REVIEW

Economic evaluation of initial antiretroviral therapy for HIV-infected patients: an update of Italian guidelines

Giorgio L Colombo[1,2]
Sergio Di Matteo[2]
Andrea Antinori[3]
Massimo Medaglia[4]
Silvia Murachelli[3]
Giuliano Rizzardini[5]

[1]Department of Drug Sciences, University of Pavia, Pavia, Italy; [2]SAVE – Studi Analisi Valutazioni Economiche, Milan, Italy; [3]National Institute for Infectious Diseases L Spallanzani, IRCCS, Rome, Italy; [4]Pharmaceutical Department, L. Sacco Hospital, Milan, Italy; [5]First Division of Infectious Disease, L. Sacco Hospital, Milan, Italy

Introduction: Highly active antiretroviral therapy (HAART) has allowed many HIV-infected patients to enjoy longer survival and a better quality of life. We performed an economic analysis to estimate the cost-effectiveness of HAART regimens in Italy for managing HIV-naïve infected patients with a viral load below 100,000 copies/mL.

Patients and methods: The population considered in the model consisted of adult subjects with an HIV viral load below 100,000 copies/mL who received antiretroviral HAART treatment for the first time, according to the Italian National Guidelines with recommendation grade A1. The incremental cost-effectiveness analysis of quality-adjusted life years (QALYs) was carried out by means of a Markov model. Both the outcomes (QALYs) and the costs were discounted by 3.5%. The time horizon adopted in the model was 10 years. The point of view of the analysis was that of the Italian national health service.

Results: The tenofovir (TDF)/emtricitabine (FTC)/rilpivirine (RPV) single-tablet regimen (STR) (€7,417.00) revealed the lowest mean treatment cost. TDF/FTC + raltegravir (RAL) showed a better quality of life (0.906 QALY/year), followed by TDF/FTC/RPV (STR; 0.900 QALY/year), TDF/FTC + RPV (multipill regimen) (0.889 QALY/year), and TDF/FTC + atazanavir (ATV/r) (0.886 QALY/year). TDF/FTC/RPV (STR) appeared to be the most cost-effective therapeutic choice (€13,655.00), followed by TDF/FTC + RPV (multipill regimen) (€15,803.00), and TDF/FTC + efavirenz (EFV) (€16,181.00). The sensitivity analysis on the main variables confirmed the validity of the base case scenario.

Conclusion: STR (TDF/FTC/RPV) is the most cost-effective treatment strategy compared with the other therapeutic regimens recommended by the Italian guidelines for the treatment of naïve patients with a viral load <100,000 copies/mL. The inclusion of adverse-event management of HIV-infected patients affects the cost-effectiveness ratio of all HAART regimens.

Keywords: HIV, HAART, single-tablet regimen (STR), Markov model, cost-effectiveness

Introduction

The predicted survival rate continues to grow for patients diagnosed with HIV infection.[1] Thanks to highly active antiretroviral therapy (HAART), many HIV-infected patients now enjoy longer survival and a better quality of life (QoL).[2,3] These changes show the positive effects of increasing efficacy and effectiveness, but they also raise the question of what happens to the consumption of resources. In fact, this success has changed HIV infection into a chronic disease. Establishing a strong adherence to HAART regimens therefore remains a challenge for most patients.[4,5] Current therapeutic options available include approved antiretroviral drugs, divided into five classes: nucleoside/nucleotide reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase

Correspondence: Giorgio L Colombo
SAVE – Studi Analisi Valutazioni Economiche, 74 Via Previati,
Milan 20149, Italy
Tel +39 02 4851 9230
Fax +39 02 7396 0369
Email giorgio.colombo@savestudi.it

inhibitors, protease inhibitors, fusion or entry inhibitors, and integrase inhibitors.

Considering the complexity of the disease, a recent update of Italian guidelines has been published recommending different treatments for the initial antiretroviral therapy (ART) for patients with a viral load below or above 100,000 copies/mL,[6] with either multipill regimens (MPRs) or single tablet regimens (STRs), which should be evaluated in terms of lifetime costs and cost-effectiveness, among other things. These recommendations and other publications also underline that STRs are more effective in the duration of viral suppression compared to more complex ones.[7–9] Moreover, rilpivirine (RPV), a new drug for HIV, (either as single agent or coformulated in STR), was licensed in Europe in 2011[10] and in Italy in early 2013,[11] and it is already included in the national guidelines.[6] How will these elements impact resource consumption in the HIV-infection care from the point of view of the Italian regional health care system? The present study, through an update of the Markov model already used in HIV settings,[12] aimed to answer this question, performing an economic analysis to assess the cost-effectiveness of initial HAART regimens in patients with a viral load <100,000.00 copies/mL.

Patients and methods

The aim of the study was to determine the incremental cost-effectiveness ratio (ICER) per quality-adjusted life years (QALYs) gained for HAART regimens, based on the 2012 Italian guidelines, for first-line treatment of HIV-infected patients.[6] The cost-effectiveness analysis was performed by applying a previously published Markov model,[12] which allowed us to carry out a comparison of studied ART regimens according to the previous 2010 Italian guidelines.[13] In this analysis, the direct costs and effectiveness (this time considering not just the efficacy in viral load reduction but also the occurrence of adverse events) of each drug were compared with the direct costs and effectiveness of the disease's natural history (absence of treatment). The seven ART regimens considered follow the latest Italian guidelines on HAART regimens in a viral load <100,000 copies/mL, which represents 68.6% of Italian HIV patients,[14] with recommendation grade A1 for initial treatment of HIV-infected patients.[6] The analysis was carried out from the point of view of the Italian national health service (Servizio Sanitario Nazionale [SSN]). The population considered in the analysis reflects patient characteristics according to one HIV/AIDS infection report of the regional surveillance systems currently operating in Italy (epidemic update as

of December 31, 2011). This population was stratified into the following health states: 25.94% of HIV-infected patients with CD4 $\geq$ 500 and viremia level (VL) $\geq$ 50; 25.94% of HIV-infected patients with 351< CD4 < 500 and VL $\geq$ 50; 33.00% of HIV-infected patients with 201< CD4 < 350 and VL $\geq$ 50; and 15.12% of HIV-infected patients with CD4 < 200 and VL $\geq$ 50.[15]

Structure of the model

The Markov model simulates the QoL and the costs for an HIV patient for 10 years, starting from the administration of the initial treatment through 1-year cycles based on the administered ART.[16] After entering the model and receiving one of the ART regimens, the patient can "move" through eight health states, defined by the CD4 cell count combined with the VLs, one AIDS state, and one death state (Figure 1).

The model assigned patients responding to the ART a VL lower than 50 copies, and allowed responders to move
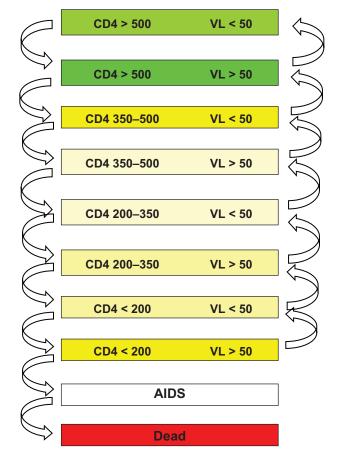

Figure 1 Structure of the Markov model.[12]
Note: Copyright © 2011, Dove Medical Press Ltd. Reproduced with permission from Colombo GL, Colangeli V, Di Biagio A, Di Matteo S, Viscoli C, Viale P. Cost-effectiveness analysis of initial HIV treatment under Italian guidelines. *Clinicoecon Outcomes Res.* 2011;3:197–205.[12]
Abbreviation: VL, viremia level; CD4, cell.

within the CD4 classification. In the case of failure of first-line treatment, the model presumed a VL > 50 copies for the patients and CD4 values following the trend of the untreated population.[17] Finally, the model was completed with appropriate occurrence values to define probabilistic knots, and with precise cost estimates, in order to finalize the comparison, as described below. The considered outcome measures were QALYs and direct health costs calculated for the year 2012. Both the outcomes (QALYs) and the costs were discounted by 3.5%.[18] The time horizon adopted in the model was 10 years. Modeling was undertaken using Excel 2010 (Microsoft, Redmond, WA, USA).

Immunologic response and quality-adjusted life years

Table 1 shows the immunologic responses for each of the therapeutic regimens studied, as indicated in the Italian guidelines, and reported in the references.[19–30] In cases of unavailable data, it was assumed that the response remained constant at the last observed value by applying the last-value-carried-forward technique.[12] The effectiveness indicators considered in this economic evaluation were QALYs. The utility values associated with the eight health states identified by CD4-cell count, published in a study by Simpson et al,[16] were calculated by means of the EuroQol five-dimension questionnaire (www.euroqol.org).

For CD4$^+$ values > 500 cells/µL, the utility score was 0.9460; for CD4$^+$ 351–500 cells/µL, the utility score was 0.9330; for CD4$^+$ 201–350 cells/µL, the utility score was 0.9310; for CD4$^+$ < 200 cells/µL, the utility score was 0.8300. Regarding the grade 3–4 adverse events considered[19–30] as a result of the specific regimen, the utility score for various states of health was reduced to −0.052.[16]

Resource consumption and cost analysis

Table 2 shows the average annual costs for each first-line regimen. The purchase costs of drugs were calculated based on the reimbursement price paid by the Italian SSN, which takes into account price updates effective from the beginning of 2013 (VAT excluded).[31] For every health state defined by the CD4 cell count, an additional health cost associated with patients was assumed, including a further consumption of health resources due to hospitalization, outpatient care, specialist examinations, laboratory tests, diagnostic procedures, and other drugs (Table 3). Costs were estimated based on the results of research by Rizzardini et al.[32] The cost of the AIDS health state was put at €10,224.63.[32] Table 1 shows the probability of adverse events for the different regimens; in addition to a utility-score decrease, we assumed a mean additional cost per year for adverse event of €2,430.12, only including hospitalization cost and other drugs.[32]

Table 1 Immunologic response and adverse events per different treatment regimen

	Year										Source
	1	2	3	4	5	6	7	8	9	10	
Response rate											
TDF/FTC + RPV (single-tablet regimen)	89.00%	89.00%	89.00%	89.00%	89.00%	89.00%	89.00%	89.00%	89.00%	89.00%	19
TDF/FTC + RPV	90.00%	84.00%	84.00%	84.00%	84.00%	84.00%	84.00%	84.00%	84.00%	84.00%	20
TDF/FTC + EFV	75.00%	90.00%	90.00%	90.00%	90.00%	90.00%	90.00%	90.00%	90.00%	90.00%	21
TDF/FTC + ATV/r	82.00%	89.00%	89.00%	89.00%	89.00%	89.00%	89.00%	89.00%	89.00%	89.00%	21
TDF/FTC + DRV/r	81.00%	81.00%	81.00%	67.50%	67.50%	67.50%	67.50%	67.50%	67.50%	67.50%	22,23
TDF/FTC + RAL	92.50%	92.50%	94.00%	93.00%	93.00%	93.00%	93.00%	93.00%	93.00%	93.00%	24–27
ABC/3TC + EFV	64.00%	85.00%	85.00%	85.00%	85.00%	85.00%	85.00%	85.00%	85.00%	85.00%	21
ABC/3TC + ATV/r	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	21
Adverse events											
TDF/FTC + RPV (single-tablet regimen)	7.00%	7.00%	7.00%	7.00%	7.00%	7.00%	7.00%	7.00%	7.00%	7.00%	19
TDF/FTC + RPV	16.00%	16.00%	16.00%	16.00%	16.00%	16.00%	16.00%	16.00%	16.00%	16.00%	20,28,29
TDF/FTC + EFV	19.65%	19.65%	19.65%	19.65%	19.65%	19.65%	19.65%	19.65%	19.65%	19.65%	21
TDF/FTC + ATV/r	19.65%	19.65%	19.65%	19.65%	19.65%	19.65%	19.65%	19.65%	19.65%	19.65%	21
TDF/FTC + DRV/r	23.00%	23.00%	23.00%	23.00%	23.00%	23.00%	23.00%	23.00%	23.00%	23.00%	22, 30
TDF/FTC + RAL	10.00%	10.00%	17.00%	17.80%	17.80%	17.80%	17.80%	17.80%	17.80%	17.80%	24–27
ABC/3TC + EFV	33.50%	33.50%	33.50%	33.50%	33.50%	33.50%	33.50%	33.50%	33.50%	33.50%	21
ABC/3TC + ATV/r	33.50%	33.50%	33.50%	33.50%	33.50%	33.50%	33.50%	33.50%	33.50%	33.50%	21

Abbreviations: TDF, tenofovir; FTC, emtricitabine; RPV, rilpivirine; EFV, efavirenz; ATV, atazanavir; DRV, darunavir; RAL, raltegravir; ABC, abacavir; 3TC, lamivudine; r, ritonavir.

Table 2 Average annual costs for each therapeutic regimen

Treatment	Annual cost of HAART regimen
TDF/FTC + RPV (single-tablet regimen)	€7,199
TDF/FTC + RPV	€7,406
TDF/FTC + EFV	€7,226
TDF/FTC + ATV/r	€8,813
TDF/FTC + DRV/r	€8,987
TDF/FTC + RAL	€10,620
ABC/3TC + EFV	€6,776
ABC/3TC + ATV/r	€8,363

Abbreviations: HAART, highly active antiretroviral therapy; TDF, tenofovir; FTC, emtricitabine; RPV, rilpivirine; EFV, efavirenz; ATV, atazanavir; DRV, darunavir; RAL, raltegravir; ABC, abacavir; 3TC, lamivudine; r, ritonavir.

Sensitivity analysis

The sensitivity analysis verified the impact of a series of variations of the base case with a large influence on the obtained results.[14] A series of univariate analyses were carried out on some parameters of the simulation model, such as virological response, HAART-cost regimen, and probability of adverse events. Each parameter was varied with ±10% with respect to the base-case scenario on the basis of Italian guidelines on economic evaluation.[18]

Results

Table 4 shows the average annual cost and the QALYs for HIV-infected patients with a viral load <100,000 copies/mL, treated with each of the first-line ART regimens in the Italian guidelines, with an A1 level of recommendation. Tenofovir (TDF)/emtricitabine (FTC)/RPV (STR, €7,417.00) shows the lowest mean treatment cost. The simulation model shows that patients treated with TDF/FTC + raltegravir have a better QoL (0.906 QALY/year), with a higher number of QALYs than with other therapeutic regimens; followed by TDF/FTC/RPV (STR, 0.900 QALY/year), TDF/FTC + RPV (MPR, 0.889 QALY/year), and TDF/FTC + atazanavir (0.886 QALY/year). Comparing the aforementioned costs and QALYs in incremental terms

(ICER) with the no-treatment strategy, the STR of TDF/FTC/RPV appears to be the most cost-effective therapeutic choice (€13,655.00), followed by TDF/FTC + RPV (MPR, €15,803.00) and TDF/FTC + efavirenz (EFV) (€16,181.00); the remaining strategies have an ICER value varying from €17,000.00 to €25,000.00 per QALY.

The sensitivity analysis carried out on the main variables does not highlight significant variations with respect to the base case (Table 5 and Figure 2). For instance, including an increase (10%) in cost for one adverse event, there is a reduction of the ICER for all therapeutic regimens. On the other hand, it is worth noting that the cost per QALY increases with the increase in HAART cost; +10% in the HAART cost means ICER increases of +15% and +20% for all different regimens (Table 5 and Figure 2).

Discussion

Since 1996, thanks to the discovery of new classes of drugs and molecules and especially with the introduction of combined therapies, the life expectancy and QoL of HIV patients have enormously improved. Considering the complexity of the disease, a recent update of Italian guidelines has been published recommending different treatments for initial ART for patients with viral load below or above 100,000 copies/mL[6] with either MPRs or STRs, which should be evaluated in terms of lifetime costs and cost-effectiveness, among other things. Adding new antiretroviral STRs to conventional therapies can help physicians in the choice of the best possible treatment to administer HIV patients with a viral load <100,000 copies/mL. Since STR is not the only available therapeutic option, it was deemed necessary to carry out a comparison with other ART regimens; the analysis therefore considered the regimens recommended, to a varying extent, by the Italian guidelines with an A1 recommendation level. The comparison was not limited to clinical efficacy, but it also evaluated adverse events and treatment costs. In particular, an incremental cost-effectiveness analysis was performed

Table 3 Average annual cost per patient and health state expressed in CD4 (excluding HAART cost)[7,32]

CD4	>500 cells/µL		351–500 cells/µL		201–350 cells/µL		<200 cells/µL	
Viremia	<50	≥50	<50	≥50	<50	≥50	<50	≥50
Other costs								
Healthcare services	€1,349	€1,490	€1,459	€1,619	€1,610	€1,794	€1,700	€1,675
Other drugs	€325	€254	€366	€377	€510	€266	€840	€648
Hospitalizations	€610	€975	€1,509	€1,488	€719	€2,733	€2,798	€5,025
Total	€2,284	€2,719	€3,333	€3,484	€2,839	€4,793	€5,337	€7,348

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Abbreviation: HAART, highly active antiretroviral therapy.

Table 4 Costs, QALYs, and incremental cost-effectiveness ratio (ICER) of the base-case scenario (10-year horizon)

Treatment	C	E	C/E	ΔC	ΔE	ΔC/ΔE
	Mean cost per patient	Mean QALYs per patient	Mean cost per QALY	Delta cost	Delta QALYs	ICER QALYs
Untreated	€3,461	0.611	€5,667			
TDF/FTC + RPV (single-tablet regimen)	€7,417	0.900	€8,238	€3,957	0.290	€13,655
TDF/FTC + RPV	€7,861	0.889	€8,842	€4,401	0.278	€15,803
TDF/FTC + EFV	€7,803	0.879	€8,877	€4,343	0.268	€16,181
ABC/3TC + EFV	€7,777	0.865	€8,987	€4,317	0.255	€16,945
TDF/FTC + ATV/r	€9,536	0.886	€10,760	€6,076	0.276	€22,045
ABC/3TC + ATV/r	€9,460	0.876	€10,802	€6,000	0.265	€22,631
TDF/FTC + DRV/r	€9,462	0.871	€10,866	€6,001	0.260	€23,069
TDF/FTC + RAL	€11,028	0.906	€12,175	€7,568	0.295	€25,637

Abbreviations: QALYs, quality-adjusted life years; TDF, tenofovir; FTC, emtricitabine; RPV, rilpivirine; EFV, efavirenz; ATV, atazanavir; DRV, darunavir; RAL, raltegravir; ABC, abacavir; 3TC, lamivudine; r, ritonavir.

for each regimen, in comparison to the no-treatment option, from the point of view of the Italian SSN. Such comparisons were carried out with the help of a Markov decision model over a 10-year time horizon. The model estimated QALYs as outcomes and direct health costs (drugs, medical examinations, hospitalizations, tests, and so on) as costs; these costs were attributed a value based on prices and rates as of 2012.

The simulation-model results show that in terms of cost per gained QALY, the STR of TDF/FTC/RPV appears to the most cost-effective therapeutic choice with an ICER of €13,655.00, compared with the other therapeutic regimens recommended by the guidelines. All the ICER values of the various regimens considered by the Italian guidelines were lower than the threshold value of €50,000.00 commonly accepted at the international level.[33] Though no officially established threshold is available for Italy, it is worth noting that recent guidelines by the Italian Health

Economics Association[18] recommend that a threshold of €25,000.00–€40,000.00 be adopted. Other acceptable references of cost-effectiveness for the Italian context are €36,500.00 and €60,000.00, and have been calculated by two different authors.[34,35] The sensitivity analysis on the main variables confirmed the validity of the base case. Furthermore, our results are in line with other recent pharmacoeconomic analyses, in particular the studies by Colombo et al[12] and Rizzardini et al,[7] and with the more recent cost-utility analyses by Moeremans et al,[36] Castagna et al,[8] and Maggiolo et al.[9,37]

We can note also that the inclusion of adverse events in the model, compared to a previously published paper in 2011,[12] greatly affected the cost-effectiveness ratio of all treatment regimens, highlighting a greater importance of evaluating these aspects during pharmacoeconomic analysis for all regimens for HIV patients. The same utility score used for other therapeutic regimens was applied to the STR of TDF/

Table 5 Results of one-way sensitivity analyses

Treatment	Incremental cost-effectiveness ratio								
	Base case	HAART cost −10%	HAART cost +10%	Other costs −10%	Other costs +10%	Response rate −10%	Response rate +10%	Adverse events −10%	Adverse events +10%
TDF/FTC + RPV (single-tablet regimen)	€13,655	€11,202	€16,107	€13,675	€13,635	€14,713	€12,821	€13,720	€13,590
TDF/FTC + RPV	€15,803	€13,185	€18,421	€15,741	€15,865	€17,070	€14,802	€15,746	€15,859
TDF/FTC + EFV	€16,181	€13,548	€18,814	€16,079	€16,283	€17,407	€15,219	€16,100	€16,262
ABC/3TC + EFV	€16,945	€14,375	€19,516	€16,691	€17,200	€18,305	€15,878	€16,736	€17,154
TDF/FTC + ATV/r	€22,045	€18,835	€25,255	€21,947	€22,143	€23,595	€20,817	€21,973	€22,116
ABC/3TC + ATV/r	€22,631	€19,472	€25,790	€22,393	€22,869	€24,388	€21,239	€22,366	€22,897
TDF/FTC + DRV/r	€23,069	€19,787	€26,352	€22,930	€23,209	€24,947	€21,574	€22,947	€23,191
TDF/FTC + RAL	€25,637	€22,069	€29,205	€25,578	€25,696	€27,289	€24,569	€25,647	€25,627

Abbreviations: HAART, highly active antiretroviral therapy; TDF, tenofovir; FTC, emtricitabine; RPV, rilpivirine; EFV, efavirenz; ATV, atazanavir; DRV, darunavir; RAL, raltegravir; ABC, abacavir; 3TC, lamivudine; r, ritonavir.
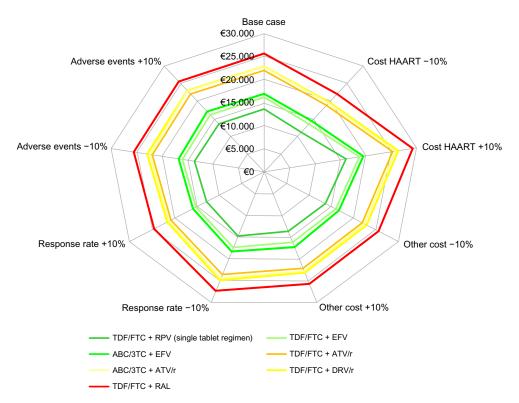
Figure 2 Results of one-way sensitivity analyses.
Abbreviations: HAART, highly active antiretroviral therapy; TDF, tenofovir; FTC, emtricitabine; RPV, rilpivirine; EFV, efavirenz; ATV, atazanavir; DRV, darunavir; RAL, raltegravir; ABC, abacavir; 3TC, lamivudine; r, ritonavir.

FTC/RPV. In the literature, however, we find a greater patient preference for STRs vs MPRs, with a better adherence of patients to treatment.[4,37–44] Based on a study by Airoldi et al,[45] it was therefore possible to identify the utility-score increment in patients switching from a TDF/FTC + EFV MPR to a TDF/FTC/EFV STR; in the reduction of the number of daily pills from two to one, the ADONE (Adherence to One Pill Once a Day) study measured a 3.9% increase in QoL, from 68.8% (95% confidence interval [CI] 67.7–70.0) to 72.7% (95% CI 71.5–73.8) ($P = 0.042$) in health perceived by patients after 6 months, for patients who switched from an MTR to an STR. In this simplification study, patients treated with the single components of the STR switched to taking STR, thus changing only the number of pills but without modifying the pharmacological content of the therapeutic regimen. When patients took the single components, adherence (as the percentage of taken doses) was 96.1% (95% CI 90.4–95.4), and reached 97.1% (95% CI 97.0–98.4) ($P = 0.014$) after patients switched to the STR. In our analysis, we confirmed the previous study results, showing an advantage in terms of QALYs gained from STRs versus MPRs, and consequently a better ICER versus the separated components, but without any adjustment in the utility score. Adding new antiretroviral STRs to conventional

therapies can help physicians in the choice of the best possible treatment to administer HIV patients. However, it is now recognized that low adherence to antiretroviral drugs is strictly linked to the failure of the therapeutic regimen,[46] and consequently to HIV disease-progression indicators, such as virological failure,[47] insufficient immunologic reconstitution, the clinical progression of the disease, and death.[4,41] Adherence to therapy is not only necessary to obtain a therapeutic result in patients starting a treatment but also to maintain effective viral suppression over the course of time.[48]

This study has a few limitations, the most important of which concerns the quality of data entered into the model: parameters such as efficacy, for example, are based on studies with a limited time frame, and hence may be inadequate for modeling the treatment of a chronic disease for a longer time.[49] We considered also 1-year Markov cycles, in order to include cost data that were evaluated for a 1-year time period.[12] Another important limitation relates to the assumptions on which the analysis is based, which may be necessary to simplify the model or in the case of incomplete data. Specifically, this regarded transition probabilities, which were lacking in some cases and thus assumed to remain constant over time, and utilities, which were derived from different literature sources and considered to be acceptable for an Ital-

ian population. A further limitation could be the adoption of a long-term simulation model (10 years) to compare the three alternative regimens, which was built on the basis of clinical information (now available in the literature) referring to a short–medium period. This is justified by the fact that the evaluation of the benefits and costs of a health program needs synthesis tools for representing a reality to study that are as faithful as possible, especially when the effects of the program have a time horizon with a long-term impact, or when the data sources are not homogeneous (ie, they derive from administrative records, clinical studies, and meta-analyses).[12,49]

Apart from the aforementioned limitations, however, the proposed results allow us to propose a pharmacoeconomic pathway to try and give a value to HIV combination therapies aimed at simplifying the daily treatment regimen in STR. The information contained in this kind of study should be supplied as a constant support to policy-makers to better allocate resources. In conclusion, it is worth observing that simulation models can assist policy-makers in comparing the relative impact and cost-effectiveness of different regimens,[50] 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.

Disclosure

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