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A decision tree to help determine the best timing and antiretroviral strategy in HIV-infected patients

L. PIROTH[1]*, I. FOURNEL[2], S. MAHY[1], Y. YAZDANPANAH[3], D. REY[4], C. RABAUD[5], J. P. FALLER[6], B. HOEN[7], M. FARDEHEB[8], C. QUANTIN[2], P. CHAVANET[1], C. BINQUET[2,8], for the Groupe InterCOrevih du Nord-Est (ICONE)

[1] *Department of Infectious Diseases, CHU Dijon, and Université de Bourgogne, Dijon, F-21000, France*
[2] *Department of medical informatics and biostatistics, CHRU Dijon, Dijon, F-21000, France*
[3] *Department of Infectious Diseases, CHU Tourcoing, Tourcoing, F-59200, France*
[4] *COREVIH Alsace, CHU Strasbourg, Strasbourg, F-68000, France Inserm, U866, Dijon, F-21079, France; Université Bourgogne, Dijon, F-21079, France*
[5] *Department of Infectious Diseases, CHU Nancy, Nancy, F-54000, France*
[6] *Department of Infectious Diseases, CHU Belfort, Belfort, F-90000, France*
[7] *Department of Infectious Diseases, CHU Besançon, Besançon, F-25000, France*
[8] *INSERM, CIE1, Dijon, F-21000, France; CHU Dijon, Centre d'investigation clinique – épidémiologie clinique/ essais cliniques, Dijon, F-21000 France; Université de Bourgogne, Dijon, F-21000, France*

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SUMMARY

Optimal antiretroviral strategies for HIV-infected patients still need to be established. To this end a decision tree including different antiretroviral strategies that could be adopted for HIV-infected patients was built. A 10-year follow-up was simulated by using transitional probabilities estimated from a large cohort using a time-homogeneous Markov model. The desired outcome was for patients to maintain a CD4 cell count of >500 cells/mm^3 without experiencing AIDS or death. For patients with a baseline HIV viral load $\geqslant 5$ $\log_{10}$ copies/ml, boosted protease inhibitor-based immediate highly active antiretroviral therapy (HAART) allowed them to spend 12% more time with CD4 $\geqslant 500$/mm^3 than did delayed HAART (6·40 *vs.* 5·69 and 5·57 *vs.* 4·90 years for baseline CD4 $\geqslant 500$ and 350–499/mm^3, respectively). In patients with a baseline HIV viral load $\leqslant 3{\cdot}5$ $\log_{10}$ copies/ml, delayed HAART performed better than immediate HAART (6·43 *vs.* 6·26 and 5·95 *vs.* 5·18 for baseline CD4 $\geqslant 500$ and 350–499/mm^3, respectively). Immediate HAART is beneficial in patients with a baseline HIV viral load $\geqslant 5$ $\log_{10}$ copies/ml, whereas deferred HAART appears to be the best option for patients with CD4 $\geqslant 350$/mm^3 and baseline HIV viral load $<3{\cdot}5$ $\log_{10}$ copies/ml.

Key words: AIDS, HIV.

INTRODUCTION

Despite the marked decrease in HIV-related mortality and morbidity since the introduction of highly active antiretroviral therapy (HAART), the best therapeutic strategy has yet to be established. In patients with CD4 cell counts >350 cells/mm^3 and HIV viral loads $<100\,000$ copies/ml, current guidelines generally recommend deferring therapy, given the low absolute risk of AIDS-defining clinical events before this threshold [1–6] and the risk of both HIV resistance and antiretroviral-related toxicity.

* Author for correspondence: Professor L. Piroth, Département d'Infectiologie CHU, Dijon, 2 boulevard du Maréchal de Lattre de Tassigny, 21079 Dijon Cedex, BP 77908, France.
(Email: lionel.piroth@chu-dijon.fr)

On the other hand, reaching and maintaining a CD4 level >500/mm³ for at least 5 years on HAART reduces mortality to a level similar to that in those without HIV infection [7]. Since the likelihood of reaching a CD4 level >500/mm³ is higher in patients starting HAART at high CD4 levels [8–10], it can thus be speculated that early HAART could be associated with a clinical benefit. The improvements in tolerance to and the efficacy of recent antiretroviral regimens, associated with a potential clinical interest of better virological control [11], and a lower risk of HIV resistance, could strengthen this approach [6, 12, 13].

Besides the 'when to start question', the 'what to start with' question needs to be answered. Most therapeutic trials observed that the efficacy of first-line HAART including two nucleoside analogue reverse transcriptase inhibitors (NRTI) plus either a boosted protease inhibitor (PI-based HAART) was similar to that using a non-nucleoside reverse transcriptase inhibitor (NNRTI-based HAART). However, the different safety profiles [14, 15], the potential difference in immunological outcome [16] and the difference regarding the genetic barrier may induce significant differences over time.

Two recent large cohort studies concluded that, in the case of immediate HAART, not only were patients with CD4 levels between 350 and 450–500/mm³ at a lower relative risk of AIDS and/or death [17, 18], but also that those with CD4 >500/mm³ were at a lower relative risk of death [18]. However, no randomized trial tested specifically the 'when and what to start' question. In addition, HIV infection has become a chronic disease. Thus, we need to identify the best strategy while bearing in mind the positive and negative consequences over a period of at least 10 years. Decision analysis using Markov modelling is known to be the most appropriate method in such cases. This is why it was applied rather frequently in the field, mainly to perform cost-effectiveness analyses [19, 20]. However, is also implies that enough data on the main inputs are available. In a previous study, we applied a Markov model to a prospective cohort of HIV-infected patients on different HAART strategies to assess the factors for clinical and immunological evolution [21]. In the present study, our aim was to build a decision tree including the different antiretroviral strategies that could be adopted, and then by using the transitional probabilities drawn from our Markov model, to determine the best strategy in HIV-infected patients according to their baseline characteristics.

METHODS

Study design

This study was conducted using a decision analysis design [22]. We used a decision tree to simulate the different treatment strategies and final outcomes for virtual patients according to their baseline characteristics and intermediate evolution (Figs 1, 2).

The decision tree included the alternative therapeutic strategies of interest. Then, the potential subsequent events of interest (clinical, immunological, therapeutic) were added. The evolution of the virtual patients towards the different events was simulated over repeated 1-year periods. For each of the subsequent events, 1-year probabilities of event occurrence were applied according to the characteristics of the virtual patients at the beginning of each period. These probabilities were obtained from a previous study [21]. Utility values were then associated with the different events (the greater the interest of an event, the higher the utility value). The combination of utility values with the distribution of probabilities allowed us to calculate an intermediate expected value (or score). The process was repeated ten times using a Markov process to simulate evolution over 10 years and to calculate a final score for each strategy (the higher the final score, the better the strategy). All analyses were performed with decision analysis software (TreeAge Pro™ 2006 HealthCare, TreeAge Software Inc., USA).

Strategies compared and decision tree structure

Four main strategies were compared: (1) no initial treatment, potentially followed by NNRTI-based HAART when the CD4 count fell to <350 cells/mm³; (2) no initial treatment, potentially followed by boosted PI-based HAART when the CD4 count fell to <350 cells/mm³; (3) immediate NNRTI-based HAART; and (4) immediate boosted PI-based HAART. It was assumed that HAART once started would never be stopped, and that the initial HAART schedule would have to be changed in some patients, in particular for tolerance or efficacy issues. In the latter, it was also assumed that a patient would receive only one NNRTI-based HAART during follow-up. For all HAART schedules, boosted-PI or NNRTI were associated with a backbone of two NRTIs.

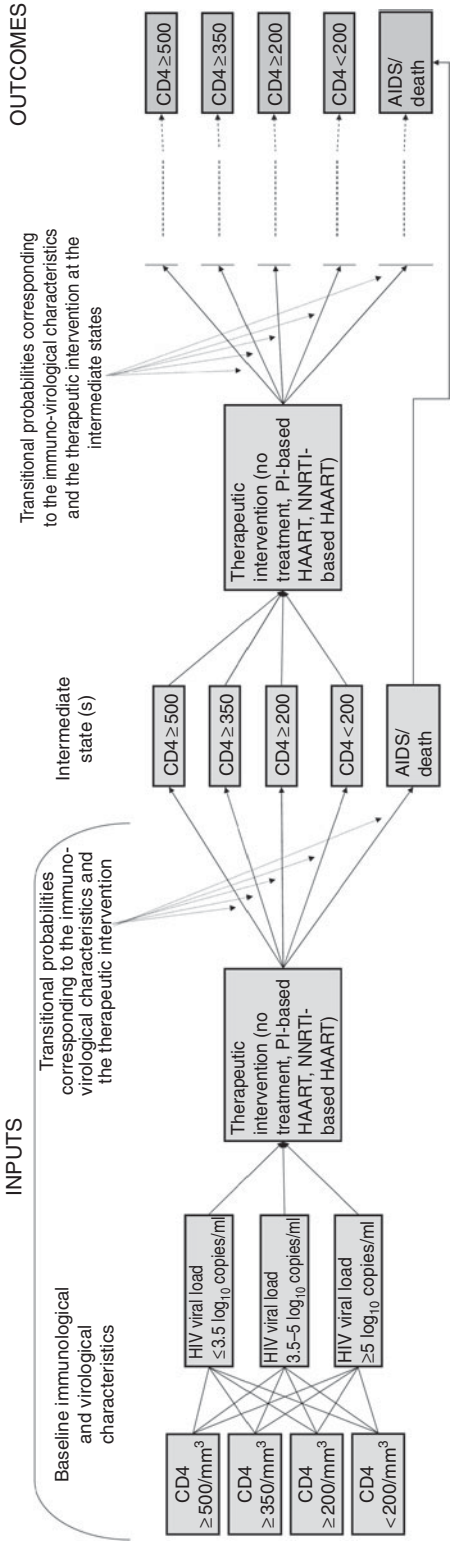

Fig. 1. Flow diagram synthetically representing the inputs, the general methodology and the outcomes (See also Fig. 2). HAART, highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Clinical and immunological events

The events in the decision tree were (1) to have a CD4 count $\geqslant 500/mm^3$, or (2) to have a CD4 count $\geqslant 350$ and $< 500/mm^3$ (350–499), or (3) to have a CD4 count $\geqslant 200$ and $< 350/mm^3$ (200–349), or (4) to have a CD4 count $< 200/mm^3$, without experiencing clinical progression (AIDS or death); or (5) to experience clinical progression to AIDS or death (whatever the CD4 count).

Probabilities of evolution

The 1-year transitional probabilities for each of the potential events were estimated in a previous study [21] from the ICONE cohort using a time-homogeneous Markov model [23]. Briefly, this cohort included 2126 consecutive HIV-1 infected adults (>15 years) seen for the first time and prospectively followed in one of the six participating centres from July 1996 to June 2004. The baseline characteristics of these patients are presented in Table 1. One-year transitional probabilities from one immunological state to another were estimated from the 44 021 transitions observed in this cohort (Table 2) according to the HIV viral load, the HAART status, the type of HAART, and the number of previous antiretroviral treatments. In HAART-treated patients, this cohort also allowed us to estimate the likelihood that a patient would remain on the same therapeutic schedule during the 1-year period, or change to another one (from one boosted-PI to another boosted-PI, from NNRTI-based to boosted-PI, or from boosted-PI to NNRTI-based for NNRTI-naive patients).

Utilities

A utility value was associated with each event as a measure of relative preference, ranging from 0 (highly unwanted) to 1 (highly desired). In the main analysis, a utility value of 1 was associated with a CD4 count $\geqslant 500/mm^3$ (i.e. in this analysis the only therapeutic goal) and a value of 0 was associated with all the other events. A secondary analysis was performed attributing a utility value of 0 to AIDS or death (in this case the only event to avoid) and 1 for all the states without clinical progression to AIDS or death.

In another secondary analysis, we used life expectancy as a measure of each outcome's 'utility'. The DEALE method was used [24]. Since our target population comprised subjects aged 35 years infected with HIV, we used the data from the ICONE cohort

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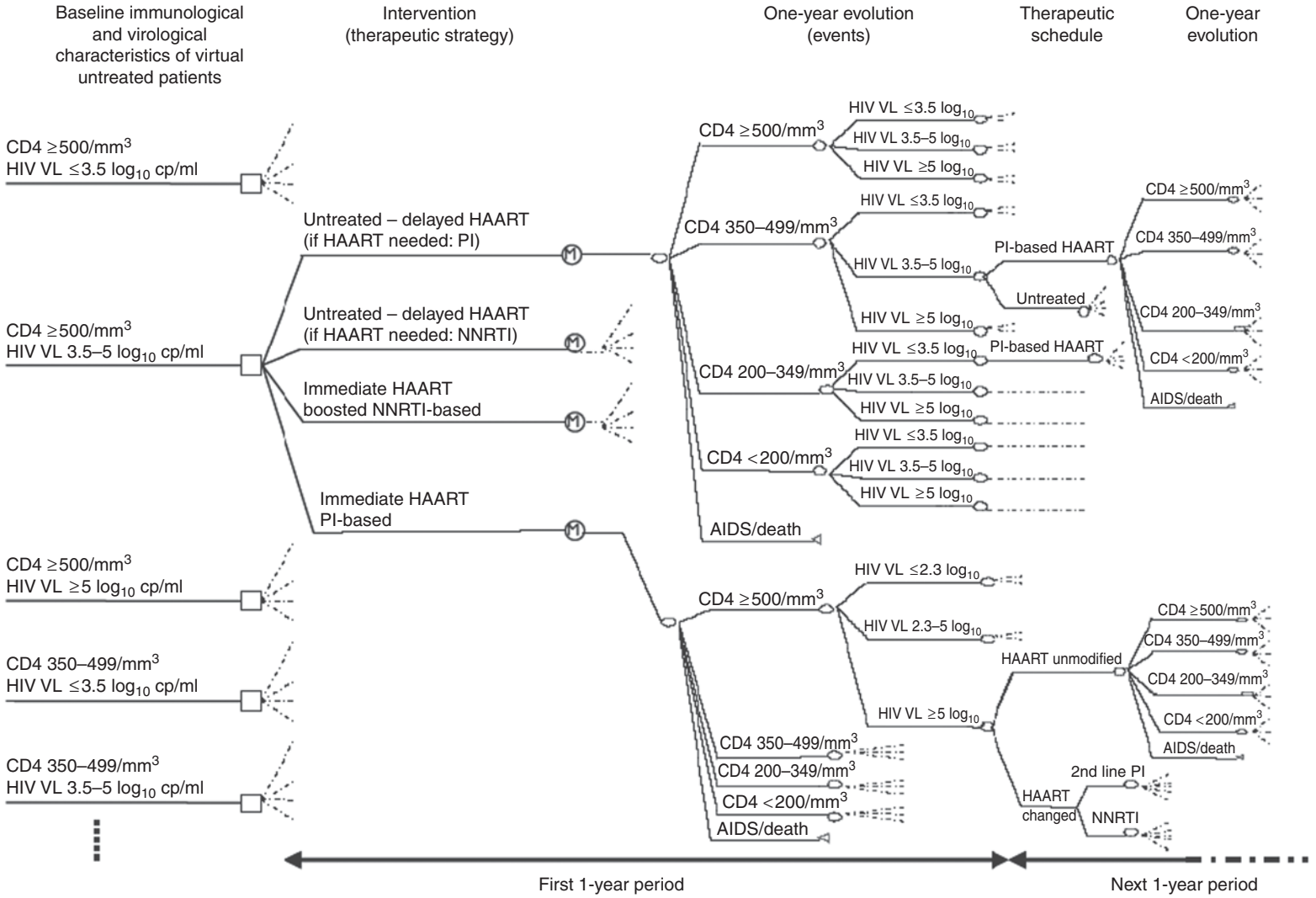

Fig. 2. Schematic representation of a part of the decision tree. From the immunological and virological baseline characteristics of the patients (left part), four different antiretroviral strategies can be used (e.g. as shown with patients with baseline CD4 $>500/mm^3$ and HIV viral load between 3·5 and 5 log_{10} copies/ml, middle part). According to the strategy used and the characteristics of the patients, subsequent clinical, immunological and virological events occur with different probabilities (estimated in a previous observational study). As examples, subsequent potential evolutions and therapeutic schedules are shown in the right upper part for initially untreated patients, and in the right lower part for those immediately treated with boosted PI-based HAART. cp/ml, copies/ml; HIV VL, HIV viral load; HAART, highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 1. *Baseline characteristics of the 2126 patients included in the study (ICONE group, 1996–2004)*

	n	%
Age (years)		
<30	640	30
30–45	1080	51
⩾45	406	19
Males	1515	71
Transmission group		
At-risk heterosexual intercourse	948	44
Men-to-men sexual intercourse	779	37
Intravenous drug use	166	8
Haemophilia/transfusion	31	2
Other	27	1
Unknown	175	8
HBs antigenemia		
Negative	1791	84
Positive	181	9
Unknown	154	7
HCV serological status		
Negative	1757	83
Positive	223	10
Unknown	146	7
Diagnosis before 1 Jan. 2000	1078	51
Baseline weight (kg)		
<60	459	22
60–90	1446	68
⩾90	137	6
Unknown	84	4
AIDS at baseline	208	10
Baseline viral load (log_{10} copies/ml)		
<2·3	171	8
2·3–5	1034	49
⩾5	497	23
Unknown	424	20
Baseline CD4 cell count (cells/mm³)*		
⩾500	652	30
350–499	436	21
200–349	530	25
<200	508	24
Antiretroviral therapy		
HAART (PI)	1062	50·0
HAART (NNRTI)	824	38·8
HAART (NRTI)	248	11·7
HAART (NNRTI + PI)	76	3·6
>6 molecules or other associations	268	12·6

HAART, Highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

* Missing values of CD4 cell count were imputed using previous or next measurement, if the time-lapse between the two follow-ups was <3 months for patients without any antiretroviral treatment, or <1 month for treated patients.

to estimate the specific mortality rates for each CD4 state. The general mortality rate (1/life expectancy) was derived from the data of the Institut National de la Statistique et des Etudes Economiques (INSEE). The specific and the general mortality rates were added to obtain the overall mortality rate, and thus overall life expectancy (1/overall mortality rate). By doing this, life expectancies were 23, 35, 38 and 39 years, for 35-year-old patients with a baseline CD4 count of <200/mm³, 200–349/mm³, 350–499/mm³, and ⩾500/mm³, respectively. A penalty was then applied for each year spent in a state <500/mm³ (penalties of 0·25, 0·5, 0·75 for the immunological states 350–499, 200–349, <200 CD4/mm³, respectively) to indirectly take into account the quality of life.

Decision analysis

In order to identify the most efficient strategy, the final expected value (or score) for each strategy was calculated by cumulating the intermediate 1-year period scores, weighted by the probability of beginning the 1-year period with these characteristics. The best strategy corresponded to the one with the best score at 10 years or the best expected life expectancy.

Sensitivity analyses

To assess the stability of the results, sensitivity analyses were performed by speculating that HAART efficacy may have improved in the last years. The 1-year transitional probabilities of reaching a higher immunological state (or staying at the same immunological level for the CD4 ⩾500/mm³ state) were thus increased by 1–8%, and in parallel the transitional probabilities of reaching a lower immunological state were decreased by 1–8%.

RESULTS

Expected outcomes according to the different antiretroviral strategies

The expected results of the different antiretroviral strategies according to baseline CD4 count and HIV viral loads are shown in Table 3. In delayed initiation of HAART, the median delays before starting HAART, estimated from the decision tree, are summarized in Table 4.

The higher the baseline CD4 state, the higher the expected value, whatever the antiretroviral strategy used. For baseline CD4 ⩾500 and 350–499/mm³,

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Table 2. *Number of transitions from one stage to another* (*ICONE group, n = 2126, 1996–2004*)

	Stage at time $t+1$				
Stage at time t	$\geqslant$500 cells/mm³	350–499 cells/mm³	200–349 cells/mm³	<200 cells/mm³	AIDS/death
$\geqslant$500 cells/mm³	11 420	1763	179	22	24
350–499 cells/mm³	1979	4625	1203	45	19
200–349 cells/mm³	200	1488	4386	568	31
<200 cells/mm³	22	54	761	3072	102

Table 3. *Decision tree analyses results of the different antiretroviral strategies: 10-year expected values* (*scores*) *according to baseline CD4 counts and HIV viral loads*

Baseline CD4 (/mm³)	Baseline HIV viral load ($\log_{10}$ copies/ml)	Immediate boosted PI-based HAART	Immediate NNRTI-based HAART	Delayed boosted PI-based HAART	Delayed NNRTI-based HAART
$\geqslant$500	$\leqslant$3·5	6·42	6·10	6·38	6·47
	3·5 to <5	6·24	6·26	6·32	6·42
	$\geqslant$5	6·40	6·09	5·69	5·80
350 to <500	$\leqslant$3·5	5·12	5·23	5·90	6·00
	3·5 to <5	5·55	5·72	5·58	5·68
	$\geqslant$5	5·57	5·39	4·90	4·98
200 to <350	$\leqslant$3·5	4·99	4·62	—	—
	3·5 to <5	5·25	5·16	—	—
	$\geqslant$5	5·57	5·40	—	—
<200	3·5 to <5	4·13	4·46	—	—
	$\geqslant$5	4·14	4·13	—	—

HAART, Highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor. The higher the score, the better the outcome. Best antiretroviral strategies for each baseline CD4 and HIV viral load stratum are indicated in light grey (difference $\leqslant$10 % with the worst strategy) or dark grey (difference >10 % with the worst strategy).

immediate HAART was associated with a better outcome in patients with a baseline HIV viral load $\geqslant$5 $\log_{10}$ copies/ml, the score for delayed strategies being 10 % lower than that for the best strategy (immediate boosted PI-based HAART). In contrast, no clear difference was observed in patients with baseline CD4 $\geqslant$350/mm³ and baseline HIV viral load <5 $\log_{10}$ copies/ml. Delayed HAART was even found to perform better than immediate HAART in patients with baseline CD4 350–499/mm³ and HIV viral load $\leqslant$3·5 $\log_{10}$ copies/ml. When HAART was implemented immediately, baseline HIV viral load did not influence the outcome, whereas with delayed therapy, the higher the baseline HIV viral load, the worse the outcome.

Starting immediate antiretroviral treatment with boosted PI-based rather than NNRTI-based HAART was associated with a slightly better outcome in patients with baseline HIV viral load $\geqslant$5 $\log_{10}$ copies/ml, whatever their baseline CD4 count (Table 3).

The direction and the magnitude of these differences were similar when attributing a utility of 0 for AIDS or death and 1 for all other situations.

Life expectancy

A difference of >1 year (for a 35-year-old patient) was observed in favour of immediate PI-based HAART in patients with CD4 $\geqslant$350/mm³ HIV viral load $\geqslant$5 $\log_{10}$ copies/ml (33·2 *vs.* 30·1 years in case of delayed HAART). Conversely, life expectancy was 1 year longer with delayed HAART than with immediate HAART for patients with baseline CD4 of 350–499/mm³ and HIV viral load $\leqslant$3·5 $\log_{10}$ copies/ml (34 *vs.* 33 years).

In case of immediate HAART, although no clear difference in life expectancy was observed for patients with baseline immunological states $\geqslant$500/mm³ (mean 33·1 years) and 350–499/mm³ (33 years), they were

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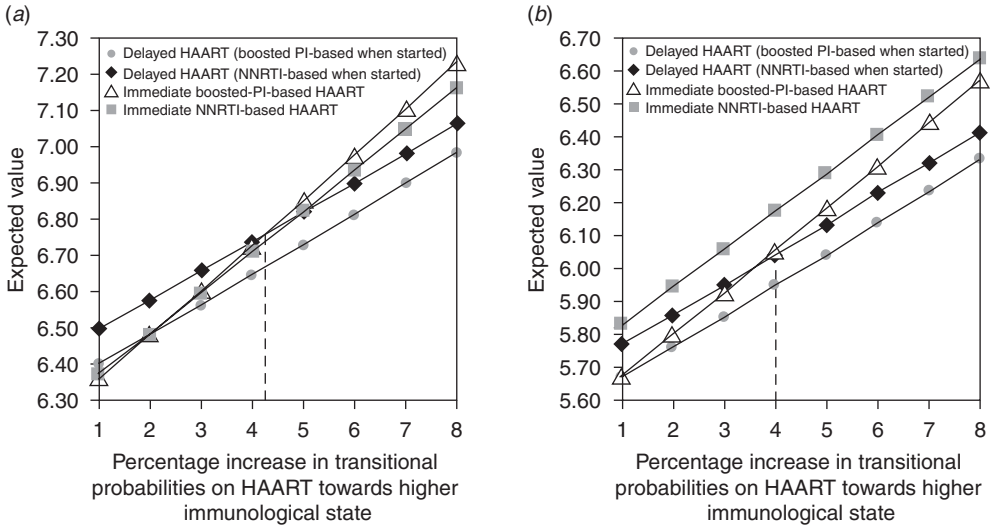

Fig. 3. Sensitivity analysis by increasing the transitional probabilities from one immunological stage to a better one (and symmetrically by decreasing the transitional probabilities to a worse one) from 1 % to 8 % in patients with baseline HIV viral load between 3·5 and 5 $\log_{10}$ copies/ml. (*a*) Baseline CD4 $>500/mm^3$ or (*b*) between 350 and $500/mm^3$, according to the antiviral strategy used.

Table 4. *Median time to HAART initiation according to baseline characteristics in case of delayed HAART*

Baseline CD4 ($/mm^3$)	Baseline HIV viral load ($\log_{10}$ copies/ml)	Median delay to boosted PI-based HAART (years)	Median delay to NNRTI-based HAART (years)
>500	$\leqslant 3{\cdot}5$	2·74	2·60
	3·5 to <5	2·69	2·54
	$\geqslant 5$	1·89	1·73
350–500	$\leqslant 3{\cdot}5$	1·96	1·82
	3·5 to <5	1·58	1·39
	$\geqslant 5$	0·97	0·97

HAART, Highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor.

higher than expected in those with baseline immunological states of $200–349/mm^3$ (32·6 years, mean difference 0·5 year) and $<200/mm^3$ (29·8 years, mean difference 3·3 years).

Sensitivity analysis

Increasing the transitional probability of passing from one immunological state to a better one by 1–8 % percent and decreasing the transitional probability of passing from one immunological state to a worse one also by 1–8 % did not modify the ranking of the different strategies for patients with baseline CD4 $\geqslant 350/mm^3$ and HIV viral load $\leqslant 3{\cdot}5$ $\log_{10}$ copies/ml. In contrast, in patients with baseline CD4 $\geqslant 350/mm^3$ and an HIV viral load between 3·5 and 5 $\log_{10}$ copies/ml, a relative increase of 4·3 % in the transitional probability did modify the ranking of the different strategies, favouring immediate *vs.* delayed HAART (Fig. 3).

DISCUSSION

In the 'when to start' and 'what to start with' debate, decision tree analysis, which has already been used in the field of HIV infection [19], may be a useful tool, Indeed, it will allow clinicians to model therapeutic approaches and subsequent outcomes in a real life setting, and may help to build a hierarchy of strategies in order to determine the best one to use in clinical practice [22]. It uses the transitional probabilities of evolution to a different state according to different covariates, which could not be obtained directly from classical time-to-event models, such as the Cox proportional hazard model. In our study, these transitional probabilities were drawn from a real-life prospective cohort, the characteristics of which are consistent with other main HIV cohorts [21]. For example, time to HAART initiation in the case of a delayed strategy in our decision tree analysis (e.g. from 1·73 to 2·74 years for patients with baseline CD4 $\geqslant 500/mm^3$) is consistent with the median $60–80/mm^3$ per year CD4 decline slope usually reported [25–27]. Moreover, it is of interest that changing the values of

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the different possible events did not significantly modify the results obtained, underlining the high stability of the decision analysis results.

The first result is that immediate HAART for patients with a baseline HIV viral load >5 $\log_{10}$ copies/ml was associated with a better immunological and clinical outcome than in those with delayed HAART. In contrast, delaying HAART appears to be the best option in patients with a baseline CD4 count $>350/mm^3$ and a low baseline HIV viral load ($\leqslant 3{\cdot}5$ $\log_{10}$ copies/ml), since the extreme hypothesis of an additional relative increase of up to 8% in the likelihood of clinical and immunological improvement on HAART did not change the ranking of the different strategies.

In patients with CD4 $\geqslant 350/mm^3$ and an HIV viral load between 3·5 and 5 $\log_{10}$ copies/ml, no clear difference was observed. The long-term potential toxicity of HAART [14, 15] could thus lead to a preference for delayed HAART in these patients, even though it has recently been shown that the higher the CD4 count at HAART initiation, the lower the risk of HAART-related side-effects such as renal insufficiency, peripheral neuropathy and anaemia [28]. Moreover, a relative increase of at least 4·3% in response to HAART made immediate HAART preferable to delayed strategies. This increase probably reflects the progress made during recent years in the management and increasing virological efficacy of HAART [18, 29, 30].

Second, no clear difference in clinical and immunological outcome was found between boosted-PI and NNRTI-based HAART, even though there was a trend towards a benefit of boosted-PI HAART in patients with a high baseline HIV viral load ($\geqslant 5$ $\log_{10}$ copies/ml). Rather than benefiting from a mild 'direct' immunological gain [16], patients with high levels of HIV replication first treated with low genetic barrier drugs, such as NNRTIs, could be at a disadvantage because of the relative weight of lack of adherence and of subsequent selection of HIV mutations [30]. On the other hand, it could be advocated that NNRTIs may be associated with faster viral decay and greater efficacy at high viral loads [31], and thus contribute to the lack of difference in patients on delayed HAART.

Of interest, the higher the baseline CD4 count, the better the expected outcome, whatever the strategy used. The baseline CD4 count still appears to have an impact on subsequent immunological and clinical evolution in patients in the HAART era [32], probably because the likelihood of reaching a CD4 count $>500/mm^3$ is greater in patients starting HAART at higher CD4 levels [8–10]. This therefore indirectly reflects the high prognostic value of the CD4 level reached on HAART [32]. Moreover, in the case of delayed HAART, the higher the baseline HIV viral load, the worse the outcome. This is consistent with the results of previous cohort studies [5, 33], and probably reflects the poorer immunological outcome in cases of uncontrolled high level HIV replication in the absence of treatment. In contrast, when HAART is implemented immediately, the significance of baseline HIV viral load is outweighed by HIV viral load on treatment, and no longer influences the outcome [32].

Nevertheless, several limitations must be acknowledged. The study period ended in mid-2004, and the transitional probabilities may not accurately reflect the impact of current HAART, even though only currently recommended therapeutic schemes (i.e. HAART including two nucleoside inhibitors plus either a NNRTI or a PI boosted by ritonavir) were considered. The impact of a provider bias on transitional probabilities cannot be excluded either [5]. In addition to the 'physiological' fluctuation of the absolute CD4 count observed on HAART in patients with CD4 $>500/mm^3$ [25], fluctuations due to adherence, tolerance and resistance were not directly assessed. These are likely to explain why the final score for patients with CD4 $>500/mm^3$ and immediately put on HAART was 6·4, far below the ideally expected duration of 10 years. This could also explain the mild gain in life expectancy observed in patients on immediate HAART in our study (3·3 years between CD4 $<200/mm^3$ and $\geqslant 350/mm^3$), since we considered that each year spent with a CD4 count $<500/mm^3$ corresponded to 4–8 months with an optimal CD4 level (which is a difficult hypothesis). This gain in life expectancy is lower than that observed in a large cohort study (>7 years [34]), but within the range of another recent study (difference from 5·7 years to 0 between CD4 $<200/mm^3$ and CD4 $\geqslant 500/mm^3$ for a 40-year-old patient, depending on the level of adherence and HAART-related toxicity) [35]. The differences in tolerance to, adherence to, and the virological efficacy of HAART probably explain these different gains. The increase in tolerance to HAART and its virological efficacy over time [18], in particular since the completion of our study, should, however, strengthen the benefits observed on HAART. On the other hand, it cannot be excluded that substantial sampling variability may have had an impact on the transitional

probabilities, even though they are consistent with those observed in other cohorts. There is no statistical variability, since only the central estimation of the transitional probabilities (but not their distribution) is available when estimated from the Markov model. Thus only one estimate for each situation is used in the decision tree analysis. The only way to control this uncertainty was to perform representative sensitivity analyses of the different conceivable scenarios, as we did. Immediate HAART was always found to be beneficial in patients with CD4 $<350/mm^3$ (data not shown).

It cannot also be excluded that 1-year transition may not be sufficient to capture important aspects of disease progression, in particular non-AIDS defining morbidity. Moreover, the outcomes did not directly include this non-AIDS-defining morbidity, of growing importance [11]. However, defining the preferred outcome as reaching and maintaining CD4 $>500/mm^3$ in the main analysis indirectly took non-AIDS-defining morbidity into account, since this threshold was associated with a lower risk not only of AIDS but also of non-AIDS morbidity and mortality in untreated and treated patients [7, 9, 11, 36]. It is important to point out that the complementary analysis focusing only on AIDS or death showed similar results and did not modify the direction and the magnitude of the differences observed.

In conclusion, this study, which relies on decision analyses that take into account not only immunological but also virological characteristics at baseline and real-life inputs, provides new data on the 'when to start' debate. While delayed HAART still appears to be the best approach in patients with a baseline CD4 count $>350/mm^3$ and an HIV viral load $<3{\cdot}5$ $\log_{10}$ copies/ml, immediate HAART is likely to be of interest in those with an HIV viral load >5 $\log_{10}$ copies/ml, with a slight preference towards boosted PI-based HAART. In those with a baseline HIV viral load between $3{\cdot}5$ and 5 $\log_{10}$ copies/ml, improvements in the management and virological efficacy of current antiretroviral drugs should favour immediate HAART. Even though these results are consistent with other recent findings [17, 18], therapeutic trials are needed to help determine the best therapeutic approach for HIV-infected patients.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Hogg RS, *et al.*** Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *Journal of the American Medical Association* 2001; **286**: 2568–2577.
2. **Cozzi Lepri A, *et al.*** When to start highly active antiretroviral therapy in chronically HIV-infected patients: evidence from the ICONA study. *AIDS* 2001; **15**: 983–990.
3. **Sterling TR, Chaisson RE, Moore RD.** HIV-1 RNA, CD4 T-lymphocytes, and clinical response to highly active antiretroviral therapy. *AIDS* 2001; **15**: 2251–2257.
4. **Anastos K, *et al.*** Risk of progression to AIDS and death in women infected with HIV-1 initiating highly active antiretroviral treatment at different stages of disease. *Archives of Internal Medicine* 2002; **162**: 1973–1980.
5. **Palella FJ, *et al.*** Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. *Annals of Internal Medicine* 2003; **138**: 620–626.
6. **Hulgan T, *et al.*** CD4 lymphocyte percentage predicts disease progression in HIV-infected patients initiating highly active antiretroviral therapy with CD4 lymphocyte counts >350 lymphocytes/mm^3. *Journal of Infectious Diseases* 2005; **192**: 950–957.
7. **Lewden C, *et al.*** HIV-infected adults with a CD4 cell count greater than 500 cells/mm^3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. *Journal of Acquired Immune Deficiency Syndrome* 2007; **46**: 72–77.
8. **Garcia F, *et al.*** Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. *Journal of Acquired Immune Deficiency Syndrome* 2004; **36**: 702–713.
9. **Kaufmann GR, *et al.*** Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. *Clinical Infectious Diseases* 2005; **41**: 361–372.
10. **Moore RD, Keruly JC.** CD4+ cell count 6 years after commencement of highly active antiretroviral therapy

in persons with sustained virologic suppression. *Clinical Infectious Diseases* 2007; **44**: 441–446.
11. **Emery S, *et al.*** Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. *Journal of Infectious Diseases* 2008; **197**: 1133–1144.
12. **Chaisson RE, Keruly JC, Moore RD.** Association of initial CD4 cell count and viral load with response to highly active antiretroviral therapy. *Journal of the American Medical Association* 2000; **284**: 3128–3129.
13. **Phillips AN, *et al.*** Durability of HIV-1 viral suppression over 3·3 years with multi-drug antiretroviral therapy in previously drug-naive individuals. *AIDS* 2001; **15**: 2379–2384.
14. **Friis-Moller N, *et al.*** Combination antiretroviral therapy and the risk of myocardial infarction. *New England Journal of Medicine* 2003; **349**: 1993–2003.
15. **Madden E, *et al.*** Association of antiretroviral therapy with fibrinogen levels in HIV-infection. *AIDS* 2008; **22**: 707–715.
16. **Bartlett JA, *et al.*** An updated systematic overview of triple combination therapy in antiretroviral-naive HIV-infected adults. *AIDS* 2006; **20**: 2051–2064.
17. **When to start Consortium.** Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009; **373**: 1352–1363.
18. **Kitahata MM, *et al.*** Effect of early versus deferred antiretroviral therapy for HIV on survival. *New England Journal of Medicine* 2009; **360**: 1815–1826.
19. **Tebas P, *et al.*** Timing of antiretroviral therapy. Use of Markov modeling and decision analysis to evaluate the long-term implications of therapy. *AIDS* 2001; **15**: 591–599.
20. **Vijayaraghavan A, *et al.*** Cost-effectiveness of alternative strategies for initiating and monitoring highly active antiretroviral therapy in the developing world. *Journal of Acquired Immune Deficiency Syndrome* 2007; **46**: 91–100.
21. **Binquet C, *et al.*** Markov modelling of HIV infection evolution in the HAART era. *Epidemiology and Infection* 2009; **137**: 1272–1282.
22. **Weinstein M, Fineberg H.** *Clinical Decision Analysis*. Philadelphia: Saunders, 1980.
23. **Alioum A, Commenges D.** MKVPCI: a computer program for Markov models with piecewise constant intensities and covariates. *Computer Methods and Programs in Biomedicine* 2001; **64**: 109–119.
24. **Beck J, Kassirer J, Pauker S.** A convenient approximation of life expectancy (The 'DEALE'). I. Validation of the method. *American Journal of Medicine* 1982; **73**: 883–888.
25. **Piroth L, *et al.*** Clinical, immunological and virological evolution in patients with CD4 T-cell count above 500/mm^3: is there a benefit to treat with highly active antiretroviral therapy (HAART)? *European Journal of Epidemiology* 2004; **19**: 597–604.
26. **Hanson DL, *et al.*** Distribution of CD4+ T lymphocytes at diagnosis of acquired immunodeficiency syndrome-defining and other human immunodeficiency virus-related illnesses. The Adult and Adolescent Spectrum of HIV Disease Project Group. *Archives of Internal Medicine* 1995; **155**: 1537–1542.
27. **Egger M, *et al.*** Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. Swiss HIV Cohort Study. *British Medical Journal* 1997; **315**: 1194–1199.
28. **Lichtenstein KA, *et al.*** Initiation of antiretroviral therapy at CD4 cell counts $\geqslant$350 cells/mm^3 does not increase incidence or risk of peripheral neuropathy, anemia, or renal insufficiency. *Journal of Acquired Immune Deficiency Syndrome* 2008; **47**: 27–35.
29. **Ewings FM, *et al.*** Survival following HIV infection of a cohort followed up from seroconversion in the UK. *AIDS* 2008; **22**: 89–95.
30. **Lima VD, *et al.*** The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. *Journal of Acquired Immune Deficiency Syndrome* 2009; **50**: 529–536.
31. **Riddler SA, *et al.*** Class-sparing regimens for initial treatment of HIV-1 infection. *New England Journal of Medicine* 2008; **358**: 2095–2106.
32. **Abrahamowicz M, Mackenzie TA.** Joint estimation of time-dependent and non-linear effects of continuous covariates on survival. *Statistics in Medicine* 2007; **26**: 392–408.
33. **Egger M, *et al.*** Prognosis of HIV-1 infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002; **360**: 119–129.
34. **The Antiretroviral Therapy Cohort Collaboration.** Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008; **372**: 293–299.
35. **Braithwaite RS, *et al.*** Do benefits of earlier antiretroviral treatment initiation outweigh harms for individuals at risk for poor adherence? *Clinical Infectious Diseases* 2009; **48**: 822–826.
36. **Wang C, *et al.*** Mortality in HIV-seropositive versus -seronegative persons in the era of highly active antiretroviral therapy: implications for when to initiate therapy. *Journal of Infectious Disease* 2004; **190**: 1046–1054.