://goto.glocalnet.net/fmsandstrom/eng/avh/avhmain.htm>.
- [50] Sackett DL, Snow JC, 1979. The magnitude of compliance and non-compliance. In *Compliance in Health Care*, Haynes RB (eds). John Hopkins University Press: Baltimore, 1979; 11 - 22.
- [51] Scharfstein D, Rotnitzky A, Robins J. Adjusting for Non-Ignorable Drop-Out Using Semiparametric Nonresponse Models (with discussion). *Journal of the American Statistical Association* 1999; 94: 1096 - 1146.
- [52] Sickles RC, Taubman P. An analysis of the health and retirement status of the elderly. *Econometrica* 1986; 54(6): 1339 - 1356.
- [53] Spire B, Duran S, Souville M, Leport C, Raffi F, Moatti JP. Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: from a predictive to a dynamic approach. *Social Science and Medicine* 2002; 54: 1481 - 1496.
- [54] Stern S and M Trajtenberg. Empirical Implications of Pharmaceutical Decision Making, NBER Working Paper, 1998.
- [55] Stone VE, Hogan JW, Schuman P, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients's understanding of their regimens: survey of women in the HER study. *J Acquir Immune Defic Syndr* 2001 ; 28: 124 - 131.
- [56] Trajtenberg M, 1989. The Welfare Analysis of Product Innovations, with an Application to Computed Tomography Scanners. *Journal of Political Economy* 1989; 97 (2): 444 -79.
- [57] Trajtenberg M. *Economic Analysis of Product Innovation*. Harvard University Press: Cambridge, 1990.

- [58] Trotta MP, Ammassari A, Melzi S, Zaccarelli M, Ladisa N, Sighinolfi L, Mura MS, d'Arminio Monforte A, Antinori A. for the AdICoNA Study Group. Treatment-related factors and highly active antiretroviral therapy adherence. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 2002; 31: S128-S131.
- [59] Weiss J, 2000. Attitudinal factors and adherence to protease inhibitor combination therapy. In: *AIDS in Europe, New Challenges for the social sciences*, Moatti JP, Souteyrand Y, Prieur A, Sandfort T, Aggleton P (eds). Collection *Social aspects of AIDS*: London, Routledge, Taylor and Francis Group, 2000; 45 - 56.
- [60] Woolridge C. *Econometric Analysis of Cross Section and Panel Data*. The MIT Press: Massachusetts, London, England, 2002.



Table 1: Characteristics of the per protocol population at inclusion

	<b>CBV / ABC</b> <b>n = 90</b>	<b>CBV / NFV</b> <b>n = 89</b>	p
<b>Demographic characteristics</b>			
<b>Risk factors</b>			
Mean age, years [min, max]	34 [18 – 68]	34 [18 – 66]	0.27
Males (%)	70%	64%	0.33
Mean weight(kg)	66 [42 – 103]	65 [38 – 115]	0.79
Alcohol addicted (%)	25%	22%	0.64
<b>Health status</b>			
Mean viral load (log <sub>10</sub> copies/ml) [min, max]	4,2 [1,3 - 5,5]	4,2 [1,3 - 5,5]	0.46
Mean CD4 cell counts (cells/mm <sup>3</sup> ) [min, max]	377 [10 - 854]	462 [27 - 836]	0.01
HIV-related diseases(%)	12%	15%	0.64
HIV transmission(%)			
<i>Homosexual</i>	31%	34%	0.71
<i>Heterosexual</i>	53%	48%	0.50
<i>Transfused</i>	12%	10%	0.65

Table 2: Percentage of patients reaching an undetectable viral load(per protocol)

Visits	Percentages [95% Confidence Intervals]		P (Khi 2)
	CBV/ABC	CBV/NFV	
W0	0%	0%	
W4	<b>59%</b> [48% - 70%]	<b>50%</b> [39% - 62%]	0,304
W8	<b>74%</b> [64% - 84%]	<b>75%</b> [65% - 85%]	0,886
W16	<b>84%</b> [74% - 93%]	<b>80%</b> [70% - 90%]	0,623
W24	<b>92%</b> [85% - 98%]	<b>97%</b> [91% - 100%]	0,301
W32	<b>94%</b> [88% - 99%]	<b>91%</b> [84% - 98%]	0,623
W40	<b>88%</b> [80% - 96%]	<b>89%</b> [81% - 97%]	0,857
W48	<b>89%</b> [81% - 97%]	<b>88%</b> [80% - 96%]	0,833

Table 3: Complete adherers (n,%)according to pill count

Time intervals	CBV/ABC	CBV/NFV	P*
W00-W04	42/71 ( <b>59%</b> )[47%,71%]**	29/62 ( <b>46%</b> )[34%,60%]**	0,17
W04-W08	34/66 ( <b>52%</b> )[39%,64%]**	32/59 ( <b>54%</b> )[41%,67%]**	0,8
W08-W16	41/59 ( <b>69%</b> )[57%,81%]**	30/58 ( <b>52%</b> )[38%,65%]**	0,06
W16-S24	30/51 ( <b>59%</b> )[45%,73%]**	17/44 ( <b>39%</b> )[24%,54%]**	0,06
W24-W32	30/53 ( <b>57%</b> )[43%,70%]**	19/49 ( <b>39%</b> )[24%,53%]**	0,08
W32-W40	30/53 ( <b>57%</b> )[42%,70%]**	17/45 ( <b>38%</b> )[23%,52%]**	0,07
W40-W48	23/43 ( <b>54%</b> )[38%,69%]**	19/35 ( <b>54%</b> )[37%,72%]**	1
W00-W48	230/396 ( <b>58%</b> )	163/352 ( <b>46%</b> )	< 0,001

\*two-sided exact Fisher Test, \*\* 95% Confidence Intervals

Table 4: Descriptive statistics of variables included in multivariate analyses

%	W04	W08	W16	W24	W32	W40	W48
= 1 if $(CD4_{t-1} - CD4_0) > 0$		35% (56/159)	49% (73/149)	55% (78/142)	75% (100/134)	72% (95/132)	73% (93/128)
= 1 if the patient received concomitant drugs	78% (130/167)	77% (122/159)	77% (115/149)	76% (108/142)	89% (120/134)	89% (118/132)	89% (114/128)
= 1 if the patients underwent side effects over $[t-1, t]$	8% (14/167)	8% (13/159)	9% (14/149)	11% (16/142)	7.5% (10/134)	9% (11/132)	9% (12/128)
= 1 if $(VL \leq 30000$ and $CD4 \geq 400)$ at W00	37% (61/167)	36% (58/159)	37% (53/142)	38% (51/134)	38% (51/134)	39% (52/132)	38% (49/128)
<i>Moyn</i> ( <i>n</i> )							
Viral Load (VL) at W00 (Log10)	4.19 (167)	4.19 (159)	4.2 (149)	4.19 (142)	4.20 (134)	4.18 (132)	4.2 (128)
CD4 at W00	421 (137)	419 (159)	417 (149)	422 (142)	421 (134)	428 (132)	428 (128)
Patients 's beliefs concerning treatment efficacy (0...6)	4.9 (141)	5.2 (143)	5.2 (132)	5.3 (127)	5.3 (94)	5.2 (96)	5.2 (90)

Table 5: Separate random-effects equations and panel bivariate probit model

ADHERENCE EQUATION	Single Probit equations		Simultaneous equations	
	Est	t	Est	t
Randomization group =1 if the patient is in the simplified arm	0.53	2.4	0.52	2.41
Side effects =1 if the subject underwent side effects at $t - 1$	-0.80	-2.10	-0.82	-2.27
Observed CD4 change at $(t - 1)$ =1 if $(CD4_{t-1} - CD4_0) > 50$	-0.22	-2.20	-0.28	-2.30
Belief that the disease is under control = 0...6 (controlled)	-0.14	-1.47	-0.13	-1.27
Visit =5,6,7,8,9,10	-0.01	-0.25	-0.01	-0.25
Baseline health status =1 if $(VL \leq 30000$ and $CD4 \geq 400)$ at Day 0	0.48	2.20	0.39	2.03
Concomitant drugs =1 if the patient received concomitant drugs	-0.52	-2.16	-0.43	-2.17
Constant	0.30	0.33	0.36	0.32
$\sigma_v$	1.01**		0.99**	
CLINICAL EFFICACY EQUATION				
Adherence behavior =1 if the patient is compliant over $t - 1, t$	0.40	2.10	0.75	1.13
Randomization group =1 if the patient is in the simplified arm	-0.03	-0.11	0.24	1.10
Visit =5,6,7,8,9,10 (LOG10)	0.29	4.83	0.32	5.33
Viral load at baseline (log10)	-0.01	-0.03	-0.10	-0.52
Constant	-1.04	-7.70	-0.85	-1.88
CD4 cell counts at baseline (/1000)	0.99	1.62	1.18	2.10
Constant	-1.04	-7.70	-0.85	-1.88
$\sigma_\eta$	0.73**		0.74**	
Covariance between individual effects ( $\sigma_{v12}$ )			0.35	2.50
Covariance between error terms ( $\sigma_{\eta12}$ )			-0.24	-2.18

\*\* significant

Table 6: Comparison of initial characteristics of randomized patients and attriters

	ITT <i>n</i> = 195	Per Protocol at W48 <i>n</i> = 128	Attrition <i>n</i> = 67	<i>P</i> *
Age (mean,std)	36.1 (9)	36.5 (9.8)	35.5 (9.3)	0.5
Sex (Female)	33%	30.5 %	37%	0.33
Weight kg (mean, std)	67 (12.2)	68 (12.7)	64.5 (11)	0.08
CDC A Classification	78%	77%	82%	0.37
HIV-related diseases	13%	12.5%	13.5%	0.85
Viral load (log10) (mean, std)	4.12 (0.6)	4.2 (0.6)	3.9 (0.5)	0.004
CD4 cell counts (mean, std)	430 (212)	428 (201)	432 (236)	0.90
Smoker	51%	54%	46.5%	0.31
Alcohol-addicted	27%	23.5%	33%	0.16
Risk factors of HIV transmission				
Homosexual	33%	37.5 %	25.5%	0.09
Heterosexual	51.5%	51.5%	51%	0.9
Transfused	11%	7%	18%	0.01

Table 7: Comparability of CBV/ ABC and CBV/ NFV groups in the per protocol population at W48 and W0

	Per Protocol at W48			Per Protocol at W0		
	CBV/ABC <i>n</i> = 63	CBV/NFV <i>n</i> = 65	<i>P</i> *	CBV/ ABC <i>n</i> = 90	CBV/NFV <i>n</i> = 89	<i>P</i> *
Age	36.5 (8.5)	36.5 (9.3)	0.9	35.2 (9.7)	36.6 (9.7)	0.27
Sex (Female)	27%	34 %	0.4	30%	36%	0.33
Weight kg	68 (11.5)	68 (12.3)	0.89	66.6 (12)	67.1 (13)	0.79
CDC A Classification	79%	74%	0.46	78%	77%	0.96
HIV-related diseases	11%	14%	0.64	12%	15%	0.64
Viral load (log10)	4.2(0.53)	4.2 (0.5)	0.42	4.16 (0.5)	4.21 (0.5)	0.46
CD4 cell counts	397 (205)	457 (194)	0.09	377 (196)	462 (200)	0.01
Smoker	57%	51%	0.47	56%	52%	0.60
Alcohol-addicted	24%	23%	0.92	28%	25%	0.64
HIV transmission						
Homosexual	35%	40 %	0.55	31%	34%	0.71
Heterosexual	54%	49%	0.59	53%	48%	0.50
Transfused	8%	6%	0.70	12%	10%	0.65

Table 8: Trivariate probit model

ADHERENCE EQUATION		
	Coef	<i>t</i>
Randomization group =1 if the patient received the simplified treatment	0.33	3.31
Side effects =1 if the subject underwent side effects at $t - 1$	-0.42	-1.92
Observed CD4 change at ( $t - 1$ ) =1 if $(CD4_{t-1} - CD4_0) > 50$	-0.22	-1.9
Visit =5,6,7,8,9,10	-0.01	-0.30
Baseline health status =1 if $(VL \leq 30000$ and $CD4 \geq 400)$ at Day 0	0.28	2.8
Concomitant drugs =1 if the patient received concomitant drugs	-0.23	-1.68
Constant	-0.31	-0.5
CLINICAL EFFICACY EQUATION		
Adherence behavior =1 if the patient is adherent at $t$	0.29	1.1
Randomization group =1 if the patient received the simplified regimen	0.21	1.41
Visit =5,6,7,8,9,10	0.17	3.29
CD4 cell counts at baseline	1.02	3.48
Constant	-0.31	-0.50
ATTRITION EQUATION		
Randomization group =1 if the patient received the simplified treatment	-0.26	-1.07
Viral Load Rebound at $t - 1$ =1 if the patient suffered from a viral load rebound at $t - 1$	-0.63	-1.95
Side effects between $t - 2$ and $t - 1$ =1 if the subject underwent side effects	-0.39	-0.82
Visit =5,6,7,8,9,10	0.07	0.82
Baseline health status =1 if $(VL \leq 30000$ and $CD4 \geq 400)$ at Day 0	0.27	1.06
Side effects between $t - 2$ and $t - 1$ =1 if the subject underwent side effects	-0.39	-0.82
Concomitant drugs at $t - 1$ =1 if the patient received concomitant drugs	0.51	1.86
Constant	-0.31	-0.5
$cov(\varepsilon_{1it}, \varepsilon_{2it})$	0.81	5.05
$cov(\varepsilon_{1it}, \varepsilon_{3it})$	-0.16	-1.27
$cov(\varepsilon_{2it}, \varepsilon_{3it})$	0.05	0.40