Cost-effectiveness analysis of HIV treatment in the clinical practice of a public hospital in northern Italy

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Introduction: We carried out an economic analysis to assess the cost-effectiveness of highly active antiretroviral therapy (HAART) regimens in Italy for the management of human immunodeficiency virus (HIV)-infected patients according to clinical practice in the Infectious Diseases Department of "L. Sacco" Hospital, Milan, Italy.

Patients and methods: The incremental cost-effectiveness analysis was completed by means of a Markov model. Through a decision-analytic approach, this enabled us to compare the studied antiretroviral regimens. The model considered a population of adult HIV subjects who received HAART therapy for the first time according to clinical practice in the Infectious Diseases Department of "L. Sacco" Hospital, Milan. Data were investigated from the standpoint of the Lombardy Regional Health Service. We considered the following outcome measures: quality-adjusted life-years (QALYs), and direct health costs calculated for the years 2008 and 2009. The time horizon adopted in the model was 2 years.

Results: The model revealed that, in terms of cost per gained QALY, the tenofovir disoproxil fumarate + emtricitabine + efavirenz (TDF+FTC+EFV) once-a-day treatment strategy seems to be the most cost-effective therapeutic choice (€34,965); the incremental cost-effectiveness ratio (ICER) values for the remaining strategies ranged from €53,000 to around €62,000 per QALY. The validity of the base case scenario was then confirmed by means of a sensitivity analysis on the main variables.

Conclusion: The TDF+FTC+EFV treatment strategy (TDF/FTC+EFV fixed-dose combination then switched to single-tablet regimen [STR]) in this setting is the most cost-effective treatment strategy compared with the other therapeutic regimens. The ICER value for the TDF+FTC+EFV once-a-day then switched to STR treatment was lower than the internationally generally accepted threshold value of €50,000. The developed model is a tool for policy makers and health care professionals for creating short- and long-term cost projections, with the aim of assessing their impact on the available budgets for HIV patients.

Keywords: AIDS, HIV, HAART antiretroviral therapy regimens, single-tablet regimen (STR), Markov model, cost-effectiveness, quality-adjusted life-years, QALYs

Introduction

The economic burden of human immunodeficiency virus (HIV) infection is well recognized globally.¹⁻³ The HIV prevalence and incidence data presented in the last report by the United Nations (UNAIDS) and World Health Organization (WHO) show that 33.3 million people in the world were HIV-infected in 2009, with 2.5 million new cases.¹ Its management requires the use of health care services for treating HIV infection and symptoms associated with acquired immunodeficiency syndrome (AIDS) and with opportunistic infections, and involves indirect costs associated with

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morbidity and premature death of working-age patients. Since the mid-1990s, highly active antiretroviral therapy (HAART) has modified the clinical course of HIV infection, reducing the rate of disease progression, the incidence of opportunistic infections, and mortality.^{4,5} Thanks to combination antiretroviral therapy, therefore, many HIV-infected patients now enjoy longer survival and a better quality of life.^{6,7}

In Italy, the universal and public National Health Service (NHS) has delegated regions with the responsibility of organizing and administering publicly financed health care. The consequence has been the creation of different models around the country, both from an organizational and a funding point of view. Lombardy is the most populated of the 20 Italian regions, with 10 million inhabitants comprising over 15% of the Italian population in 2011.⁸ Moreover, the Lombardy Region has the highest prevalence of AIDS cases in Italy, with a strong impact on the regional health care budget. According to data from the Italian Seroconversion Study,^{9,10} Lombardy has also one of the highest incidence rates in Italy (3.2 cases per 100,000 inhabitants). This inevitably has a great bearing on the regional health care system (the total expenditure for the care of HIV/AIDS patients, including the cost of care outside hospitals and residential homes, ie, in semiresidential housing, hospices, etc, now hovers around 300 million per year).¹¹ In particular, the cost of antiretroviral therapy has gradually increased from about €92 million in 2004 to more than €193 in 2010.¹² However, the need for regimens with powerful antiviral activity, proven long-term safety, good adherence, and a low rate of antiviral resistance should also be evaluated in terms of lifetime costs, since HIV is a long-lasting disease and its treatment may continue for many years.¹³ In a context of limited health care resources, pharmacoeconomic considerations are crucial to help policy makers make the most appropriate decisions on resource allocation. We therefore performed an economic analysis to assess the cost-effectiveness of the HAART regimens in the Lombardy Region for managing HIV-infected patients according to clinical practice in the Infectious Diseases Department of “L. Sacco” Hospital, Milan, Italy.

Methods

Structure of the model

The study aimed to determine the incremental cost-effectiveness ratio (ICER) per quality-adjusted life-years (QALYs) gained for HAART regimens of HIV-infected patients, according to clinical practice in the Infectious Diseases Department of “L. Sacco” Hospital, Milan.

We performed an incremental cost-effectiveness analysis by using and adapting a recently published Markov model¹⁴ to case series of HIV-positive patients treated in the Infectious Diseases Department of “L. Sacco” Hospital, Milan during 2 years of observation. The Markov model simulates the quality of life and costs for an HIV patient, starting from the administration of the initial antiretroviral treatment and followed up in 1-year cycles.¹⁵ The model assigned patients responding to the antiretroviral therapy a viremia value lower than 50 copies and allowed responders to move within the CD4 classification.¹⁴ After entering the model and receiving one of the antiretroviral regimens, the patient can “move” through eight health states, defined by the CD4-cell count combined with the viremia levels (VL), one AIDS state, and one death state. The analysis was carried out from the point of view of the Lombardy Regional Health Service (RHS) in Italy. QALYs were considered as outcomes; the costs considered were direct health care costs, valued for the year 2011. The model adopted a 2-year time horizon. The studied antiretroviral regimens represent the pharmacological options used that had homogeneous characteristics during the period observed. The analyzed antiretroviral regimens represented the most frequently used pharmacological options during the study period. This economic evaluation considered QALYs as effectiveness indicators. The utility values, associated with the eight health states identified by the CD4-cell count, were calculated by Simpson et al.^{15–18}

Patients and transition probabilities

The enrolled subjects are HIV patients who were referred to the HIV center at the First Infectious Diseases Department at the “L. Sacco” Hospital in Milan in the period between 2008 and 2009. The population included and evaluated in the model consists of subjects having similar and superimposable sociodemographic characteristics at the time of enrollment (2008). The patients’ characteristics, which determined their selection in the group of pooled data, were divided into five macrogroups: demographics, comorbidities linked with hepatitis C virus (HCV) disease and comorbidities linked with hepatitis B virus (HBV) disease, treatment line, and adherence. The required data for these five large areas are reported in Table 1. The analysis was carried out on four therapeutic combinations, which are summarized in Table 2.

The criteria for inclusion were as follows: age ≥ 18 years, confirmed HIV infection, being resident in Lombardy, and being followed at the First Infectious Disease Department of “L. Sacco” Hospital in Milan during the observation

Table I Patient characteristics at enrollment

	Treatment regimens												Total	
	TDF FTC EFV		TDF FTC ATZ RTV		TDF FTC LPV/r RTV		AZT 3TC LPV/r RTV		M		F			
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)		n
Age														
<30	0	0.0	2	4.2	1	1.9	0	0.0	2	1.4	1	2.1	3	1.5
30–39	22	37.9	11	22.9	18	34.0	10	28.6	45	30.6	16	34.0	61	31.4
40–49	28	48.3	26	54.2	23	43.4	19	54.3	73	49.7	23	48.9	96	49.5
50–59	5	8.6	4	8.3	8	15.1	4	11.4	19	12.9	2	4.3	21	10.8
≥60	3	5.2	5	10.4	3	5.7	2	5.7	8	5.4	5	10.6	13	6.7
HCV infections?														
Pos	16	27.6	21	43.8	15	28.3	10	28.6	47	32.0	15	31.9	62	32.0
Neg	37	63.8	24	50.0	34	64.2	23	65.7	89	60.5	29	61.7	118	60.8
Unknown	5	8.6	3	6.3	4	7.5	2	5.7	11	7.5	3	6.4	14	7.2
HCV RNA detectable?														
HCV negative	37	63.8	24	50.0	34	64.2	23	65.7	89	60.5	29	61.7	118	60.8
Y	8	13.8	14	29.2	8	15.1	6	17.1	27	18.4	9	19.1	36	18.6
N	4	6.9	4	8.3	6	11.3	4	11.4	14	9.5	4	8.5	18	9.3
ND	9	15.5	6	12.5	5	9.4	2	5.7	17	11.6	5	10.6	22	11.3
Treated for HCV in 2008/09?														
HCV negative	37	63.8	24	50.0	34	64.2	23	65.7	89	60.5	29	61.7	118	60.8
Y	3	5.2	3	6.3	3	5.7	0	0.0	6	4.1	3	6.4	9	4.6
N	10	17.2	14	29.2	10	18.9	10	28.6	34	23.1	10	21.3	44	22.7
Unknown	8	13.8	7	14.6	6	11.3	2	5.7	18	12.2	5	10.6	23	11.9
HBsAg?														
Pos	2	3.4	5	10.4	5	9.4	1	2.9	11	7.5	2	4.3	13	6.7
Neg	51	87.9	38	79.2	44	83.0	32	91.4	125	85.0	40	85.1	165	85.1
Unknown	5	8.6	5	10.4	4	7.5	2	5.7	11	7.5	5	10.6	16	8.2
Naive in early 2008?														
Y	5	8.6	5	10.4	5	9.4	4	11.4	14	9.5	5	10.6	19	9.8
N	53	91.4	43	89.6	48	90.6	31	88.6	133	90.5	42	89.4	175	90.2
If naive, treatment started in 2008/09?														
N	53	91.4	43	89.6	48	90.6	31	88.6	133	90.5	42	89.4	175	90.2
Y	5	8.6	5	10.4	5	9.4	4	11.4	14	9.5	5	10.6	19	9.8
Is patient in first line?														
Y	19	32.8	8	16.7	16	30.2	11	31.4	46	31.3	8	17.0	54	27.8
N	38	65.5	37	77.1	37	69.8	24	68.6	97	66.0	39	83.0	136	70.1
ND	1	1.7	3	6.3	0	0.0	0	0.0	4	2.7	0	0.0	4	2.1
Adherence														
Missing data	2	3.4	0	0.0	4	7.5	2	5.7	3	2.0	5	10.6	8	4.1
Y	56	96.6	44	91.7	43	81.1	32	91.4	137	93.2	38	80.9	175	90.2
N	0	0.0	4	8.3	6	11.3	1	2.9	7	4.8	4	8.5	11	5.7
Treatment change in 2008/2009?														
Y	8	13.8	11	22.9	18	34.0	13	37.1	32	21.8	18	38.3	50	25.8
N	50	86.2	37	77.1	35	66.0	22	62.9	115	78.2	29	61.7	144	74.2

Abbreviations: TDF, tenofovir; FTC, emtricitabine; EFV, efavirenz; ATZ, atazanavir; RTV, ritonavir; LPV/r, ritonavir-boosted lopinavir; AZT, zidovudine; 3TC, lamivudine; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HCV RNA, hepatitis C virus ribonucleic acid.

period (2008–2009), with at least one laboratory test (CD4 cell count and/or VL) per year during the study period.¹³ Patients were excluded in case of missing clinical data (subjects not referring to the center for more than 12 months) or cost information (patients not resident in Lombardy). The personal details for each patient (sex, age, ethnicity, risk

factor for HIV acquisition) were recorded, as well as clinical information (highest VL and lowest CD4+ cell count in each year, antiretroviral treatment [ART] history, HCV and HBV coinfection). These data were collected from the medical records of the First Infectious Diseases Department of the “L. Sacco” Hospital. During the first visit at the HIV center,

Table 2 Patient distribution per treatment, based on CD4-cell count and viremia

CD4 viremia treatment	>500 cells/ μ L		351–500 cells/ μ L		201–350 cells/ μ L		<200 cellule/ μ L		Total patients treated
	<50	$\geq$ 50	<50	$\geq$ 50	<50	$\geq$ 50	<50	$\geq$ 50	
TDF FTC EFV	23	4	11	1	7	4	5	3	58
TDF FTC ATZ RTV	16	6	11	3	3	2	4	3	48
TDF FTC LPV/r RTV	18	4	9	3	8	4	4	3	53
AZT 3TC LPV/r RTV	11	4	5	4	3	4	1	3	35
Total	68	18	36	11	21	14	14	12	194

Abbreviations: TDF, tenofovir; FTC, emtricitabine; EFV, efavirenz; ATZ, atazanavir; RTV, ritonavir; LPV/r, ritonavir-boosted lopinavir; AZT, zidovudine; 3TC, lamivudine.

patients signed a one-time general informed consent to the use of their data. All data were anonymously processed and analyzed.¹³ Tables 1 and 2 show the characteristics of patients considered in the model, with respect to the CD4 cell count. Data were gathered at 6-month intervals during the 2 years, with four total data collection intervals. Atripla® (Gilead Sciences Inc, Foster City, CA) became available in the hospital in July 2008. So all patients taking tenofovir disoproxil fumarate + emtricitabine + efavirenz (TDF+FTC+EFV) once a day until that moment used a fixed-dose combination of TDF+FTC and EFV, and then switched to a single-tablet regimen (STR).

Resource consumption and costs

The perspective assumed was the Lombardy RHS. The consumption of resources for the patients considered in the model is associated with the administration of the anti-retroviral regimens and with other direct health care costs, such as hospitalizations, medical examinations, laboratory tests, and so on. We were able to perform a patient-based analysis, because we collected cost data from the Integrated Patients' Database (Banca Dati Assistito) of the Lombardy Region. This data warehouse contains three main databases (outpatient activity, pharmaceuticals, and inpatient activity) recording all health care services provided to each patient by any (public or accredited private) hospital or clinic in the RHS.¹³ The RHS provides reimbursement for outpatient activities (medical examinations, laboratory and diagnostic procedures), hospital admissions, HAART, and non-HAART

drugs to each regional health care structure. The data collected are therefore the real costs incurred by the RHS, ie, the bills paid to the (both public and private) providers for services delivered to each patient. Data on non-HAART drugs include all drugs prescribed to a patient and collected at any provider within the Lombardy Region, such as hospitals and pharmacies. These data were collected for the study period and anonymously linked to the clinical and personal data through a univocal code. All economic data collected referred to the year in which they were incurred. Costs were then discounted at the 2011 level, based on the Italian inflation rates of average consumer prices. In the cost analyses, the evolution of both total cost and of each cost category between 2008 and 2009 was considered. All clinical data were then analyzed to identify patient characteristics which may be related to the costs in each year, taking into account CD4 cell count (<200, 200–350, 351–499, $\geq$ 500 cells/mm³).

Information on the consumption of resources such as hospitalizations, outpatient care, general practitioner and specialist examinations, laboratory tests, and diagnostic procedures expressed as CD4 cell count in patients involved in the survey is shown in Table 3, whereas Table 4 shows the average annual costs for each first-line regimen used at the “L. Sacco” Hospital, based on the reimbursement price paid by the RHS, which takes into account the price updates effective from January 1, 2011.^{19,20}

The Mann–Whitney or Kruskal–Wallis tests were used to compare cost data, for two-group and three-or-more

Table 3 Average annual cost per patient and health state expressed in CD4 (excluding HAART cost)

CD4 viraemia Other costs	>500 cellule/ μ L		351–500 cellule/ μ L		201–350 cellule/ μ L		<200 cellule/ μ L	
	<50	$\geq$ 50	<50	$\geq$ 50	<50	$\geq$ 50	<50	$\geq$ 50
Healthcare services	€1349	€1490	€1459	€1619	€1610	€1794	€1700	€1675
Other drugs	€325	€254	€366	€377	€510	€266	€840	€648
Hospitalizations	€610	€975	€1509	€1488	€719	€2733	€2798	€5025
Total	€2284	€2719	€3333	€3484	€2839	€4793	€5337	€7348

Note: Data on file: “L. Sacco” Hospital, Milan; Integrated Patients' Database (Banca Dati Assistito) of the Lombardy Region; 2012.

Abbreviation: HAART, highly active antiretroviral therapy.

Table 4 Average annual costs for each first-line therapeutic HAART regimen

Treatment	Annual costs HAART treatment
TDF FTC EFV	€7226
TDF FTC ATZ RTV	€9016
TDF FTC LPV/r RTV	€9018
AZT 3TC LPV/r RTV	€7642

Note: Data on file: "L. Sacco" Hospital, Milan – Prices 2011; 2012.

Abbreviations: HAART, highly active antiretroviral therapy; TDF, tenofovir; FTC, emtricitabine; EFV, efavirenz; ATZ, atazanavir; RTV, ritonavir; LPV/r, ritonavir-boosted lopinavir; AZT, zidovudine; 3TC, lamivudine.

group comparisons, respectively. In order to include all significant variables affecting the costs of care in the univariate analysis, we applied a generalized linear model with a log link and a gamma distribution, as recommended for heavily skewed or tailed data. SAS for Windows software (v. 9.1; SAS Institute Inc, Cary, NC) was employed to perform all analyses.

Cost-effectiveness analysis

The ICER was utilized to assess cost-effectiveness. In the assessment of the value of a therapeutic option, the ICER provides the additional resources needed to achieve the additional benefit (QALYs). The ICER is the difference in cost (ΔC) divided by the difference in effect (ΔE) between two alternatives. This analysis compared the direct costs and effectiveness of each drug with the direct costs and effectiveness of the disease natural history (absence of treatment). The cost and QALYs of the disease natural history were taken from the model in Colombo et al¹⁴ based on literature and epidemiologic data.

Sensitivity analysis

The sensitivity analysis verified the impact of a series of variations of the base case having a large influence on the obtained results. Some parameters of the simulation model were subjected to a series of univariate analyses, taking into account²¹ Italian guidelines, the variation ($\pm 20\%$) of the HAART cost, the variation ($\pm 20\%$) of other costs associated

with the HIV patient and, lastly, the variation ($\pm 5\%$) of the utility parameter.

Results

Table 5 shows the average annual cost and the QALYs for a patient with HIV treated with each of the first-line antiretroviral regimens used in the First Infectious Diseases Department of "L. Sacco" Hospital, Milan. The simulation model shows that patients treated with a once-daily TDF+FTC+EFV treatment strategy (0.982 QALYs/year) have a better quality of life, with a higher number of QALYs than with other therapeutic regimens. Table 5 also shows the annual average cost of treatment (therapeutic regimens + other medical costs) for a patient with HIV. TDF+FTC+EFV has a lower mean treatment cost (€10,140). The comparison of the above-mentioned costs and outcomes in incremental terms (ICER) with the no-treatment strategy showed that the TDF+FTC+EFV once-daily treatment strategy is the most cost-effective therapeutic choice (€34,965); the ICER values for the remaining strategies range from €53,000 to about €62,000 per QALY.

The sensitivity analysis of the main variables does not highlight significant variations with respect to the analyzed base case (Figure 1).

Discussion

Since 1996, owing to the discovery of new classes of drugs and molecules capable of hindering viral replication on various fronts, and especially with the introduction of combined therapies, the life expectancy and quality of life of people with HIV have enormously improved. The addition of new antiretroviral regimens to conventional therapies can help clinicians in the choice of the best possible treatment for HIV patients.²² We therefore performed an incremental cost-effectiveness analysis for each treatment regimen for HIV patients, from the RHS standpoint. A recently published model was used for this analysis. The input data were the clinical evolution of consecutively enrolled patients at the

Table 5 Costs, QALYs, and incremental cost-effectiveness ratio of the base case scenario

Treatment	Mean cost per patient	Mean QALYs per patient	Mean cost per QALYs	Delta cost	Delta QALYs	ICER QALYs
Untreated	€3431	0.790				
TDF FTC EFV	€10,140	0.982	€10,327	€6709	0.192	€34,965
TDF FTC ATZ RTV	€12,101	0.930	€13,008	€8670	0.140	€61,812
TDF FTC LPV/r RTV	€12,026	0.932	€12,900	€8595	0.142	€60,423
AZT 3TC LPV/r RTV	€10,927	0.931	€11,731	€7496	0.141	€53,008

Abbreviations: QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; TDF, tenofovir; FTC, emtricitabine; EFV, efavirenz; ATZ, atazanavir; RTV, ritonavir; LPV/r, ritonavir-boosted lopinavir; AZT, zidovudine; 3TC, lamivudine.

Figure 1 Results of one-way sensitivity analyses: ICER per QALYs in different scenarios.

Abbreviations: QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; TDF, tenofovir; FTC, emtricitabine; EFV, efavirenz; ATZ, atazanavir; RTV, ritonavir; LPV/r, ritonavir-boosted lopinavir; AZT, zidovudine; 3TC, lamivudine.

First Infectious Diseases Department of “L. Sacco” Hospital, Milan, during 2008–2009, for whom the annual health care data were known. Thus it was possible to observe and simulate the cost per QALY of the different treatment regimens adopted in clinical practice within a 2-year time horizon, and to develop some considerations on the various treatments for the treated patients in terms of cost per QALY.

The TDF+FTC+EFV once-daily regimen, with a cost per QALY of €34,965, was shown to be the most cost-effective treatment strategy by the results of the model, based on the clinical practice of a hospital center of reference, in the comparison with the other therapeutic regimens. This regimen is the only one of the four analyzed therapeutic regimens having a lower cost per QALY than the threshold value of €50,000, commonly accepted at an international level.²³ This value expresses the willingness of the decision makers to spend in order to obtain additional health units, or to make new therapies available to citizens. Though no officially established threshold is available for Italy, it is worth noting that recent guidelines by the Italian Health Economics Association²¹ recommend the adoption of a threshold of €25,000–40,000. Other acceptable cost-effectiveness references for the Italian context are €36,500 and €60,000, as calculated by two different authors.^{24,25} The favorable result of the TDF+FTC+EFV once-daily treatment strategy is probably due to a better patients’ adherence (see Table 1), which determines an increase in the quality of life of patients with HIV.²⁶ However, low adherence to antiretroviral drugs is now recognized to be strictly linked with therapeutic regimen failure²⁷ and, consequently, with the indicators of the HIV-disease progression, such as virological failure,²⁸ insufficient immunologic reconstitution, the clinical progression of the disease and, lastly, death.^{29–31}

The sensitivity analysis of the main variables confirmed the validity of the base case. It is interesting to note the differences between this model, built on the base of real practice data, and the recently published model built on the base of literature data,³² also regarding Italy. The development methods and the QALYs are identical in both simulations, whereas there is a difference in the evolution data for patients in the various levels of CD4, in costs and in the used time horizon (2 years vs 10 years in the literature model used as benchmark). Table 5 indicates that, in our clinical practice simulation, the cost per QALY is 18% higher than the literature model on average although still with differences favorable to TDF+FTC+EFV. Such differences in literature data can be due to the presence of coinfections (which increases the total annual cost of treatment), and to the lower duration of the simulation interval (2 years of this analysis vs 10 years or lifetime). These differences also need to be integrated with some clinical considerations regarding the group of observed patients. First of all, our model only considers 9.8% of patients to be naïve in early 2008, in comparison to the hypothetical cohort of 100% of naïve patients included in the simulation based on literature data.³² Also, Atripla (STR) became available in the hospital in July 2008. So all patients taking TDF+FTC+EFV once a day until that moment used a fixed-dose combination of TDF+FTC and EFV, and then switched to STR. Moreover, the majority of groups followed in the clinical practice had a previous longer disease duration, which certainly had an impact on the result expressed in terms of costs saved per year of life. With the analysis of naïve patients only, under the same terms used in our analysis, and within a 10-year time horizon, the results of the two research studies would certainly converge.

There are a few limitations to the study, the most important of which concerns the quality of data entered into model: for example, parameters such as efficacy are based on data analysis in a limited time frame (2 years) and may therefore be inadequate for modeling the treatment of a chronic disease for a longer time. Another critical limitation concerns the utilities, which were derived from different literature sources and considered to be acceptable for an Italian population. Furthermore, as mentioned previously, the presence of a limited number of naive patients might have influenced the rate of response of patients to the treatments. In conclusion, it is worth observing that the developed model is a dynamic instrument that can be adapted to various health care settings (overall in chronic diseases such as HBV or HIV), since it can be run using different input data (ie, efficacy, costs, and epidemiological data).³² Mathematical models can assist policy makers in comparing the relative impact and cost-effectiveness of different regimes, generalizing the results of randomized controlled trials to the local setting, identifying threats to program success, identifying opportunities for maximizing intervention impact/efficiency, and evaluating the extent to which observed trends in HIV prevalence are attributable to HIV/AIDS program success.³³ Because it allows simulations of different scenarios, the model is an invaluable tool for policy makers and health care professionals to make short- and long-term cost projections and thus assess their impact on the available budgets.

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