Patient welfare : an economic analysis of patient compliance in a randomized clinical trial.

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Abstract

This paper offers a measure of patient welfare based on whether patients comply with the prescription they receive. Compliance behavior reveals patients subjective valuations of particular therapies. We write a simple theoretical model of patient compliance behavior, that reflects the trade-off between perceived costs and observed regimen efficacy; this discrete choice model is then estimated on clinical trial data. The analysis focuses on identifying patient and drug characteristics associated with non-compliance. Renewing the analysis of adherence data, our econometric approach is implemented through a panel two-equation simultaneous system.

The data come from a clinical trial conducted in France between 1999 and 2001 and comparing the efficacy of 2 tritherapy strategies. We show that a welfare approach based on compliance may add valuable information to conclusions drawn by a mere biostatistical analysis. In particular, we interpret 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 compliant with one regimen. We show that the utility level associated with drug consumption versus no drug intake is significantly higher in the compliance enhancing arm than in the other. Furthermore we identify the observed health outcome as a significant contributor to adherence behavior. Our results based on panel data also stress that unobserved patient characteristics account substantially for compliance behavior.

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1 Introduction

Compliance is "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 medical regimens, especially drug regimens in HIV disease. Since the introduction of highly active antiretroviral treatment (HAART), 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-compliance 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 compliance rates reflect patients'valuations of particular therapies. Consequently, adherence behavior provides information that is useful in the evaluation of the treatment. Our proposed estimator for patient welfare depends on whether patients comply with the treatment they receive.

Within a rational choice framework, we begin by modeling the patient trade-off between perceived costs and observed regimen efficacy before implementing an econometric approach. The key assumption is that observed consumer choices reveal their subjective preferences, and may be used to assess consumer welfare. Relying on a discrete choice model, this analysis focuses on identifying patient and drug characteristics associated with non-compliance. Whereas previous studies dealing with non-compliance factors used transversal datasets and establishes no relationship with the medical literature dealing with the impact of compliance on health status, our econometric approach is implemented through a panel, two simultaneous equation, approach. The data come from a clinical trial conducted in France between 1999 and 2001 and comparing the efficacy and toxicity of 2 tritherapy strategies. Patients were followed for 48 weeks and 10 visits were planned. Compliance was assessed at each visit by an objective measure based on pill count and a subjective measure based on self-report. In the last section, we present the results of our estimations and lay the emphasis upon the major findings of our study.

2 A rational choice framework

2.1 Another look at compliance

Most health researchers take it for granted that non-compliance results from an irrational behavior. Very few approaches are patient-targeted. Besides, poor adherence has generally been viewed as a statistical issue that shoud be controlled for (Scharfstein et al., 1999) and what is missing from most adherence analyses is a discussion of patient welfare. However, many authors point out that compliance could be the result of a rational trade-off operated by the patient. We capture this trade off in a simple theoretical model.

The idea of a rational non-compliance behavior was initially highlighted by 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, 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, the whole notion of "compliance "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 perspective (1951), where noncompliance is a form of deviance in need of explanation. A patient-centered perspective has been developed by Conrad (1985). This approach 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. Conrad argues that from a patient's perspective, the issue is more one of self-regulation than compliance. When "non compliance" is examined beyond difficulties with side effects and drug efficacy, the meanings of self-regulation include testing, controlling dependence, and creating a practical practice. This patient-centered perspective regards patients as active agents in their treatment rather than as "passive and obedient recipients of medical instructions ".

Furthermore a couple of empirical studies suggest that patients are responding to perceived costs and benefits, when choosing whether or not to comply. For example, patient compliance was used as a measure of efficacy of non-steroidal anti-inflammatory drugs (NSAID) in the treatment of patients with rheumatoid arthritis (Capell et al., 1979). The authors argue that a drug which does not adequately relieve pain or which causes intolerable side-effects will quickly be discarded by the patient. NSAIDS are not thought to

influence the natural history of rheumatoid arthritis in the long-term, therefore there can be no reason for a continued use of these drugs if side-effects are severe or symptoms are not relieved. Patients diairies (Johnston-Roberts and Mann, 2003) also relate intentional nonadherence and unveil that patients are weighing the costs of adherence with the benefits of non-adherence. For example, a poor adherent patient reports: "ridding myself of the side effects has been the best thing ; questioning my health status of the future is another".

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), indicating a sizeable difference between the benefits perceived by physician and patient.

In sum, the evidence clearly indicates that patient compliance is an important empirical phenomena, with far reaching economic consequences. Adherence behavior could provide information that is useful in the evaluation of the treatment.

In the microeconomic field, a growing literature aims at acknowledging the information value inherent in patient decision-making and the effect of patient choice over health care outcomes (Philipson and Posner, 1993 ; Meltzer, 1999). In particular, Philipson and Desimone (1997), Philipson and Hedges (1998), Chan and Hamilton (2002) argue that dropout behavior provides information that is useful in the evaluation of the treatment. Philipson and Hedges (1998) assume that the statistical evaluation of clinical trials must account for the active role that subjects play in evaluating treatments. Specifically, patients' decision to withdraw from an experiment reflects their evaluation of the effectiveness of the therapy (which the patient knows may be simply a placebo). Those patients who receive the greatest disutility from being placed on the placebo may opt out of the clinical trial, leading to a downward bias in the measured effectiveness of the drug as calculated by a difference between the (ex-post) treated and control groups. Philipson and Desimone (1997) argue that participants engage in "subject sampling" in which they attempt to learn about the direct and side effects of the treatment, since they have a strong incentive to do so. Consequently, dropout behavior provides insight not only into the direct effect of the treatment, but also potential side effects that may not be easily measured or are privately observed by the subject, as well as treatment options that lay outside the clinical trial. Chan and Hamilton (2002) construct a structural

model of randomized clinical trial (RCT) subject behavior in which trial participants decide whether to drop out by comparing the utility generated by remaining in the trial, which is a function of both direct and side effects of the treatment received, with the returns obtained by seeking care outside the trial. However attrition is only a special case of non-compliance. 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. They aim at performing a welfare analysis based on regimen compliance. Their proposed estimator of patient welfare depends on whether patients comply with the prescriptions they receive from physicians and the motives of physicians in their prescription behavior. However the authors do not build any theoretical framework and the implementation of their approach is not provided due to the lack of relevant data.

2.2 A simple model

We assume that the individual adherence behaviour is the result of some trade-off between the immediate and noticeable side effects that affect negatively her quality of life, denoted by q, and the treatment effects on her health, denoted by h. To take that 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 $u_{hq} \geq 0$). 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. Moreover, we limit this first approach to a static decision set-up.

To keep the model as simple as possible, we assume that the treatment effects on both variables are linear. If we denote the adherence level by θ and the health state without treatment by h, then the health state is equal to $h' = h + k\theta$; k denotes the treatment effect on health. Similarly, quality of life is also a linear function of θ, given by: $q' = q - c\theta$; c denotes the subjective costs associated to the treatment, i.e. the magnitude of the negative side effects. We assume that the patient knows the value of k, and immediately induces the subjective value of c from personal experience with the drug[1].

[1]This assumption of perfect information is not satisfactory. Indeed, the trial is precisely designed to assess the value of k. A "learning by complying" model in which the patient observes the effects (on her own health h and quality of life q), and updates her beliefs accordingly would be a natural, but complex, extension of the current model.

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 ($\theta = 0$). The utility level is respectively given by $u(h + k, q - c)$, and $u(h, q)$. The following proposition characterises the optimal behaviour.

Proposition 1 *For any health level h, there exists a threshold level $q(h)$ on quality of life, with $q(h)$ increasing with h, such that:*

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

PROOF:

For any given h, $q(h)$ is implicitly determined by the equation $\Delta(h, q) \equiv u(h+k, q-c)-u(h, q) = 0$. Under the above assumptions on u, 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 $u_{qq} < 0$). Similarly, $\Delta_h < 0$ (since $u_{hq} \geq 0$ and $u_{hh} < 0$). Therefore, by the implicit function theorem, we have that $q_h = -\frac{\Delta_h}{\Delta_q} > 0$, whenever the solution to $\Delta(h, .) = 0$ exists. Notice that, for some low values of h, we may have that $\Delta(h, q) > 0$ for any q; in that case we set by convention $q(h) = -\infty$: the individual is adherent even for very low values of q. Similarly, for large values of h, we may have that $\Delta(h, q) < 0$ for any q; in that case we set $q(h) = +\infty$.

■

The function $q(h)$ summarises the trade off: for small values of q, the marginal utility of quality of life is high (adverse side effects are particularly costly), and therefore the optimal behaviour tends to favour $\theta = 0$; in terms of initial health h, the converse is true: 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. Put differently, for a given h, quality of life must be sufficiently large for the individual to comply with the prescription. Naturally, as h gets lower, the individual is more and more sensitive to the treatment effect on health, which means that even for a low level of quality of life, she may choose adherence.

To fix the ideas, under a Cobb-Douglas specification $u(h, q) = h^{1-\alpha}q^{\alpha}$, we have that the threshold function $q(h)$ is (after straightforward computations) equal to:

$$q(h) = \frac{c}{1 - \left(1 + \frac{k}{h}\right)^{\frac{\alpha-1}{\alpha}}},$$

which may be (for small k) approximated[2] by: $q(h) \simeq \left(\frac{\alpha}{1-\alpha}\right)\frac{ch}{k}$.

Notice that an increase in c or a decrease in k increases the threshold value $q(h)$; therefore, not surprisingly, it reduces the propensity to choose $\theta = 1$ The ratio c/k may be interpreted as a cost-benefit ratio: c is the subjective cost (in terms of poor quality of life because of adverse side effects), and k is the treatment benefit on health. The following figure summarises this issue.

INSERT HERE FIGURE 1

2.2.1 Empirical implications

Assume that the population is split in two sub-populations $i = A, B$. Individuals in group i receive treatment i, which 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:

$$P(\theta = 1|i = A) < P(\theta = 1|i = B). \tag{1}$$

Under the linear approximation above, $(\theta = 1|i = A)$ is equivalent to $\left(\frac{q}{h}\right) > \left(\frac{\alpha}{1-\alpha}\right)\left(\frac{c^A}{k^A}\right)$. Therefore if the distribution of (h, q) is identical across the two groups (which should be the case if the groups have been determined by an adequate randomisation procedure), the inequality (1) directly implies that $\frac{c^A}{k^A} > \frac{c^B}{k^B}$. In short, a lower adherence level reveals that the cost benefit 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 $c^A > c^B$.

INSERT HERE FIGURE 2

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. In line with the discrete choice framework of the theoretical model, we want to estimate $\Delta(h, q) \equiv u(h + k, q - c) - u(h, q)$.

[2] An approximation of Δ, for small values of k and c, directly gives: $\Delta/u \simeq (1-\alpha)k/h - \alpha c/q$.

3.1 A discrete choice framework

We begin by restating the commonly held assumption 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 in 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 comply at date t, or in other words whether or not to consume the prescribed drug at date t. Adherence is analyzed as a dichotomous variable, which can be considered as relevant in the treatment of HIV disease, existing data suggesting that it is necessary to take a high proportion (95 % or more) of antiretroviral drug doses to maintain suppression of viral replication (Paterson et al., 2000). Let us consider θ_{it} the dichotomous compliance variable defined above: $\theta_{it} = 1$ (respectively, $\theta_{it} = 0$) when the patient i is compliant (resp., non compliant) at time t.

This discrete choice approach requires us to identify the various factors influencing the patient's adherence behavior. If the patient is responding to observed outcomes and perceived costs, the decision to be adherent is expected to depend not only on the impact of treatment on observed measures of health status, but also on private information observed by the patient such as pain or discomfort, after usual covariates have been controlled for. To this respect, we can rely on numerous studies dealing with the determinants of compliance. Four sets of factors are generally studied: patient-related, treatment-related, disease-related factors and variables related to the patient-physician relationship.

We assume that each patient maximizes the utility derived from drug consumption. Let us note $U_{it}(1, X_{1i}, \varepsilon_{1i})$ the utility level associated with being adherent at time t and $U_{it}(0, X_{1i}, \varepsilon_{1i})$ the utility level associated with not being adherent at time t. X_{1i} is a vector of baseline or time-

dependent observed patient-related, disease-related and treatment-related variables (including $h_{i,t-1}$). ε_{1i} is a vector of unobserved (by the econometrician) patient and regimen characteristics.The patient i is adherent at time t if $U_{it}(1, X_{1i}, \varepsilon_{1i}) \geq U_{it}(1, X_{1i}, \varepsilon_{1i})$ The choice problem determines the probability that a patient of a given type chooses to be adherent at time t. The econometric estimation is founded on the latent variable θ^*_{it}, which can be interpreted as the difference between the utility levels presented above $U_{it}(1, X_{1i}, \varepsilon_{1i}) - U_{it}(0, X_{1i}, \varepsilon_{1i})$. In this framework, patient compliance represents an economic choice which should allow for identification of the incremental benefits of a given drug over the alternative of no drug at all.

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 and constructed on the latent variables (Butler and Moffitt, 1982 ; Guilkey and Murphy, 1993 ; Greene, 2000 ; Lollivier, 2001).

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

$$\left\{ \begin{array}{c} \theta^*_{it} = x'_{1it}\beta_1 + h_{it-1}b_1 + \varepsilon_{1it} \\ h^*_{it} = x'_{2it}\beta_2 + \theta_{it}\gamma_{21} + \varepsilon_{1it} \end{array} \right.$$

$$\varepsilon_{it} = \left(\begin{array}{c} \varepsilon_{1it} \\ \varepsilon_{2it} \end{array} \right) = \left(\begin{array}{c} v_{1i} \\ v_{2i} \end{array} \right) + \left(\begin{array}{c} \eta_{1it} \\ \eta_{2it} \end{array} \right) = v_i + \eta_{it}$$

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

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

$$\Sigma_\eta = \left(\begin{array}{cc} \sigma^2_{\eta 1} & \sigma_{\eta 12} \\ \sigma_{\eta 12} & \sigma^2_{\eta 2} \end{array} \right)$$

$$\Sigma_v = \left(\begin{array}{cc} \sigma^2_{v1} & \sigma_{v12} \\ \sigma_{v12} & \sigma^2_{v2} \end{array} \right)$$

where $h_{it} = 1$ if health status is good (= 0 if health status is bad). (eg undetectable vs detectable viral load). The literature, such as Girard, Katlama and Pialoux (2003) suggests that the following variables might be expected to affect the subject-level treatment impact on h_{it}, and hence will be inluded in X_{2it} : demographic variables (such as age and gender) ; variables measuring the extent of disease at baseline, such as whether the subject has a symptomatic HIV infection (which suggests a greater spread of the disease) or whether the subject had been exposed to prior antiretroviral therapy.

We can notice that this way of analyzing compliance data addresses some major caveats of current methods based on cross sectional studies and regarding adherence as an exogenous variable which does not depend on the clinical outcome. Furthermore, 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.

3.3 Model estimation

We estimate a panel non linear simultaneous two-equation system. This system is logically consistent (Maddala, 1983) and can be fully identified. Two main difficulties must be dealt with. First, we are faced with dichotomous dependent variables, for which standard simultaneous equation techniques are inappropriate. Second, the panel data structure makes the problem a bit worse.

We make a point of considering a full information method of estimation. The estimation treats all equations and all parameters jointly. It takes into account the possible correlation between the individual unobserved specific terms and the disturbances in the two equations. We can first note that our model is a recursive, simultaneous-equation model, with only one endogenous variable appearing on the right-hand side of the other equation. The endogenous nature of the adherence variable on the right-hand side of the second equation can be ignored in formulating the log-likelihood (Maddala, 1983 ; Greene, 1998). We can proceed as if there were no simultaneity problem for the estimation in the bivariate probit framework.

The model determines the values of two endogenous variables, it contains one predetermined variable (h_{it-1}). This is obviously not exogenous, but with regard to the current values of the endogenous variables, it may be regarded as having already been determined. The key point is whether or not it is uncorrelated with the current disturbances, which we might assume.

A maximum-likelihood method involving evaluation of double integrals is used and was implemented through a specific programmation on gauss software[3].

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 CNAF3007/Ecureuil multicenter, comparative, open label, randomized Phase IIIB trial which evaluated and compared the safety and efficacy of two different combination therapies in HIV-1 infected antiretroviral therapy naive patients. The study was conducted from November 1998 to July 2000. The overall trial strategy was to judge the utility of a "protease inhibitor-saving regimen" for first line antiretroviral treatment. At 60 centers throughout France, patients were sequentially randomized into two groups: one received a 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 a combination of two reverse transcriptase inhibitors and a protease inhibitor (one Combivir©tablet twice a day, plus Viracept©(nelfinavir) three capsules q8h)). The 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, were A/B category according to the 1993 CDC classification and had viral plasma HIV-1 RNA loads in the range 1000 - 500 000 copies/ml at the time of the screening visit. A total of 195 screened patients were randomized and underwent 48 weeks of treatment and a 4-week post-treatment follow-up. 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 undectable level by the end of the trial. Health status (Viral Load and CD4 cell counts) and toxicity were evaluated at each visit.

We checked that subjects were initially comparable in both groups for age, gender, stage of disease, plasma HIV-1 RNA and CD4 cell count (al-

[3]We thank Jacques Huguenin for decisive help on this implementation.

though CD4+ cell count was slightly higher in the NFV group). The triple nucleoside combination showed similar antiretroviral activity to that of a PI containing regimen as measured by plasma HIV-1 RNA and CD4+ cell responses following 48 weeks of treatment. In the Intention to Treat (switch = failure) population 61% subjects in the CBV/ABC group versus 60% in the CBV/NFV group had plasma HIV-1 RNA < 400 copies/ml at weeks 48 (difference and 95%CI = 1%[-12,15]). In this study in antiretroviral therapy naive subjects, both treatment regimens (CBV/ABC and CBV/NFV) were generally well tolerated.

Further information on the trial protocol and results have been published elsewhere (Descamps et al., 2001 ; Matheron et al., 2003).

4.2 Methods used to estimate adherence and definition

Adherence was recorded at weeks 4, 8, 16, 24, 32, 40 and 48 through three different measurement methods: the appraisal by the investigator; the pill count; and a patient self-administered questionnaire. Following an interview with the patient, the investigator was asked to estimate whether adherence corresponded to full compliance, partial compliance or non-compliance for each drug in the study regimen. Tablet count was based on an inventory of study drugs supplied to the patient and subsequently returned to the investigational site. Unused material was recorded by site pharmacists and checked by trial monitors. A Treatment Review and Satisfaction Questionnaire was completed by the patient at week 4, week 8 and then every 8 weeks until week 48 or, in the case of premature cession of treatment, at the time of leaving the trial. All questions addressed the 4 weeks preceding the visit. In particular, the patient was asked to estimate the frequency of lapses and average length of delays in taking medication respectively.

None of these methods can be regarded as a gold-standard method. The physician appraisal seems to be the less reliable measurement method (Paterson et al., 2000). As a result, we decided to study compliance through the pill count and the self-questionnaire, respectively an objective and a subjective measure.

Compliance was then summarized by a dichotomous variable. According to the pill count, a patient is adherent if the adherence rate is higher than 95%. According to the questionnaire, the patient is adherent if no drug dose has been missed for the past four weeks.

4.3 Adherence evaluation during the trial

Data concerning adherence are 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. Descriptive statistics showed that compliance tended to decrease over time though not linearly. The percentage of compliant patients turned out to be higher in CBV/ ABC group (simplified arm), with significant differences at weeks 4, 5, 7 and 8 (Khi 2) and 6, 7, 8 and 9 depending on the measure.

INSERT HERE TABLES 1 and 2

Another interesting feature stressed by the descriptive analysis was a certain stability of the decision whether to comply or not. According to the self questionaire, 82 out of 100 poor adherent patients at a given time point remained poor adherent at the subsequent visit. In the mean time, 74% of good adherers maintained a high adherence behavior. Empirical transition probabilities seemed to be comparable through the pill count measure. Furthermore, some patients remained in the same state, as far as adherence was concerned, all over the trial. 33 patients remained good adherers and 37 patients remained poor adherers. However, it turned out that the adherence variable measured through the self-questionnaire was not correlated with the Viral Load, which questioned the reliability of this measure in our study. As a result, our estimations will be based on the pill count measure.The efficacy measure refers to an undetectable viral load at 400 copies/ml level. All variables significant at a 10% level in univariates analyses were included in the multivariate regressions.

5 Estimations and major findings

Separate equation results (performed with a probit random effects model) and non linear panel simultaneous estimations are presented in Table 3.

INSERT HERE TABLE 3

5.1 Factors associated with compliance

We identify a couple of factors associated with compliance, while controlling for the impact of adherence on health status. Factors independently associated with high adherence are a simplified regimen (randomization group CBV/ ABC), a less advanced virological and immunological stage of the disease before treatment initiation. Factors independently associated with poor adherence are the treatment duration, the consumption of concomitant drugs and the experience of side effects. A positive health outcome observed at the previous follow-up visit is also a predictor of poor adherence, which illustrates our initial assumptions expressed in the theorectical model.

Our findings confirm the factors emphasized upon in other studies. Studies conducted in HIV disease have found that noncompliance 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) ; when the initial clinical or immunological stage of the disease is less advanced (Gordillo et al., 1999 ; Ostrop, Hallet and Gill, 2000). However, the impact of observed health status had never been assessed before, certainly due to methodological issues (endogeneity problems associated with the health status variable) that we were able to overcome through the implementation of a simultaneous equation system. Up to now most authors have concentrated upon the perceived efficacy, that is to say patients beliefs about benefits and risks of treatment (Weiss, 2000) or patients'subjective experience with HAART therapy during the course of treatment(Spire et al., 2002).

On the contrary, we do not confirm findings about other patients's characteristics that were identified as determinants of adherence in previous research like female gender (Roca et al., 1999),drug or alcohol consumption (Haubrich et al., 1999 ; Moatti et al., 2000), anxiety (Gordillo et al., 1999). .

5.2 The panel data and simultaneous equation approach

Our results based on panel data also stress that unobserved patient characteristics account substantially for compliance behavior. These unobserved individual terms are likely to capture the pain or discomfort that the patient feels when taking the treatment medication, or more generally all that as been referred to as quality of life in our microeconomic framework.

We can still notice that the covariance between error terms is significant,

thus suggesting that it is appropriate to take the endogenous nature of compliance into account in a two-equation system. Adherence was significantly associated with treatment success in the single efficacy equation. After controlling for endogeneity, the compliance variable is no longer associated with the completion of an undetectable viral load. This astonishing result is simply attributable to the correlation between the compliance variable and the disturbances. In our data, high compliers probably tend to be healthier to begin with, or engage in healthier behaviors. As a result, the effect of adherence is overstated in the separate equation approach when endogeneity is overlooked. In fact, what matters here is a structural healthy attitude more than a change in adherence behavior between two time periods. This interpretation is supported by the baseline immunological status becoming a significant predictor of treatment success once the endogeneity of compliance has been taken into account. Other 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 no difference between treatment arms.

Finally, the estimations confirm our main assumptions concerning the patient's response to observed health outcome and unobserved individual-specific experience and make it possible for us to draw welfare inference.

5.3 Welfare inference

Meanwhile, the discrete choice framework allows us to interpret the latent variable of the adherence equation as the incremental benefit provided by treatment consumption as expressed by full compliance over no drug intake as expressed by noncompliance. The utility level associated with treatment consumption is significantly higher in the simplified regimen arm (CBV/ ABC) than in the PI containing regimen, whereas the triple nucleoside combination CBV/ ABC was found to have comparable antiviral activity to CBV/ NFV. 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. In terms of well being, the drug-enhancing compliance must be favored. Our estimation assesses the incremental returns from a "twice a day" regimen versus a "three-times a day" regimen combination. Our estimation could also be used to perform the welfare loss associated with a year of delay in regulatory approval for

example.

Thus, our proposed estimator for patient welfare depends on whether patients comply with the prescription they receive. This method is based on indirect inference through observed choice behavior, as opposed to contingent evaluation methods (Diener, O'Brien and Gafni, 1998) measuring directly the preferences of individuals for health outcomes and placing the patient in hypothetical situations (for example "Imagine that you will have to spend 4 months in one of the following dysfunctional health conditions. Please, rank them in order of preference", or "how much would you be willing to pay for..."). In such evaluation frameworks as QALYs or Willingness to Pay, there is no incentive for the patient or the doctor to tell the truth and they may find it difficult to answer questions. Patients are likely to behave in a different way from their declarations. In contrast, our approach does not suffer from these limitations as it uses a genuine behavior choice encountered by the patient.

6 Conclusion

Within a structural and econometric framework, we show that patient compliance behavior relies on a choice which should allow for identification of the incremental benefits of a drug consumption over the alternative of no drug intake. We propose an new way of comparing and evaluating treatments, which is based on compliance behavior. 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 therapies. Our method both complements usual efficacy and toxicity analyses performed in clinical trials and traditional economic evaluations based on direct approaches.

Furthermore, 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 decisionmaking as whether to accept such a procedure or not.

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Table 1: Perfect adherers (n,%)according to self-questionnaire)

Study period	CBV/ABC	CBV/ NFV	P^*
Day 0-Week 4	61/80 (76%)	42/77 (55%)	0.001
Week 4-Week 8	45/71 (63%)	36/73(49%)	0.096
Week 8-Week 16	34/69 (49%)	27/63(43%)	0.489
Week 16-Week 24	30/62 (48%)	21/65(32%)	0.073
Week 24-Week 32	27/45(60%)	19/48(40%)	0.063
Week 32-Week 40	25/50(50%)	17/47(36%)	0.219
Week 40-Week 48	20/42(48%)	16/43(37%)	0.384
Day 0-Week 48	242/419	178/416	0.001

*exact fisher test

Table 2: Complete adherers (n,%)according to pill count

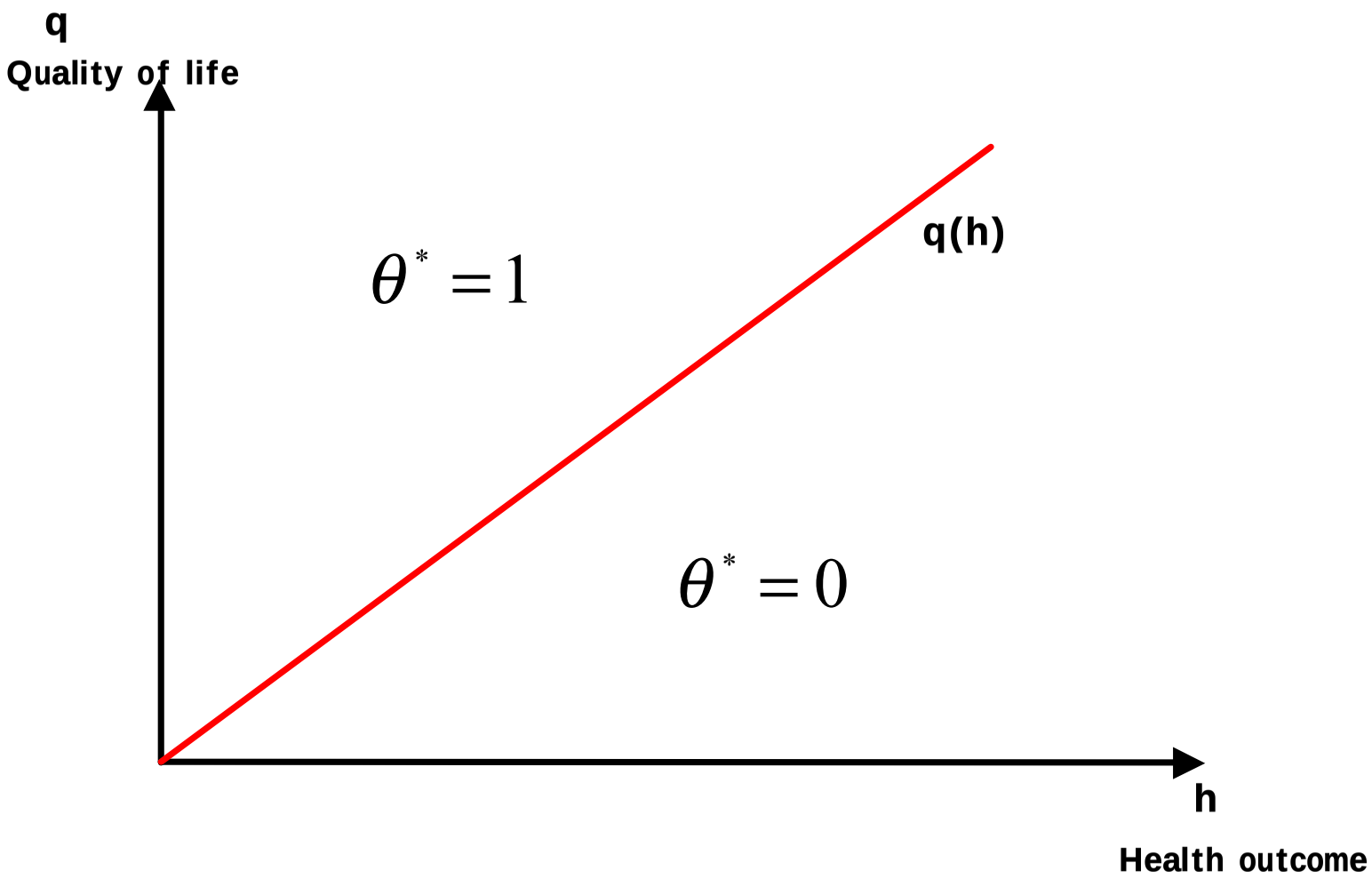
Study period	CBV/ABC	CBV/ NFV	P^*
Day 0-Week 4	42/71 (59%)	29/62 (46%)	0.17
Week 4-Week 8	34/66 (52%)	32/59(54%)	0.8
Week 8-Week 16	41/59 (69%)	30/58(52%)	0.06
Week 16-Week 24	30/51 (59%)	17/44(39%)	0.06
Week 24-Week 32	30/53(57%)	19/49(39%)	0.08
Week 32-Week 40	30/53(57%)	17/45(38%)	0.07
Week 40-Week 48	23/43(54%)	19/35(54%)	1
Day 0-Week 48	66/372	128/344	0.001

*exact fisher test

Table 3: Separate random-effects equations and panel bivariate probit model

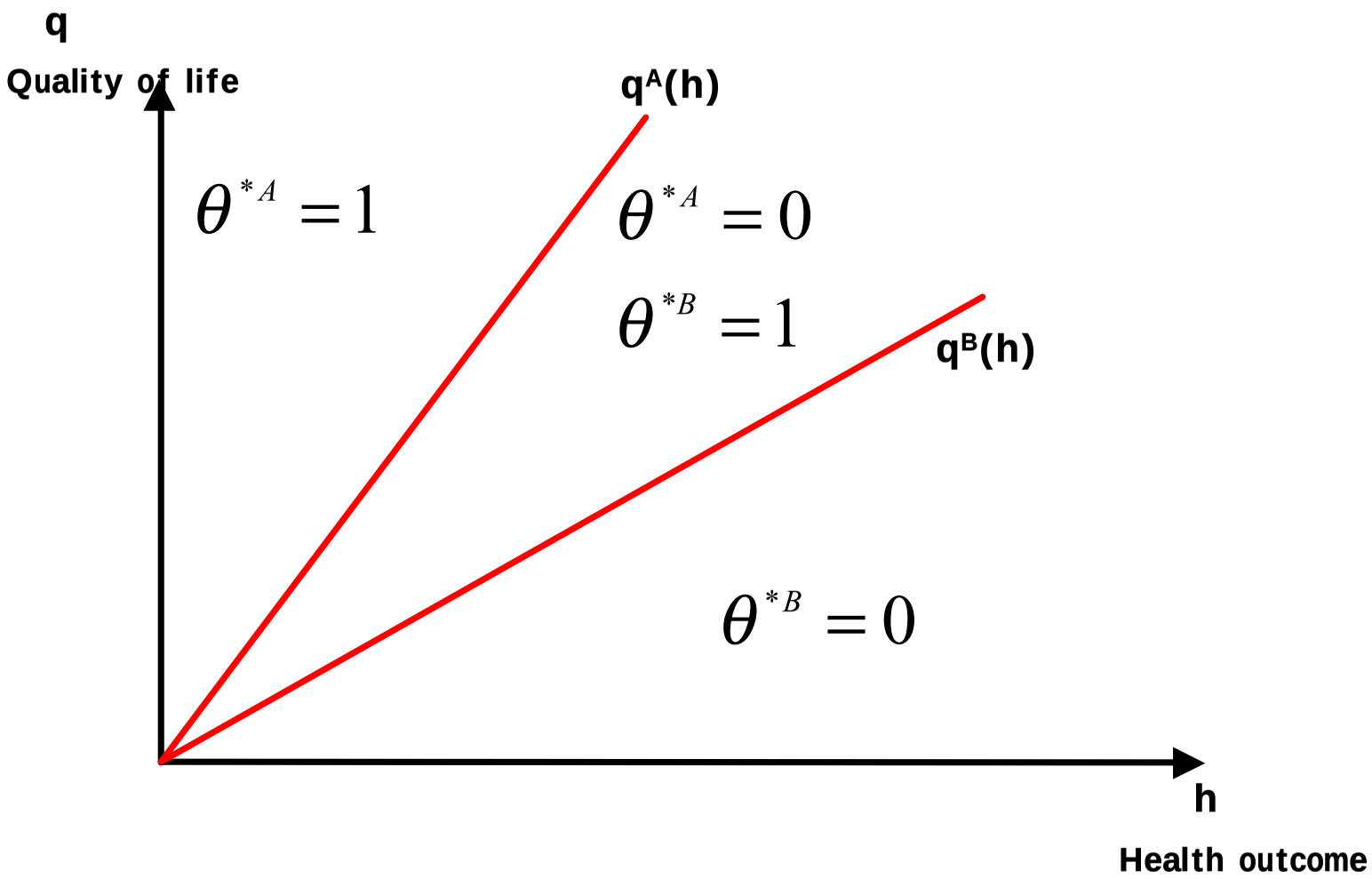
ADHERENCE EQUATION	Single Probit equations			Simultaneous equations		
	Est	Std	P	Est	Std	P
Observed health status at $(t-1)$ =1 if the viral load is undetectable at $(t-1)$	-0.32	0.18	0.07	-0.40	0.18	0.02
Randomization group =1 if the patient received the simplified treatment	0.52	0.24	0.03	0.53	0.24	0.03
Visit =5,6,7,8,9,10	-0.01	0.04	0.87	0.01	0.04	0.95
Baseline health status =1 if (VL$\leq$ 30000 and CD4$\geq$ 400) at Day 0	0.40	0.24	0.09	0.43	0.23	0.06
Side effects =1 if the subject underwent side effects	-0.70	0.34	0.03	-0.61	0.35	0.08
Concomitant drugs =1 if the patient received concomitant drugs	-0.48	0.29	0.09	-0.58	0.28	0.03
Constant	0.43	0.40	0.27	-0.26	1.2	0.82
σ_v	1.05	0.29		1.02	0.28	
CLINICAL EFFICACY EQUATION						
Adherence behavior =1 if the patient is compliant at t	0.40	0.20	0.04	-0.79	0.63	0.21
Randomization group =1 if the patient received the simplified regimen	-0.03	0.27	0.90	0.15	0.30	0.62
Visit =5,6,7,8,9,10 (LOG10)	0.28	0.06	0.01	0.232	0.08	0.01
CD4 cell counts at baseline	0.98	0.61	0.10	1.14	0.56	0.04
Constant	-1.04	1.35	0.44	-0.26	1.2	0.82
σ_η	0.72	0.31		0.64	0.26	
Covariance between individual effects (σ_{v12})				0.39	0.25	0.11
Covariance between error terms ($\sigma_{\eta 12}$)				0.66	0.33	0.04

Figure 1: Patient trade-off and threshold line



θ^* denotes the optimal adherence behavior

Figure 2: Patient trade-off and threshold line - implications



θ^* denotes the optimal adherence behavior