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Newer drugs and earlier treatment: Impact on lifetime cost of care for HIV-infected adults

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Abstract

Objective—To determine the component costs of care to optimize treatment with limited resources.

Design—We used the Cost-Effectiveness of Preventing AIDS Complications Model of HIV disease and treatment to project life expectancy (LE) and both undiscounted and discounted lifetime costs (2010€).

Methods—We determined medical resource utilization among HIV-infected adults followed from 1998 to 2005 in Northern France. Monthly HIV costs were stratified by CD4 count. Costs of CD4, HIV RNA and genotype tests and antiretroviral therapy (ART) were derived from published literature. Model inputs from national data included mean age 38 years, mean initial CD4 count 372/μl, ART initiation at CD4 counts <350/μl, and ART regimen costs ranging from €760/month to €2,570/month.

Results—The model projected a mean undiscounted LE of 26.5 years and a lifetime undiscounted cost of €535,000/patient (€320,700 discounted); 73% of costs were ART-related. When patients presented to care with mean CD4 counts of 510/μl and initiated ART at CD4 counts <500/μl or HIV RNA >100,000 copies/ml, LE was 27.4 years and costs increased 1–2%, to €546,700 (€324,500 discounted). When we assumed introducing generic drugs would result in a 50% decline in first-line ART costs, lifetime costs decreased 4–6%, to €514,200 (€302,800 discounted).

Conclusions—As HIV disease is treated earlier with more efficacious drugs, survival and thus costs of care will continue to increase. The availability in high-income countries of widely-used antiretroviral drugs in generic form could reduce these costs.

Keywords

cost; France; HIV infection; simulation model

Introduction

Over the past two decades, survival among HIV-infected patients has increased substantially, largely due to the availability of more efficacious antiretroviral agents [1–3]. Guidelines have continued to move toward treating patients earlier in the course of disease [4,5], leading to increased use of both antiretroviral therapy (ART) and laboratory tests [6]. Recently updated HIV treatment guidelines in France and several other high-income countries [6,7] have also added newer and more expensive drugs to an increasing list of effective ART regimens. Despite the emergence of generic drugs, recommendations to reduce the frequency of laboratory tests, and efforts to replace inpatient hospitalizations with outpatient visits whenever possible [8], increased routine costs and improved survival are likely to have increased the lifetime cost of care for HIV-infected patients in the last decade, and may continue to do so in coming years.

As costs of care for HIV-infected patients rise, national policy makers must determine the most efficient and cost-effective methods for managing HIV disease. Estimates of the monthly and lifetime cost of care can help health policy makers understand the budget impact of HIV and allocate scarce resources. Although several studies have evaluated the overall costs of HIV care in Europe [9,10], an updated assessment that isolates cost components (e.g., ART, hospital visits, and laboratory tests) can aid in budget planning and treatment optimization. Our objective is to evaluate the current lifetime costs of medical care for HIV-infected adults, from the perspective of the healthcare system. We use a clinical database of patients followed in Tourcoing, France, and the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) Model of HIV disease. We also evaluate the impact of new antiretroviral drugs and ART initiation criteria on these costs.

Methods

Analytic framework

We estimated healthcare utilization among HIV-infected adults at different stages of disease using data collected at the Tourcoing AIDS Reference Center in Northern France [11–13]. Healthcare utilization was defined as the use of units of medical services, including inpatient and outpatient visits, laboratory tests, and drugs. We excluded costs of treatment among patients who were diagnosed but not in care. Health care utilization in this group was negligible from the healthcare system perspective. We applied a unit cost to each identified resource to develop disease stage-specific cost estimates. Disease stages were defined as chronic HIV with no history of or ongoing AIDS-defining disease (Stage 1); acute AIDS-defining disease, lasting from one month before to two months after diagnosis (Stage 2); chronic HIV with a history of AIDS-defining disease (Stage 3); and the month before death (Stage 4). We incorporated cost estimates as well as mainly French natural history and treatment characteristics into the CEPAC Model [4,10,14,15] to determine the individual time spent in each disease stage and project the lifetime direct medical cost of care for HIV-infected patients. Stage-specific cost and utilization estimates excluded the costs of antiretroviral drugs and CD4 count, HIV RNA and genotype tests. By including this information separately into the CEPAC Model, we were able to vary ART initiation criteria, the cost of newly available antiretroviral drugs, and laboratory testing frequencies in sensitivity analysis. We report life expectancies in projected years and lifetime medical costs in 2010€. Costs are reported both undiscounted and discounted at 3% per year [12].

Model overview

The CEPAC Model is a first-order state-transition Monte Carlo simulation of the natural history, clinical management and costs of HIV [14,16,17]. Patients transition monthly between “health states” characterized by current CD4 count, HIV RNA level, history of AIDS-defining diseases and costs. The model records the time spent in each health state, other clinical outcomes, and lifetime costs from entry into the simulation until death. Model specifications are described in detail in the Technical Appendix as well as in previous publications [10,14,15,18]. We ran 10 million HIV-infected patients through the CEPAC Model for each analysis. We used results for the entire cohort to estimate both individual life expectancy and average lifetime cost of care.

Cost and utilization of medical services

Study sample and data collection—We assigned healthcare costs to each “health state” using healthcare utilization data obtained from a clinical database of 1,775 HIV-infected adults who were followed at the Tourcoing AIDS Reference Center in France (January 1998 to December 2005). Details on this cohort have been published elsewhere [10,19]. We used 2004– 2005 utilization data for Stage 1 and 3 costs, to account for the

rapid changes in ART that have occurred in the last two decades. Because the incidence of both AIDS-defining diseases and death has decreased considerably since 1996, our sample size was not large enough to stratify Stage 2 and 4 costs into two-year periods. We therefore used data from the entire follow-up period for Stage 2 and 4 costs.

We estimated the frequency and length of inpatient hospitalizations (>1 day), inpatient day-care visits (≤1 day, excluding overnight admissions), and outpatient visits, as well as utilization of laboratory tests (excluding CD4, HIV RNA and genotype tests) and clinical procedures, HIV- and AIDS-related disease prophylaxis and treatment, and treatment for hepatitis B virus (HBV), hepatitis C virus (HCV), and lipid and metabolic abnormalities.

Inpatient utilization and costs—We estimated inpatient visit costs using a macrocosting approach [12], in which we assigned a national average reimbursement rate derived from the French diagnosis-related group (DRG) classification system [20] to each inpatient stay. The DRG system classifies diseases into medically and economically homogenous groups. DRG costs from the French "Echelle Nationale de Coûts" [21,22] includes physician and nurse fees as well as mean cost of diagnosis, clinical procedures, laboratory tests, drugs dispensed during hospitalization, and hotel/overhead costs (details in Technical Appendix).

Outpatient utilization and costs—We derived the cost of outpatient visits using a microcosting approach [12], in which we enumerated and determined the cost of each resource utilized by patients, including physician fees, laboratory tests (excluding CD4 count, HIV RNA and genotype tests), and clinical procedures. Unit costs for laboratory tests are from the French "Nomenclature des actes de biologie médicale" [23], while unit costs of clinical procedures are from the French "Classification commune des actes médicaux" [24]. The clinical database recorded the type, but not the quantity, of medications prescribed at each visit. Outpatient medications included chemoprophylaxis and treatment for AIDS-defining diseases as well as treatment for HBV, HCV, hyperlipidemia and diabetes, but not ART (Technical Appendix, Table A1). When evaluating outpatient medication use, we assumed patients received non-ART medications in accordance with the French standard of care (see Technical Appendix) [6].

To determine costs for each stage of disease, we first multiplied resource utilization per patient per stage by unit cost per resource. After adding all healthcare costs incurred in each stage, we estimated per-person monthly costs by dividing stage costs by total per-person time spent in each stage. Finally, we determined mean cost per person-month in each stage. Details on the derivation of monthly costs by Stage are in the Technical Appendix.

CEPAC Model inputs

Simulated patient characteristics and disease progression—In the base case scenario, simulated patients had the same characteristics as the newly diagnosed French HIV-infected population in 2005 (Table 1) [25]. Mean age at entry into the model was 38 years (SD, 9). Mean initial CD4 count was 372/μl and 15% of patients presented to care with a history of AIDS-defining disease.

CD4 count-stratified mortality and incidence of AIDS-defining diseases were derived from two French cohorts [14,19]. Monthly decreases in CD4 count before patients initiate ART are from the Multicenter AIDS Cohort Study (MACS), the best long-term study to have followed disease progression in the pre-ART era [26].

Treatment characteristics—Simulated patients initiated ARTat CD4 counts <350/μl or at the onset of a severe AIDS-defining disease, as recommended by the national guidelines

in 2005 [27]. Clinic visits, CD4 counts, and HIV RNA tests occurred every 3 months [6], while genotype tests were performed before the initiation of any new ART regimen, including the first. Patients could receive up to six sequential lines of ART (Table 1). They switched ART regimens upon observed failure, defined as two successive HIV RNA tests ≥500 copies/ml or an increase of ≥1 $\log_{10}$ copies/ml [6].

ART and laboratory costs—ART regimen costs were €760/month for first-line ART and ranged from €990/month to €2,570/month for subsequent regimens [28]. Individual antiretroviral drug costs are from the Tourcoing Hospital Pharmacy database and are reflective of costs throughout France. CD4, HIV RNA, and genotype test costs (Table 1) were included in the model separately from Stage costs, as discussed above [23].

Sensitivity analyses—We performed sensitivity analyses on major model parameters to determine their impact on the lifetime cost of care for HIV-infected patients. We first varied CD4 counts at initial presentation to care. We determined the average lifetime undiscounted cost and life expectancies of HIV-infected persons in France who presented to care early (defined as CD4 counts ≥200/μl and no AIDS-defining disease), with advanced disease (defined as CD4 counts <200/μl or AIDS-defining disease), and with base case characteristics [29]. We used these results to estimate the annual and lifetime cost of providing care to three cohorts of 7,360 patients – the estimated annual diagnosed number of HIV-infected patients in France [30] – presenting with the above-mentioned characteristics.

We evaluated the impact on life expectancy and costs of treating patients with newer and more expensive ART regimens, and of reducing the frequency of CD4 and HIV RNA tests. We reduced inpatient and day-care visits in response to the recent recommendations by the French Ministry of Health to replace inpatient hospitalizations with inpatient day-care visits, and to replace inpatient day-care visits with outpatient visits whenever possible [8]. We also increased ART efficacy and costs to account for the recent development of more effective antiretroviral drugs. French law sets the price of generic drugs to a maximum of 50% of brand-name prices [31]. We reduced the cost of ART by this amount to examine the impact of the future availability of generic drugs. We also evaluated alternative assumptions in areas where data were uncertain. In the “lowest virologic efficacy” scenario, the efficacies of ART regimens 3–6 corresponded to the lower bound of published efficacies, as in Table 1 [32– 37]. In the “highest efficacy” scenario, these efficacies corresponded to the upper bound of published efficacies [36–39].

Results

Monthly cost of care in the Tourcoing cohort

Stage 1 costs (excluding CD4, HIV RNA and genotype tests, and antiretroviral drugs) in the Tourcoing cohort ranged from €220/month (standard deviation [SD], €240) at CD4 counts >500/μl to €1,200/month (SD, €1,590) at CD4 counts ≤50/μl (Table 2). Stage 2 costs ranged from €6,180 (SD, €5,070) for fungal infections to €11,700 (SD, €5,610) for *Pneumocystis jirovecii* pneumonia (PCP). Stage 3 costs ranged from €270/month (SD, €330) at CD4 counts >500/μl to €1,070/month (SD, €1,190) at CD4 counts 51 –100/μl. Costs within one month of death (Stage 4) ranged from €7,400 (SD, €7,970) to €14,070 (SD, €8,000), depending on the cause of death.

Life expectancy and costs using the CEPAC Model

In the base case scenario, when mean CD4 count at presentation was 372/μl and patients initiated ART at CD4 counts <350/μl, projected life expectancy was 26.5 years and the lifetime cost of care was €535,000 (€320,700 discounted), or €20,170/year. On average,

patients spent 55% of their lifetimes in Stage 1 and 73% with CD4 counts >500/μl, either before initiating ART or as a result of successful ART. Overall, 73% of lifetime costs and 76% of yearly costs were for ART (Fig. 1). On average, patients spent 18% of their time on ART (4.7 years) on first-line ART, 16% (4.6 years) on second-line ART, 13% (4.2 years) on third-line ART, 11% (4.0 years) on fourth-line ART, and 7% (2.6 years) on fifth-line ART. The 61% of patients who reached sixth-line ART remained on this regimen for an average of 14.1 years, or 34% of their total time on ART. Patients spent the largest fraction of their time on sixth-line ART, because they remained on it until death, even after observed failure. The average overall costs of each ART regimen were €43,100, €54,680, €60,250, €95,980, €80,030, and €219,730 for ART lines 1–6, respectively.

The average yearly cost of care was €36,540 among patients with CD4 counts ≤50/μl. This cost consisted predominantly of ART (41%) and inpatient hospitalizations (38%) (Fig. 1). At CD4 counts >500/μl, the average yearly cost was €19,240, ofwhich 81% was ART-related. At CD4 counts 351–500/μl, the average yearly cost was €15,970, ofwhich 70% was ART-related. Yearly costs were higher in the former group, because a larger proportion of patients in the CD4 count >500/μl group were on ART (Fig. 1).

Sensitivity analyses: impact on lifetime cost

Timing of presentation to care—Life expectancy was highest, at 27.5 years, when patients presented to care early (mean CD4 count, 510/μl). Undiscounted lifetime costs for these patients were €534,800/person (Table 3). Life expectancy and undiscounted lifetime costs were lowest for patients presenting with advanced disease (mean CD4 count, 97/μl), at 23.8 years and €513,200. Figure 2 shows the annual undiscounted costs of providing care to three hypothetical cohorts of 7,360 HIV-infected persons presenting to care at the different disease stages described above [30]. These simulated patients initiated ARTwhen their CD4 counts were observed to be <350/μl, and were followed for 20 years. The cost of providing care to a population of 7,360 patients in the first year after HIV diagnosis was €134 million when all patients presented with advanced disease [29]. In this population, annual costs to the health system were highest in the first year of care. Annual costs decreased substantially in the following two years. For the first 12 years of care, however, annual costs to the health system in this population were higher than among patients who presented to care early.

Newer ART regimens—Changes in ARTefficacy and costs had the greatest impact on lifetime costs (Table 3). When third-line ART consisted of raltegravir, etravirine and ritonavir-boosted darunavir (six-month probability of virologic suppression, 90%) [38] and fourth-line ART consisted of etravirine, ritonavir-boosted darunavir and enfuvirtide (six-month probability of virologic suppression, 75%) [31,35], both life expectancy and costs increased. In this scenario, life expectancy increased from 26.5 to 27.9 years and undiscounted lifetime costs increased 17–18% to €634,000 (€374,700 discounted). Of these costs, 77% were for ARTand 7% were for hospitalizations. When we substituted first-line efavirenz with raltegravir and increased the cost but not the efficacy of the regimen, lifetime cost increased 4–6% to €559,100/patient (€341,300 discounted). Of these costs, 74% were for ARTand 8% were for inpatient hospitalizations. Lifetime costs decreased 4–6% when we reduced the cost of first-line ART alone by 50% (to €514,200 undiscounted; €302,800 discounted), to examine the impact of the future availability of generic drugs [31]. Of these costs, 72% were for ART and 9% were for inpatient hospitalizations. They decreased 36–37% when we reduced the cost of all antiretroviral medications by the same amount (€339,400 undiscounted; €203,800 discounted) [31]. Of these costs, 58% were for ARTand 13% were for inpatient hospitalizations.

Other sensitivity analyses—Variations in ART initiation criteria had a smaller impact on the results. When patients presented to care with a mean CD4 count of 372/μl and initiated ART at CD4 counts <500/μl or HIV RNA >100,000 copies/ml, life expectancy remained the same but lifetime costs increased 2–3%, from €535,000 to €543,400 (€329,000 dis counted). Of these costs, 74% were for ARTand 8% were for inpatient hospitalizations. When patients presented early (mean CD4 count, 510/μl) and initiated ART at CD4 counts <500/μl or HIV RNA >100,000 copies/ml, life expectancy increased by almost one year to 27.4 years compared to the base case, and lifetime costs increased 1–2%, to €546,700 (€324,500 discounted). Of these costs, 76% were for ART and 8% were for inpatient hospitalizations.

Modifications in inpatient day-care, inpatient hospitalization and outpatient utilization had little impact on total costs (data not shown). Changes in laboratory test utilization had little impact on results (Table 3).

Discussion

Using cost and resource utilization data from a national database and a widely published HIV simulation model, we projected survival and costs of HIV care. Although it is difficult to compare studies on the lifetime costs of HIV directly, due to differences in costing methodology, our results are consistent with those reported by Schackman *et al*. in 2006, as well as other studies [40]. Our study demonstrates that total lifetime costs of care have increased, but that the overall annual costs of care have remained remarkably stable over time. The main driver of the increase in total lifetime costs of care is the dramatic improvement in survival generated by both earlier ART initiation and more efficacious treatment. In 2002, we used the same database and the same model to estimate the undiscounted lifetime cost of HIV care at €382,000 (€264,200 discounted) over a lifetime of 16.4 years, or €23,200/year (inflation-adjusted to 2010€) [10]. In our current study, we found a projected life expectancy of 26.5 years and a lifetime cost of care of €535,000 (€320,700 discounted), or €20,170/year. This finding is consistent with other published cost analyses. In 2008, for instance, Krentz *et al*. estimated the cost of medical care for HIV-infected patients in the Southern Alberta Cohort over a nine-year period. They found that annual costs of care had remained relatively stable for most HIV patients, except those with CD4 counts <75 cells/mL [41]. Some studies have stated that, although overall annual costs have remained similar throughout the combination ART era, the cost distribution has changed, with a progressive decline in inpatient costs and increase in ART costs [42]. This is not consistent with studies that were published more recently, however [41].

It is notable that almost three quarters of the cost of care for HIV-infected patients is for antiretroviral drugs, consistent with previous analyses [40]. Potential changes in the cost of ART will therefore have a considerable impact on results. The United States Department of Health and Human Services, for instance, recently added raltegravir-based regimens as one of the preferred options for ART-naïve patients [7]. When we replaced efavirenz with raltegravir in first-line ART, the lifetime cost of care increased. Although raltegravir-based first-line ART has been shown to be a well-tolerated and effective alternative to efavirenz in ART-naïve patients [43], a less expensive generic form of efavirenz will likely become available soon [7]. When we assumed using generic efavirenz reduced first-line ART costs by 50% [31], undiscounted lifetime costs decreased only slightly, perhaps because we did not simultaneously consider generic drugs for the five subsequent ART regimens. This scenario is realistic, because the older drugs used in first-line regimens are close to or past their 20-year patent protection period. Although the use of generics in first-line ART makes only a small difference at the individual level, it would play an important role in budget planning at the population level. As an increasing number of safe and effective first- and

second-line HIV medications becomes available and resources for care become increasingly constrained in high-income settings, national and international policy makers may need to consider drug prices when selecting preferred regimens, similar to the process for selecting cardiovascular and other chronic disease treatments in low-income settings [44]. Moreover, as recommendations for earlier ART initiation increase the market for antiretroviral drugs [6,7], lower drug prices could make earlier care more feasible.

Delayed entry into HIV care resulted in reduced life expectancy and higher immediate costs after treatment initiation. This finding is consistent with results recently reported by Fleishman *et. al*. in the US. They demonstrated that after 7–8 years of care, HIV-infected patients who initiated care late had substantially higher medical costs than patients who were diagnosed and started care earlier [45]. Interventions such as routine HIV screening, which was recently recommended in France [46], could reduce the number of patients initiating care with advanced HIV. We recently demonstrated that this strategy would be both effective and cost-effective in France [47].

The United States Department of Health and Human Services and the French Ministry of Health also recently recommended that HIV-infected patients initiate ART with CD4 counts <500/μl [5–7]. The current model-based analysis suggests that modifying treatment initiation criteria may have little impact on life expectancy under current conditions, because a substantial proportion of patients continue to present to care with initial CD4 counts <350/μl [29,48,49].

Although this analysis aims to inform budget planning and HIV financing policy in France, we realize that most global HIV policy decisions are directed toward low- and middle-income countries (LMIC), and that budget impact analyses in these settings are necessary. While overall costs of care are lower in LMIC, the distribution of costs is also very different. For example, because most HIV treatment programs in LMIC use cheaper centrally-sourced generic antiretroviral drugs, laboratory monitoring costs play a larger role in overall costs than in high-income settings like France. Findings, particularly the impact of introducing generics and earlier ART initiation, will therefore likely be different in LMIC settings [18].

This analysis has several limitations. First, the clinical database we used to estimate cost of care was not from a national sample and may not be representative of other areas of France. However, since treatment guidelines are the same across France [6], standards of care are probably similar, and our results are likely generalizable to the rest of the country. Second, in calculating the monthly cost of care by disease stage, we did not consider the cost of care for cancer treatments that occur outside our HIV inpatient and outpatient clinics, palliative care, or home healthcare received outside of the Tourcoing AIDS Reference Center. For example, we did not include utilization data for patients with oncological diseases other than Kaposi’s sarcoma who were treated at other hospitals and specialty clinics. Third, to estimate the life expectancy and lifetime cost of HIV disease we used a simulation model that relies on multiple assumptions. The long-term efficacy of some ART regimens and the durability of their virologic and immunologic benefits are not fully known, because randomized trials generally report short-term outcomes. However, the results were only minimally sensitive to variations in ART efficacy. Finally, we note the mounting evidence pointing to the preventive benefits of ART in reducing HIV transmission [50]. Since this analysis restricts attention to the impact of treatment on the individual infected patient, it does not account for any life expectancy gains or resource savings that might accrue from preventing the further spread of infection. Our findings may therefore underestimate the health benefits and overestimate the costs of expanding ART initiation criteria.

Although the financial impact of care and treatment of HIV-infected individuals continues to grow, few studies worldwide have estimated the lifetime cost of treating HIV disease with current regimens [9]. Even when estimates are available [51–53], the limited period of time during which cost and utilization data are collected makes it difficult to extrapolate future expenditures. With current clinical and cost data, we projected the lifetime cost of treating HIV disease in France. We showed that earlier presentation to care reduces annual costs to the health system in the first decade of treatment, and also improves survival, thus increasing ARTutilization costs in this group in later years. We found that lower antiretroviral costs associated with the availability of generic drugs could dramatically reduce individual lifetime costs in developed countries. Policy makers can use these projections to prioritize HIV-related health interventions and to ensure that sufficient resources are committed to HIV care.

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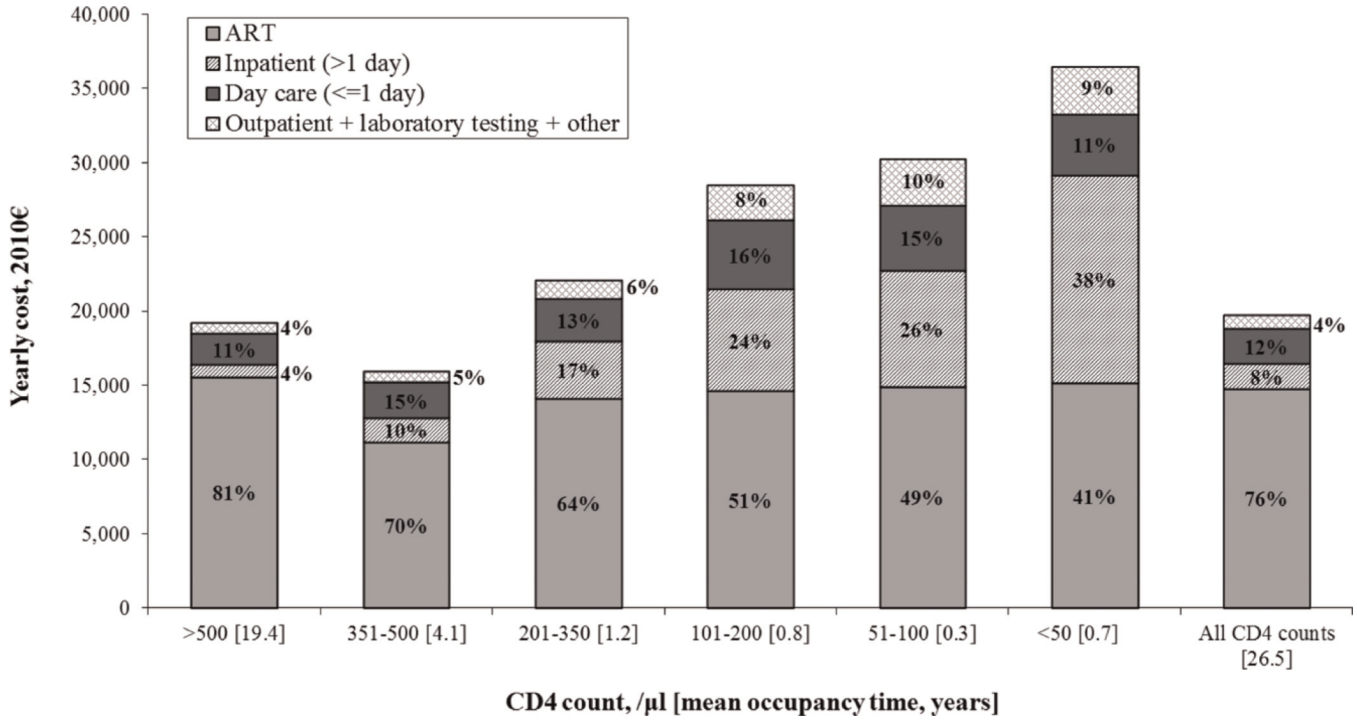

Fig. 1. Components of annual cost of HIV care by CD4 count

Annual costs were higher when simulated patients had CD4 counts >500/µl than when they were 351–500/µl, because the majority of patients with CD4 counts >500/µl were on antiretroviral therapy (ART).

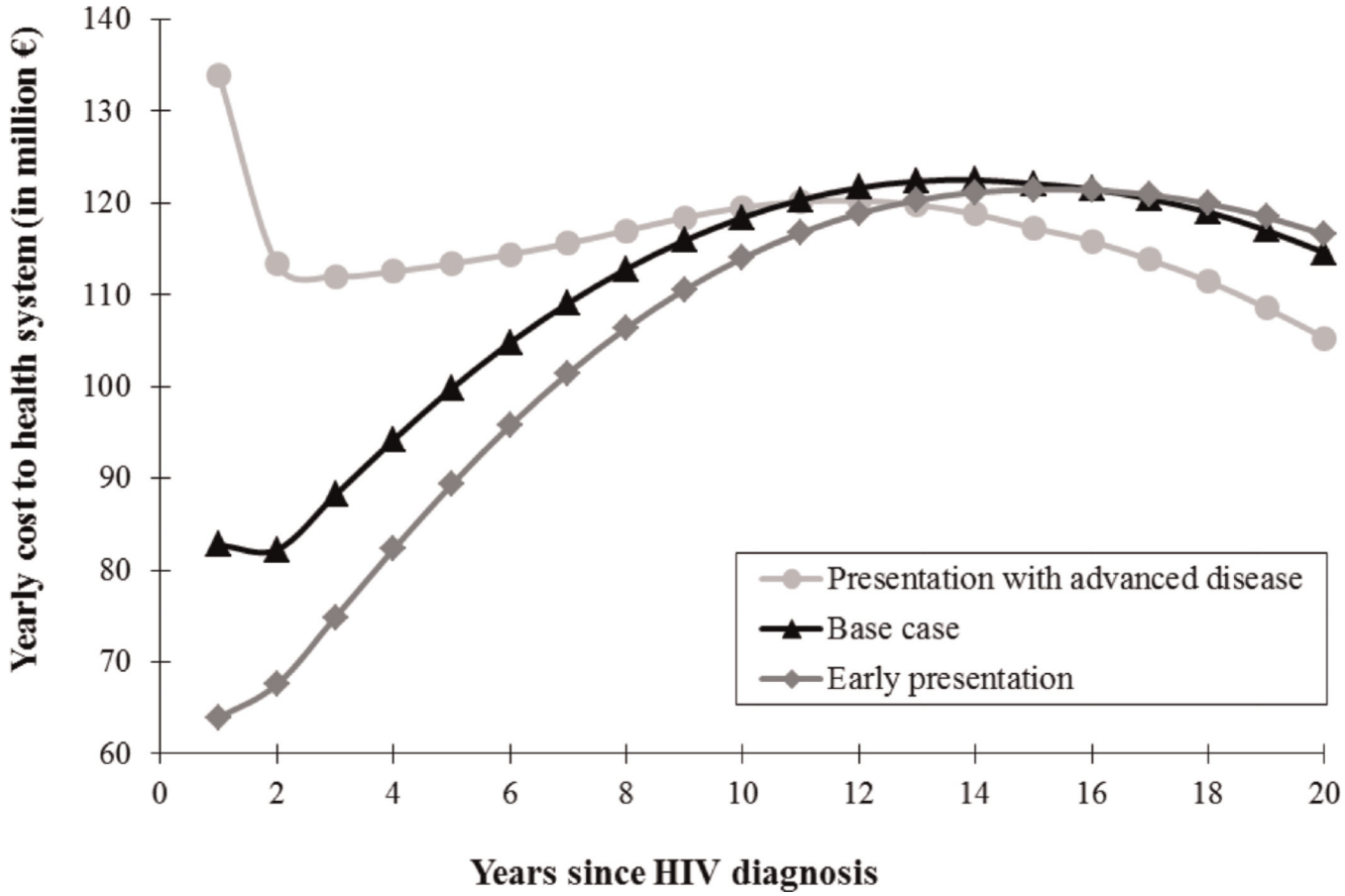

Fig. 2. Distribution of annual undiscounted cost to the health system of providing care to a cohort of 7,360 persons recently diagnosed with HIV, by disease stage

This figure shows results for three cohorts of simulated patients: (a) Presentation with advanced disease: patients presenting to care with advanced disease, defined as CD4 counts <200/μl or AIDS-defining disease (mean CD4 count, 97/μl); lifetime cost; lifetime cost was €513,200 (€322,500 discounted). (b) Base case: patients presenting to care with base case characteristics, similar to those of patients presenting to care in France in 2005 (mean CD4 count, 372/μl); lifetime cost was €535,000 (€320,700 discounted). (c) Early presentation: patients presenting to care early (mean CD4 count, 510/μl); lifetime cost was €534,800 (€313,000 discounted). Simulated patients in each of these cohorts initiated antiretroviral therapy (ART) at CD4 counts <350/μl or severe AIDS-defining disease. Undiscounted lifetime costs are similar in the base case and early disease groups, but discounted costs are €7,700 higher in the base case group. This substantial difference may be explained by the earlier deaths and thus decreased discounting of expensive end-of-life costs in the base case.

Table 1

Summary of input parameters for the CEPAC model of HIV disease and treatment in France.

Variable	Base case value	Sensitivity analysis range[a]	Reference
Mean age at study entry, years (SD)	38 (9)	—	[25]
% male	62	—	[25]
Mean CD4 at enrollment, cells/μl (SD)	372 (257)	97 – 510	[54]
HIV RNA distribution at initiation of HIV care (copies/ml), %			
> 100,000	18.8	—	[54]
30,001 – 100,000	21.1	—	[54]
10,001 – 30,000	15.2	—	[54]
3,001 – 10,000	13.9	—	[54]
501 – 3,000	11.2	—	[54]
≤500	19.8	—	[54]
History of opportunistic disease at enrollment, %	15	—	[55]
Time interval between laboratory tests			
CD4 count, months	3	3–6	[6]
HIV RNA, months	3	3–6	[6]
Genotype	Before any new regimen	—	[6]
Antiretroviral therapy efficacy, % HIV RNA level suppressed to <400 copies/ml at 24 weeks (mean increase in CD4 cell count at 48 weeks, cells/μl)			
TDF/FTC + EFV	86 (190)	76 – 96	[56]
ATV/r + 2 NRTIs	70[b] (110)	63 – 83	[57]
3rd-line[c]	58[b] (121)	60 – 90	[32,33,38,57]
4th-line[c]	65 (102[d])	50 – 75	[34,35,39,58]
5th-line[c]	40 (121)	20 – 50	[36,37,59]
6th-line[c]	15 (45)	10 – 40	[36,37]
Protective effect of antiretroviral therapy on risk of AIDS-defining diseases and death, %	46	0 – 73	[60]
Antiretroviral therapy costs, 2010€/month			
TDF/FTC+ EFV	760	380 – 1,200	[28,31]
ATV/r + 2 NRTIs	990	500 – 990	[28,31]
3rd-line	1,190	600 – 2,410	[28,31]
4th-line	2,000	1,000 – 2,080	[28,31]
5th-line	2,570	1,280 – 2,570	[28,31]
6th-line	1,290	640 – 1,290	[28,31]
Laboratory tests, 2010€/test			
CD4 count	22	—	[23]
HIV RNA	59	—	[23]
Genotype	297	—	[23]

ATV/r, ritonavir-boosted atazanavir; EFV, efavirenz; FTC, emtricitabine; NRTI: nucleoside reverse transcriptase inhibitor; SD, standard deviation;TDF, tenofovir.

[a] See Technical Appendix for details on the endpoints used in the sensitivity analysis ranges.

[b] at 48 weeks

[c] Once patients start third-line therapy, genotype tests generally determine individualized regimens. ART lines 3–6 are therefore modeled as standard regimens with wide ranges of efficacy and costs, represented by various recent studies.

[d] at 24 weeks

Table 2

Summary of resource utilization and costs in the Tourcoing AIDS Reference Center: inputs for the CEPAC model of HIV disease and treatment in France.

Variable	Average monthly cost, 2010€ (SD)[a]	Time spent in stage (person-months)
Stage 1: No history of AIDS-defining event by CD4 count (cells/μl)[b]		
>500	220 (240)	290,226
351 – 500	290 (390)	181,888
201 – 350	370 (590)	51,898
101 – 200	810 (2,270)	20,507
51 – 100	870 (930)	5,240
≤50	1,200 (1,590)	3,953
Stage 2: Acute AIDS-defining disease[c]		
Pneumocystis jiroveci pneumonia	11,700 (5,610)	1,230
Mycobacterium avium complex	6,390 (2,900)	160
Toxoplasmic encephalitis	9.420 (6,400)	533
Cytomegalovirus infection	11,640 (3,780)	359
Candida esophagitis	6,180 (5,070)	2,297
Other AIDS-defining event	6,340 (6,890)	8,963
Stage 3: History of at least one AIDS-defining event by CD4 count (cells/μl)[b]		
>500	270 (330)	32,376
351 – 500	390 (850)	29,649
201 – 350	760 (1,840)	16,135
101 – 200	1,050 (2,230)	9,828
51 – 100	1,070 (1,190)	2,198
≤50	920 (580)	2,200
Stage 4: Month of death[c]		
No history of an AIDS-defining event	7,400 (7,970)	1,077
≤30 days after an AIDS-defining event	14,070 (8,000)	566
>30 days after an AIDS-defining event	11,750 (8,670)	475

SD, standard deviation.

[a] Stage-specific cost estimates excluded the costs of antiretroviral drugs and CD4 count, HIV RNA and genotype tests. These costs were added individually to the stage-specific costs to allow for variations in laboratory testing frequency, ART initiation criteria, and the cost of newly available antiretroviral drugs.

[b] From the Tourcoing AIDS Reference Center, January 2004 – December 2005.

[c] From the Tourcoing AIDS Reference Center, January 1998 – December 2005.

Table 3

Projected life expectancy and lifetime costs of care for HIV-infected adults in France.

	Undiscounted			Discounted
	Life expectancy, years (SD)	Annual cost, 2010€	Lifetime cost, 2010€ (SD)	Lifetime cost, 2010€ (SD)
Base case	26.5 (14.0)	20,170	535,000 (308,000)	320,700 (146,200)
Sensitivity analyses				
Timing of presentation to care				
Presentation with advanced disease (mean CD4 count, 97/μl)[a]	23.8 (14.2)	21,600	513,200 (314,200)	322,500 (154,600)
Early presentation (mean CD4 count, 510/μ1)	27.5 (13.9)	19,440	534,800 (307,100)	313,000 (144,600)
Probability of virologic suppression after six months of ART regimen				
Third-line, 90%; fourth-line, 75%	27.9 (14.7)	22,700	634,000 (369,400)	374,700 (177,200)
"Lowest efficacy" scenario[b]	25.6 (13.5)	19,890	509,100 (293,400)	309,200 (139,600)
"Highest efficacy" scenario[c]	28.1 (14.7)	20,280	569,200 (329,400)	332,400 (153,000)
ART cost				
Raltegravir-based first-line ART: €1,200[d]	26.5 (14.0)	21,080	559,100 (312,500)	341,300 (149,300)
First-line ART reduced by 50%[e]	26.5 (14.0)	19,380	514,200 (305,200)	302,800 (145,000)
All lines of ART reduced by 50%[f]	26.5 (14.0)	12,790	339,400 (1 87,000)	203,800 (87,200)
ART initiation criteria				
Expanded ART initiation criteria[g]	26.4 (13.9)	20,560	543,400 (308,300)	329,000 (146,800)
Immediate[h]	26.4 (13.6)	20,970	554,000 (306,300)	339,200 (145,600)
Early presentation + expanded ART initiation criteria	27.4 (13.8)	19,960	546,700 (307,400)	324,500 (145,500)
Protective effect of ART on morbidity and mortality (base case: 46%)				
None	22.6 (13.7)	20,440	461,100 (306,400)	287,800 (153,900)
73%	30.2 (14.1)	20,350	615,000 (318,400)	353,300 (142,000)
Outpatient visit and laboratory test frequencies				
25% decrease in outpatient visits; CD4 and HIV RNA tests every 4 months	26.5 (14.0)	20,150	534,500 (307,700)	320,400 (146,100)
50% decrease in outpatient visits; CD4 and HIV RNA tests every 6 months	26.5 (14.0)	20,130	534,000 (307,400)	320,100 (146,000)

ART, antiretroviral therapy; SD, standard deviation.

[a] In the cohort followed at the Tourcoing AIDS Reference Center from 1 998 to 2005, the mean CD4 count of patients presenting to care with advanced disease, defined as CD4 counts <200/μl or AIDS-defining disease [29], was 97/μl. Undiscounted lifetime costs are similar in the base case and early presentation groups, but discounted costs are €7,700 higher in the base case group. This substantial difference may be explained by the earlier deaths and thus decreased discounting of expensive end-of-life costs in the base case.

[b] In the "lowest efficacy" scenario, the efficacies of ART regimens 3–6 correspond to the lower bound of published efficacies, as in Table 1 [32]–[37].

[c] In the "highest efficacy" scenario, the efficacy of ART regimens 3–6 correspond to the upper bound of published efficacies [36–39].

[d] This is the cost of tenofovir + emtricitabine + raltegravir. This regimen may become the standard first-line ART regimen in the near future [7].

[e] This scenario represents the potential emergence of generic efavirenz in the near future [7,31].

[f] The emergence of generics could reduce the price of ART in the near future [7,31].

[g] Expanded ART initiation criteria: CD4 count <500/μl, HIV RNA >100,000 copies/ml, or AIDS-defining disease.

[h] Immediate: ART initiation at presentation to care, regardless of CD4 count and HIV RNA.