Effect of HAART on Health Status and Hospital Costs of Severe HIV-Infected Patients: A Modeling Approach

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Purpose: The purpose of this study was to assess the impact of highly active antiretroviral therapy (HAART) on health status and hospital costs in severe HIV-infected patients who were followed in a French hospital. **Method:** The first 500 patients who received HAART, with CD4+ cell count below 250/mm^3, were considered. Evolution of the distribution of patients among different health states, including death, was modeled through a continuous time Markov model. Hospital financial charges and antiretroviral treatment costs were computed. Health states defined by both CD4 counts and viral load were used to show clinical changes in the patient population over a 14-month period after HAART initiation. The economic impact of HAART initiation was assessed using a simplified model based on CD4 counts only over two 14-month periods, before and after initiation. **Results:** Between day 0 and month 14, the proportion of patients in the least severe state (CD4+ >100/mm^3 and viral load <500 copies/mL) increased from 1% to 50%, and the proportion with more than 100 CD4+ cells/mm^3 increased from 17% to 80%. Antiretroviral treatments amounted to Fr 2,141 per patient-month before HAART initiation and to Fr 3,093 after. Conversely, hospital charges fell from Fr 5,138 per patient-month to Fr 3,136. **Conclusion:** Our model gives a representation of the effect of HAART on (1) the improvement of patients' health status, (2) the increase of treatment costs, and (3) the reduction of hospital financial charge. Important savings in hospital charges can compensate for the extra cost associated with the initiation of HAART. **Key words:** *HAART, cost, Markov model*

Since 1996, the development of more effective treatments for HIV-infected patients, including the multiplication of antiretroviral therapies and the appearance of protease inhibitors, has dramatically changed both the medical management of the disease[1,2] and the evolution of patients' health status. However, drug treatment costs have consequently risen due to the high price of new agents and the fact that patients are treated earlier and for a longer time. It has thus become necessary to study both the full treatment cost, including savings mainly in hospital costs that may balance to a large extent the drug cost, and the cost-effectiveness ratio of the new therapeutic strategy.

This is obviously a major issue as cost considerations may impair accessibility to treatment in a context of financial restrictions in health care expenditure. Budgetary restrictions have led to situations in which HIV-related drug expenditure is, implicitly or not, in competition with other types of health care expenditure.

A program of economic evaluation of the treatment of HIV infection was therefore initiated using data from a cohort of HIV-infected patients that were followed since 1986 in the Rothschild University Hospital, Paris, France. As a first step, the present analysis is designed to show and measure patterns of improvement of severely immunosup-

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pressed patients treated by a combination of several treatments and to assess the comparative costs of these treatments in relation to the evolution of hospital costs. Although our study sample is not fully representative of the HIV-treated population, it represents the first source of data on HAART prescriptions in the real life available in France at the time of the initiation of our economic evaluation program. Continuous time Markov decision models (CTMM) provide a convenient framework for such analyses and have already been applied in advanced epidemiological studies of the "natural" history of HIV disease[3–6] but not specifically to assess the impact of new treatments on health status and costs. Such models aim to describe and predict the dynamics of patient transitions between different health states. Transitions are described by instantaneous "transition intensities" estimated from cohort observational data. Transition intensities account for both the frequency of passages from one state to another and for the time spent in a state before the transition occurs. CTMMs represent a major improvement over standard discrete time models in which transitions are allowed only at fixed time intervals. Our model includes reversibility,[7] which allows patients in a given state to move in either direction, either improving or deteriorating. We used this technique to give an accurate representation of the process of patients' evolution in terms of clinical status and cost, while we had a limited number of visits per patient. After a technical presentation of this model, we use it as a "gridline" to quantify the effects of HAART on costs and patients' clinical status.

MATERIALS AND METHOD

Patient Population

The clinical records of all patients followed for HIV infection at the Rothschild Hospital since 1986 are computerized in the form of a continuously updated database. At each visit, a large set of clinical and biological data is collected in real time as well as clinical events, disease related to HIV infection, treatments, consultations, and so on, with an on-line upgrade of the database by the clinician. Since 1986, around 6,000 patients were included, of whom 2,260 were currently followed. Among these patients, we selected the first 500 (458 men and 52 women) who received HAART, defined as a combination of at least three antiretroviral agents including one protease inhibitor, between April and October 1996. There were no other inclusion or exclusion criteria (e.g., age, sex, mode of contamination, status, treatment, CD4 cell count, or viral load) apart from being followed for HIV infection in the Rothschild Hospital and having given formal consent. Mean age of these patients was 40 years old (± 9 years). All these patients had CD4+ cell counts below 250/mm^3, and 456 (91.2%) of them were previously treated by at least one antiretroviral agent, including 50 (10%) under monotherapy, 395 (79%) under dual therapy, and 11 (2.2%) under tri therapy. The most frequent associations of treatment were zidovudine plus lamivudine (AZT+3TC; 41.6%) and zidovudine plus zalcitabine (AZT+DDC; 13.6%). At the time of inclusion (day 0), 406 patients (81.2%) received two antiretroviral therapies in addition to the protease inhibitor and 54 (10.8%) received only one antiretroviral therapy. Thirty-nine patients (39; 7.8%) received exclusively the protease inhibitor. For each of these 500 patients, we extracted a set of prospective data over the 14-month period after the initiation of HAART and a set of retrospective data over the preceding 14 months, thus representing 28 months of follow-up within the overall period February 1995 to December 1997.

Model

For the first objective, the model consisted of nine states defined by combinations of viral load and CD4 cell counts and a 10th state, death. A series of studies[2,8–12] have shown that viral load is a better marker than CD4 cell count for predicting the evolution of the disease. Nevertheless, we considered that information carried by these two markers is complementary. Indeed, CD4 counts reflect damage already inflicted by the disease on the immune system and thus allow assessment of the risk of developing an opportunistic infection, while viral load accounts for viral replication. There is no linear relation between these two markers, which are only partly correlated (the level of viral replication, measured through viral load, is related to the destruction rate of T4 lymphocytes but not directly to their absolute value). We adopted a partition into three CD4 count ranges determined from both the distribution of patients and the prognostic levels

for opportunistic infections (e.g., toxoplasmosis, bacterial, and cytomegalovirus infections): (1) greater than 100/mm^3, (2) from 50 to 100/mm^3, and (3) lower than 50/mm^3. These CD4 count ranges were coupled to a partition into large ranges of viral load: (A) less than 500 copies/mL (the detection threshold at the time of the study), (B) from 500 to 100,000 copies/mL, and (C) greater than 100,000 copies/mL. The last two categories were determined to reach homogenous groups of patients over the follow-up study. The model was implemented from the moment of initiation of HAART.

Transitions were allowed to occur from any state (except death) to any other state. Indeed, as the entry in the model follows the initiation of HAART, patients may transit not only to adjacent states. Thus, we first computed 90 transition intensities for each possible transition from one state Sα to another state Sβ, including 81 transitions between the 9 transient states ($\lambda_{\alpha\beta}$; α,β=1,…,9) plus 9 transitions to death ($\lambda_{\beta D}$; β=1,…,9).

Due to the significant number of transitions allowed in our model, we used the theoretical model defined by Chiang as "a general illness-death process"[7(pp450–476)] for the estimation of transition intensities. In this theoretical model, we have to monitor for each individual i, the following information:

- $t_{\alpha i}$ the time passed in state Sα;
- $m_{\alpha\beta i}$ the number of transitions from Sα to Sβ;
- $d_{\beta i}$ an indicator taking value 1 if the individual dies from Sβ.

The maximum likelihood estimators (MLE) $\hat{\lambda}_{\alpha\beta}$ of transition intensities between transient states and $\hat{\lambda}_{\beta D}$ of transition intensities to death are[7]:

$$\hat{\lambda}_{\alpha\beta}=\frac{\sum_{i=1}^{500} m_{\alpha\beta i}}{\sum_{i=1}^{500} t_{\alpha i}},\alpha,\beta=1..9,\beta\neq\alpha$$

$$\hat{\lambda}_{\beta D}=\frac{\sum_{i=1}^{500} d_{\beta i}}{\sum_{i=1}^{500} t_{\beta i}},\beta=1..9$$

For each α, transition intensities have to satisfy the fundamental equality:

$$\sum_{\beta=1}^{9}\lambda_{\alpha\beta}+\lambda_{\alpha D}=0$$

so that all $\lambda_{\alpha\alpha}$ are computed by subtraction. Because $t_{\alpha i}$, the time passed in state a before the occurrence of the transition to the next step, is not perfectly known, we used the time to the following visit as an estimator. This seems reasonable as intervals of time between two consecutive visits are short in our study. Conversely, the time to death was perfectly known, because the date of death was automatically recorded.

Thus, transition intensities $\lambda_{\alpha\beta}$ are computed in a similar way to disease incidences, depending on the number of observed transitions between stages and on the corresponding interval of time. Consequently, if numerous transitions are reported in a short period of time between a given state Sα and another given state Sβ, this will lead to a high estimate of the corresponding transition intensity $\hat{\lambda}_{\alpha\beta}$ between states α and β. After suppression of nonsignificant transition intensities, we obtained a (9 x 9) matrix with 46 significant intensities of transitions between transient states, and a (9 x 1) column matrix with 5 significant transition intensities to death.

The following step was the estimation of transition probabilities from state Sα to state Sβ ($P_{\alpha\beta}$) and probability of death from state β ($P_{\beta D}$). A transition probability between two given states α and β is a continuous function of time. Its shape depends on the values of α and β. We assumed that time homogeneity, that is transition probabilities, for a given patient does not depend on the specific origin of time. Thus, probabilities could be computed relative to a unique origin of time. This hypothesis appears reasonable because, in our study, patients are included over a short period of time (from April to October 1996). Finally, we estimated the percentages of patients in each state as a function of time since HAART initiation by applying the transition probabilities to the initial distribution of patients among states.

To assess specifically the impact of HAART initiation on both patients' health status and the economic cost of AIDS treatment (pharmaceutical and hospital costs), we used a simplified model. Because viral load data were nearly completely missing before 1996, the year of the introduction of

HAART, the nine predeath states were reduced to three based on CD4+ count only. This second model was implemented over the full period of 28 months (14 months before and 14 months after HAART initiation). However, due to our method of data collection, patients could die only during the post-HAART initiation period. Thus, we adjusted cost results on the actual durations of follow-up and presented them in terms of costs per patient-month. In addition, as patients were recruited in the hospital, we excluded a 30-day period around day 0 (D0) to avoid a possible artificial rise in hospital costs at the time of HAART initiation.

Cost Data

Two items of cost were evaluated in our study: antiretroviral treatment cost and hospital cost divided into outpatient consultations, day hospital attendance, and inpatient care.

Hospital cost assessment was made from daily prices of French public hospitals: Fr 6,984 for day hospital, Fr 4,510 per day of hospital ward, and Fr 150 per outpatient consultation. All hospital stays recorded during the follow-up period were costed. The use of hospital daily prices represents a full financial charge, including laboratory tests performed and other consumption of resources. To estimate the cost of antiretroviral therapy, we used all data on prescriptions available in the database to reconstitute, for each patient, the exhaustive history of antiretroviral treatment. We assumed that each patient was treated throughout the follow-up period, with no discontinuation. When treatment data were missing, the last data available were carried forward. Indeed, when there was no change in antiretroviral prescriptions, only the names of treatments were recorded in the database, with no supplementary information on start and stop dates or dosage. For the concerned periods of time, we simply used the last information reported by the clinician. Unit costs were mean prices observed in French hospitals,[13] VAT included.

Table 1. Distribution of patients among states at day 0

Viral load (Keq/mL)	CD4/mm³ >100		CD4/mm³ 50–100		CD4/mm³ <50	
< 0.5	A1	5 1.1%	A2	4 0.9%	A3	4 0.9%
0.5–100	B1	49 11.0%	B2	52 11.6%	B3	91 20.4%
> 100	C1	25 5.6%	C2	50 11.2%	C3	167 37.4%

RESULTS

Evolution of the Distribution of Patients by State

Effects of HAART Initiation on Patients' Health Status

At the time of inclusion, day 0, the mean (median) value of CD4 cell count and viral load were respectively 52.7/mm³ (34/mm³) and 280,800 copies/mL (129,000 copies/mL). About 37% of patients were in the most severe state, C3 (i.e., CD4 count less than 50/mm³ and viral load greater than 100,000 copies/mL), while only 1% were in the least severe state, A1 (i.e., undetectable viral load and CD4+ >100/mm³) (see Table 1). Almost 60% of patients had CD4 counts below 50/mm³. This initial distribution of patients reflects the advanced stage of their infection at the time of HAART initiation.

From the moment of the initiation of HAART, the estimated mean times of stay in the least severe state, A1 (i.e., CD4+ >100/mm³ and viral load below the detection threshold), and in state B1 (i.e., CD4+ >100/mm³ and viral load between 500 and 100,000 copies/mL) were much longer than that in any other states, with 191 and 125 days respectively compared with <15 days in any of the other states.

Figure 1 shows the evolution of the distribution of patients by health state during the 14 months after HAART initiation, as estimated by the model. Over this period, patients' health status improved significantly. Between day 0 and day 420, the proportion of patients in the least severe state, A1 (CD4+ >100/mm³ and undetectable viral load) increased from 1% to an estimated 50%, with a maximum effect at about 135 days of treatment, when 55% of patients were in this state.

An overall improvement in immune status is indicated by the significant increase in the proportion of patients with more than 100 CD4+ cells/mm³ from about 17% to 80% in 14 months. Over the

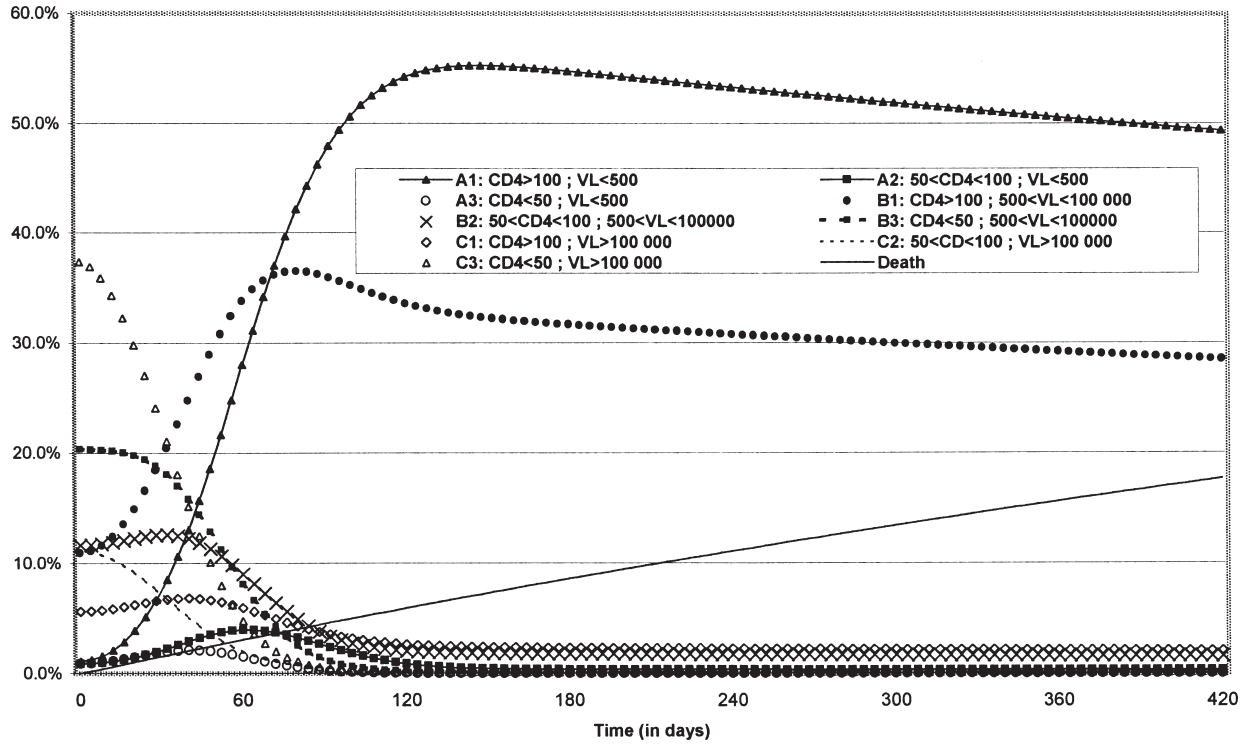

Figure 1. Evolution of patients' distribution after HAART initiation.

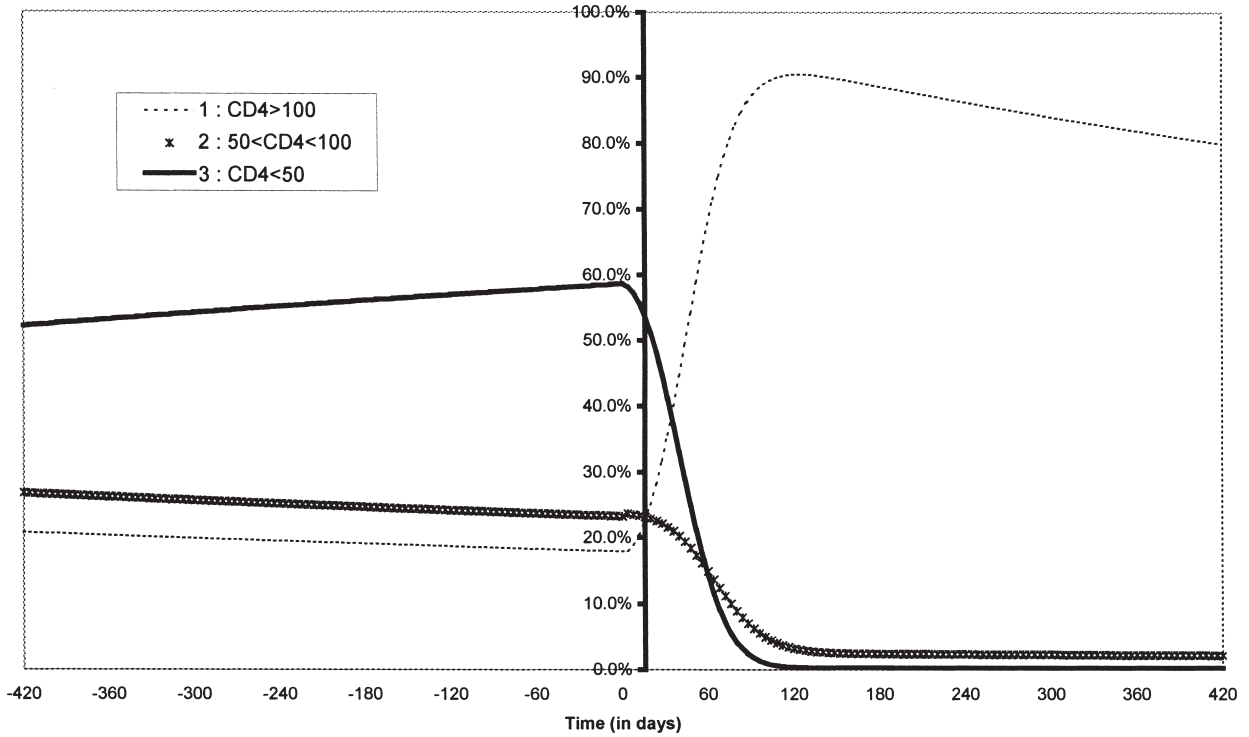

Figure 2. Evolution of patients' distribution before and after HAART initiation, mean (median) times of stay (in days).

same period, viral load became undetectable (<500 copies/mL) in 50% of patients.

At month 14, only 0.1% of patients were in the most "severe" state. The maximum effect was observed after 2 months of treatment. The proportion of deceased patients increased continuously over time to reach 17.6% at month 14.

Evolution of Patients' Health Status

Before HAART initiation, the mean (median) time of stay was highest in state 3 (CD4+ <50/mm^3), with an estimated 234 (162) days (see Fig. 2). After day 0, patients remained in the least severe state (A1) for the longest time, 304 (212) days. This evolution reflects the improvement and the stability of patients' health status.

Fourteen months before HAART introduction, an estimated 52.2% of patients had CD4+ cell counts below 50/mm^3 and 20.8% of patients had CD4+ cell counts above 100/mm^3. Subsequently, a progressive deterioration of patients' health status was observed until day 0, by which time almost 60% of patients had CD4+ cell counts below 50/mm^3 (see Fig. 2). With the inclusion of HAART in the treatment of patients, the proportion of patients with CD4+ <50/mm^3 dropped from 58% at day 0 to 0.2% at 14 months after HAART initiation. This trend reflects the improvement of patients' health status. Indeed, after 14 months of HAART, 80% of patients had CD4+ cell counts greater than 100/mm^3 (i.e., the least severe state) compared with only 17.7% at day 0.

The combined effect of several antiretroviral therapies on health status is seen very quickly. After 60 days of treatment, 67% of patients had CD4+ cell counts above 100/mm^3. The maximum effect was estimated to be observable after about 3 months of treatment.

Cost Analysis

Cost of Antiretroviral Therapy

The mean daily antiretroviral treatment cost per patient increased from about Fr 71 before HAART initiation to Fr 141 after. The protease inhibitor price (i.e., Fr 65 per day) and the change in type of nucleoside analogues combined explain the main part of the difference in costs.

Evolution of Hospital Cost per State

From the moment of HAART initiation, the daily hospital cost attached to the healthiest state (CD4+ >100/mm^3) decreased from Fr 155 before day 0 to Fr 63 per day at 14 months (see Fig. 3). Conversely, the hospital cost of the most severe state (CD4+ <50/mm^3) increased from Fr 219 before day 0 to Fr 427 at 14 months. This can be seen as a process of adverse selection. Indeed, patients who remain in the most severe state after HAART initiation tend to be those who do not respond to any antiretroviral treatment, leading to more frequent occurrence of opportunistic infections that need long and costly hospitalizations.

Effects of HAART on the Evolution of Total Hospital Costs

The evolution of hospital costs (see Fig. 4) results from a combination of the evolution of costs per state (see Fig. 3) and the evolution of the distribution of patients among CD4 states (see Fig. 2). Thus, even though the cost of the most severe state (3, CD4+ <50/mm^3) significantly increased after HAART initiation, the proportion of patients in this state dropped dramatically from 58% to 0.2%. Over the same period, the cost of patients in the least severe state (1, CD4+ >100/mm^3) decreased significantly, while the proportion of patients in this state increased from 17% to 80%.

Finally, drug costs and hospital costs were integrated over two 14-month periods (see Fig. 5), before and after HAART initiation. As a whole, antiretroviral treatments amounted to Fr 2,141 per patient-month before HAART initiation and to Fr 3,093 per patient-month after HAART initiation. Conversely, hospital costs dropped from Fr 5,138 per patient-month before day 0 to Fr 3,136 per patient-month after day 0. The cost of outpatient visits per patient-month remained roughly stable (Fr 96 vs. Fr 85), while hospital ward and day hospital costs both dropped by about 40%.

DISCUSSION

CTMM with reversibility constitutes a relevant tool to give a dynamic representation of the economic impact of new therapeutic strategies. It is particularly well adapted when, as will always be

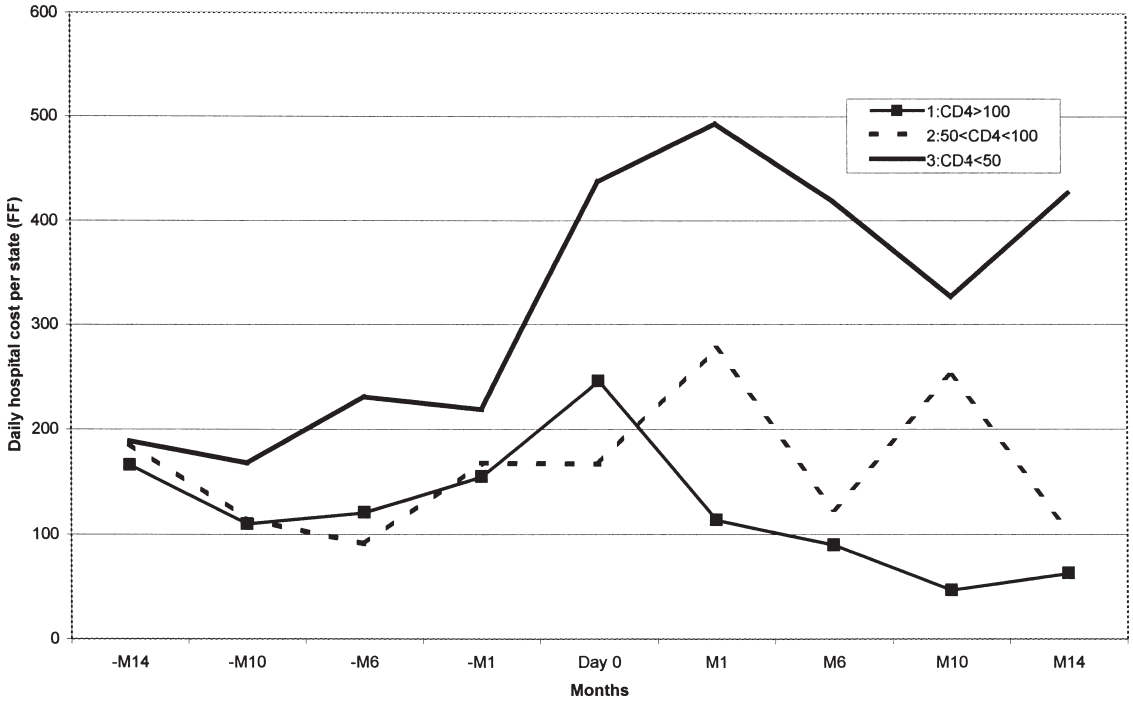

Figure 3. Evolution of mean daily hospital costs per state (Fr).

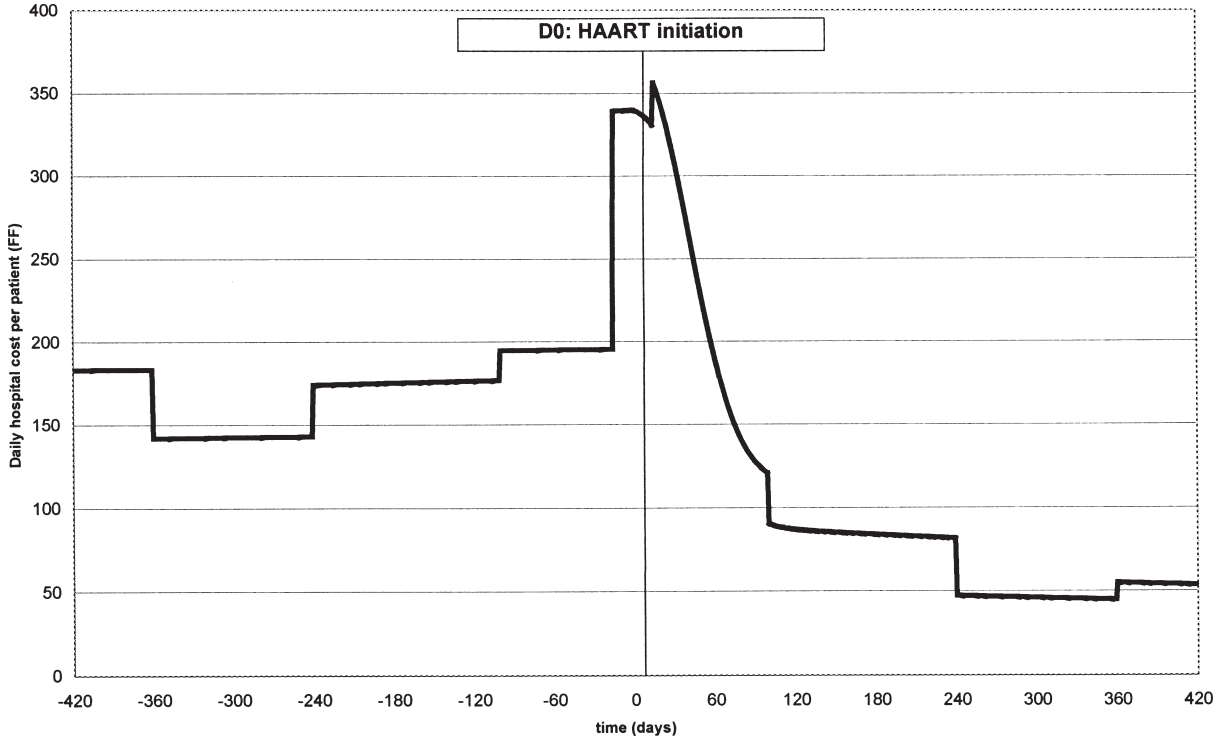

Figure 4. Evolution of mean daily hospital costs per patient (Fr).

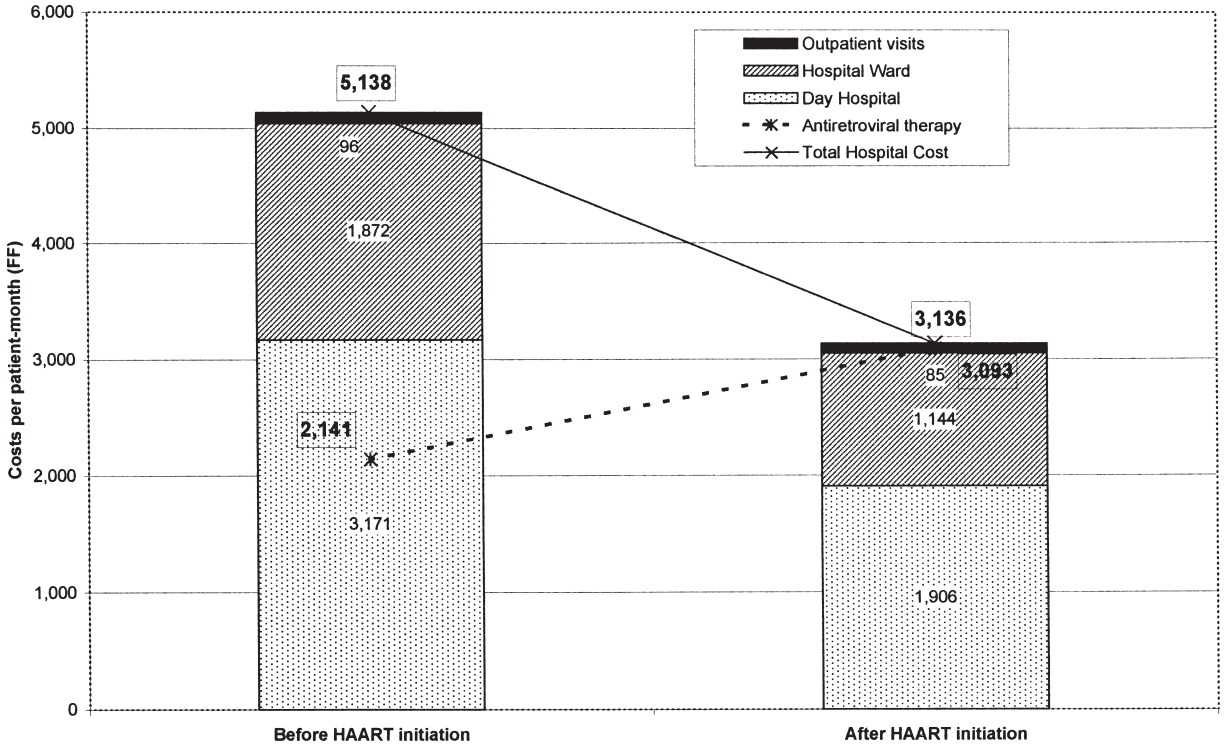

Figure 5. Mean hospital and antiretroviral treatment costs per patient-month before and after HAART initiation (Fr).

the case with population-based studies such as this one, data collected during patients' hospitalizations are sporadic and are not collected at the same dates or with the same frequency for all patients. In such circumstances, direct estimates of changes in health status as a function of time are not possible and some form of modeling is necessary. The development of a discrete time Markov model would have required the a priori definition of fixed time intervals (e.g., 1 month) to allow transitions between states and to calculate transition probabilities. Modeling in continuous time describes in a more natural way the clinical trend of HIV-infected patients under treatment. Treatments aim at slowing down (and even reversing) disease progression. In this context, it is more relevant to model the time passed in one state rather than transitions from one state to another at fixed time intervals that are defined in an arbitrary way. Moreover, this type of model has been used in the most advanced epidemiological research into the natural history of HIV disease and thus may be regarded, in spite of its complexity, as standard methodology.

Nevertheless, a CTMM would necessitate fully continuous time information. In the present case, patients' viral load and CD4 count would have to be monitored each day of the follow-up period or even several times a day. This is impossible to implement in practice, and information is always limited to consecutive discrete observations. This is why we used the time between two consecutive visits to estimate the time spent in a state. This is the first limitation of our model, even though this was possible as consecutive visits were relatively close. In addition, due to the advanced stage of the disease in our study population, it is reasonable to think that a change in viral load and CD4 count could have a rapid impact on a patient's health status, leading to a visit to his/her physician. The other main limitation of our model is that we do not use it to forecast the costs and effects of HAART in the long run (i.e., 10 or 20 years), as this is the case for most economic models. Even though our model is technically capable of such projections, they could not be presented with an acceptable level of confidence. Indeed, we had neither mid-term data to check the stability of the coefficients of our model over time nor other published

economic models for comparison. The other limitations are related to our costing methodology, mainly due do the lack of specific data recording for the use of resources. Thus, we extrapolated the full scheme of antiretroviral treatments taken by patients from their hospital files, but we had no data on observance to compute the doses actually taken. We assumed a perfect observance and consequently we probably overestimated the costs of antiretroviral treatments. Nevertheless, in a recent unpublished study, we found that the overall rate of observance, in a sample of HIV patients under various tri therapies, was very high (about 98%).

Although many studies have incorporated CD4 cell counts or other immunological markers in models of HIV disease progression, few have included plasma viral load and none have implemented a Markov model with a combination of these two markers. The reversibility effect imbedded in our model allows it to deal with health status improvement of treated patients, whereas previous models were aimed only at describing the continuous progression from the infection to major clinical complications and death. The arrival of new therapies leading to improvements in patients' health status, with increases in CD4 cell count and decreases in viral load, requires that reversibility effects be taken into account.

Our modeling approach was based on the assumption that changes in total hospital cost in the treatment of HIV-infected patients resulted from two conflicting tendencies: (1) the cost per state remains stable over time and is higher in more severe states, and (2) the distribution of patients across states changes, which reflects their improved health status. The first hypothesis is verified to a certain extent, as the cost per state slightly increases with severity. Nevertheless, the cost of the most severe state significantly increases after the initiation of HAART. This can be explained by a selection process, through which the patients who remain in this state after beginning HAART are determined to be those with the most damaged immune systems. On the other hand, the second hypothesis has clearly been demonstrated. As a result, the evolution of the mean hospital cost per patient, on a daily basis, shows three distinct stages: a stable cost before HAART initiation, a narrow peak around day 0, and a significant decrease shortly after HAART initiation.

Finally, when we compared two 14-month periods, we found that hospital costs per patient-month dropped from Fr 5,138 to Fr 3,136, in spite of a doubling treatment cost (from Fr 2,141 to Fr 3,093 per patient-month). In a context of limitation of health care expenditures, these results prove that the extra financial burden in association with the initiation of ambitious HAART-dispensing programs can be compensated by important savings. This study reflects from a physician point of view a process already demonstrated in several macro-economic studies,[14,15] showing that AIDS centers encountered significant drops in their total spending.

The selection criteria of this study (i.e., the first patients who received HAART in a hospital-based patient population) induced the constitution of a sample of severely afflicted patients. Indeed, at the time of its arrival in France in March/April 1996, this treatment was exclusively intended for patients at an advanced stage of infection. This can explain the significant proportion, in our model, of patients deceased after 14 months of HAART (20%). Nevertheless, several studies have shown that HAART reduces mortality among patients with advanced HIV infection.[16]

Although our results have intrinsic interest in relation to severe HIV-infected patients, it would also be interesting to extend them by applying our approach to less severe patients and to the initiation of HAART at an earlier stage in the spectrum of HIV infection.

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