

Antiretroviral therapy in HIV-infected patients: a proposal to assess the economic value of the single-tablet regimen

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Background: The aim of this study was to assess the economic value of a reduced number of pills in patients infected with the immunodeficiency virus (HIV) and on highly active antiretroviral therapy by a cost-effectiveness model.

Methods: An incremental cost-effectiveness analysis of efavirenz, tenofovir, and emtricitabine (TDF-FTC-EFV) as a single-tablet regimen versus a multipill regimen, with reference to untreated HIV-infected patients, was carried out from the perspective of the Italian National Health Service. The comparisons were performed with the help of a Markov decision model over a 10-year time horizon. Based on the ADONE (ADherence to ONE pill) study, it was then possible to identify the utility score increment in patients switching from a multipill regimen of TDF-FTC + EFV therapy to a single-tablet regimen.

Results: The single-tablet regimen (0.755 quality-adjusted life-years [QALYs]/year) resulted in better patient quality of life, with a higher number of QALYs than for the TDF-FTC + EFV multipill regimen (0.716 QALYs/year). The single-tablet regimen was the most cost-effective treatment strategy, with an incremental cost-effectiveness ratio of €22,017.00 versus €26,558.00 for the multipill regimen. A 24% decrease in cost of the multipill regimen determined equivalence with the single-tablet regimen in terms of the incremental cost-effectiveness ratio. Univariate sensitivity and probabilistic analysis carried out on the main variables did not highlight significant variations with respect to the base case scenario.

Conclusion: The single-tablet regimen resulted in better adherence, and therefore better quality of life as perceived by patients, corresponding to a €4541.00 lower cost-effectiveness ratio per QALY versus the multipill regimen, with a 17% lower cost in favor of the single-tablet regimen. The value determined could be used to identify a maximum potential “premium price” of 29% to be assigned to therapeutic regimens proposing a single-tablet regimen for HIV-infected patients.

Keywords: tenofovir, emtricitabine, efavirenz, single-tablet regimen, highly active antiretroviral therapy, quality of life, pharmacoconomics, adherence

Introduction

Highly active antiretroviral therapy (HAART) has changed the clinical course of immunodeficiency virus (HIV) infection, decreasing the rate of disease progression, the incidence of opportunistic infections, and mortality.¹ Owing to this prolonged survival, HIV infection can now be considered a chronic disease,² with combination antiretroviral therapy resulting in longer survival and better quality of life for many HIV-infected patients.³ The therapeutic options currently available in Italy and Europe include over 20 approved antiretroviral drugs which are divided into five classes, ie, nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse

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transcriptase inhibitors, protease inhibitors, fusion or entry inhibitors, and integrase inhibitors. Each of these groups attacks HIV via a different pathway. The most common HAART regimen administered to patients entering treatment consists of two nucleoside/nucleotide reverse transcriptase inhibitors combined with either a non-nucleoside reverse transcriptase inhibitor or a “boosted” protease inhibitor.⁴ Each drug varies greatly in terms of efficacy, resistance, pill burden, safety, adherence, and price. Researchers have recently contemplated the possibility of considering not only the simple prolongation of life expectancy, but also the quality of residual life for patients, with clear implications for clinical practice. In other words, they are wondering if it could be possible to increase survival without altering, or possibly further increasing, the quality of life.^{5,6}

The recent development of the once-daily single-tablet regimen has been an important development in the optimization of antiretroviral regimens.⁴ Such optimization has the potential to improve long-term adherence, virologic efficacy, clinical outcomes, and quality of life.⁷ Optimization strategies using antiretroviral agents that are currently approved or under study include once-daily dosing regimens. Multiple studies have shown that adherence to antiretroviral therapeutic regimens is among the most powerful predictors of sustained virologic suppression, reduces the risk of developing drug resistance, limits disease progression, and improves patient survival.^{8,9} In the past, several studies showed how treatment simplification strategies could enhance patient adherence with HAART.^{10–12} Although it has been postulated that this type of intervention works by improving patient quality of life, some studies have specifically addressed the relationship between quality of life and adherence.¹³ ADONE (ADherence to ONE pill) was a multicenter, open-label, comparative, prospective study with the objective of verifying if simplification of the antiretroviral regimen, measured as reduction in pill burden, might affect the patient adherence rate and quality of life.¹³ An important feature of this study is that the variables were evaluated without varying the drug components in the HAART regimens. All patients were on treatment with efavirenz in combination with tenofovir-emtricitabine or lamivudine-tenofovir which was simplified into a single-tablet regimen containing efavirenz, tenofovir, and emtricitabine (EFV-TDF-FTC), with the only modification being the number of pills needing to be taken daily. In this trial, the investigators evaluated how simplification of therapy could affect adherence, quality of life, and subjective perception of health status, and how these variables influenced one another. The patients did not

change their therapy in terms of active ingredients or doses of the same molecules, but simply reduced the number of pills in their daily regimen from three or two to one. This simple change had a significant impact on quality of life and the patients’ perception of their health in the subsequent 6 months. Therefore, the current objective of HAART is to prolong survival while guaranteeing and preserving quality of life, but there is a possible further development of its objectives in the future, based on the significant effectiveness of the HAART regimens and their tolerability, increased economic convenience, and consequent prolonged durability. For this reason, it seems important to verify how switching to a single-tablet regimen, which determines a simultaneous improvement in patient adherence and quality of life, may translate into a potential economic value as a result of the reduced number of pills needed in HIV-infected patients on HAART using a model of cost-effectiveness.

Materials and methods

We considered an economic analysis that estimates the cost-effectiveness of HAART regimens for managing HIV-infected patients versus untreated HIV-infected patients in Italy, based on Markov model simulation.¹⁴ The objective of the current study was to attribute a value to the difference in cost-effectiveness of a once-daily single-tablet regimen versus a multipill regimen, based on data on adherence and quality of life from the ADONE study.¹³

An incremental cost-effectiveness ratio (ICER) analysis was performed by applying a previously published Markov model¹⁴ enabling comparison of outcomes in HIV-infected patients treated with the study antiretroviral regimens versus untreated HIV-infected patients according to the Italian guidelines.⁴ In this analysis, the direct costs and effectiveness of each drug were compared with the direct costs and effectiveness of the natural history of the disease in the absence of treatment.¹⁵ The Markov model simulates quality of life and the cost of treating an HIV patient for ten years, starting from administration of the first dose, through one-year cycles, based on the antiretroviral therapy administered.¹⁶ After entering the model and receiving one of the antiretroviral regimens, the patient can “move” through eight health states, defined by CD4 cell count and viremia levels, one acquired autoimmune deficiency syndrome (AIDS) state, and one death state (Figure 1). Modeling was undertaken using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

The analysis was carried out from the point of view of the National Healthcare Service in Italy. The

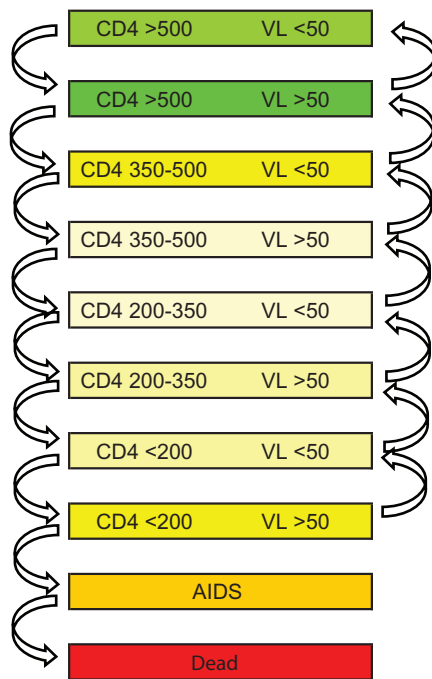


Figure 1 Structure of the Markov model.
Abbreviations: AIDS, acquired immunodeficiency syndrome; VL, viral load.

outcome measures considered were quality-adjusted life-years (QALYs), and the direct costs were updated for the year 2011.¹⁷ Both outcomes (QALYs) and costs were discounted by 3.5%.¹⁸ The time horizon adopted in the model was ten years. The population considered in the analysis reflects typical patient characteristics, according to reports by one of the regional surveillance systems for HIV/AIDS infection currently operating in Italy.¹⁹

Transition probabilities and quality of life

The percentage distribution of patients considered in the model with respect to the proposed CD4 cell count takes into account observations on HIV infection/AIDS in Emilia Romagna (epidemics update as of December 31, 2009). The immunologic response to each of the two therapeutic study regimens, ie, TDF-FTC + EFV (multipill regimen) and the single-tablet regimen, was considered comparable, with 80% response rates in the first year, 67% in the second year, 64% in the third year, and 64% in the following years throughout ten observation years.^{20–22} When data were not available, it was assumed that the response remained constant at the last observed value by applying the last value carried forward technique.

QALYs were used as effectiveness indicators in this economic evaluation. The utility values associated with

the eight health states identified by the CD4 cell count, as published in the report by Simpson et al,²³ were calculated using the EQ-5D® questionnaire.²⁴ The utility score was 0.9460 for CD4+ values > 500 cells/ μ L; 0.9330 for CD4+ 351–500 cells/ μ L; 0.9310 for CD4+ 201–350 cells/ μ L; and 0.8300 for CD4+ < 200 cells/ μ L.

Based on the study by Airoldi et al,¹³ it was possible to identify the utility score increment in patients switching from a twice-daily TDF-FTC + EFV multipill regimen to a once-daily single-tablet TDF-FTC-EFV regimen. With regard to the reduction in number of pills needing to be taken daily from two to one, the ADONE study measured a 3.9% increase in quality of life, 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 after 6 months by patients who switched from a multipill regimen to a single-tablet regimen (Figure 2). The different utility values thus obtained for the response to the two therapeutic regimens were used to compare the costs of the two treatments versus those in untreated HIV-infected patients.

Resource consumption and costs

Resource consumption in the model was linked with administration of antiretroviral regimens (annual costs of €7226.00) and other direct health care costs, including for hospitalizations, visits, and laboratory tests. The average annual costs for each first-line regimen and the purchase cost of the drugs were calculated based on the reimbursement price paid by the National Health Service, which takes into account price updates valid from January 1, 2011.²⁵ For every health state defined by the CD4 cell count, additional patient health care costs associated was assumed, including further consumption of health resources due to hospitalization, outpatient care, examinations by general practitioners and specialists, laboratory tests, and diagnostic procedures. These costs were estimated based on indications from studies published by Colombo et al¹⁴ and Garattini et al.¹⁷ The cost data stratified by CD4 count were then discounted to 2011.²⁶

Sensitivity analysis

The sensitivity analysis modified some of the initial assumptions, namely the most uncertain or relevant ones, with the aim of verifying if the results obtained in the base case could be considered reliable enough to support rational decisions about resource allocation.²⁷ Univariate, threshold value, and probabilistic sensitivity analyses were carried out.^{27,28}

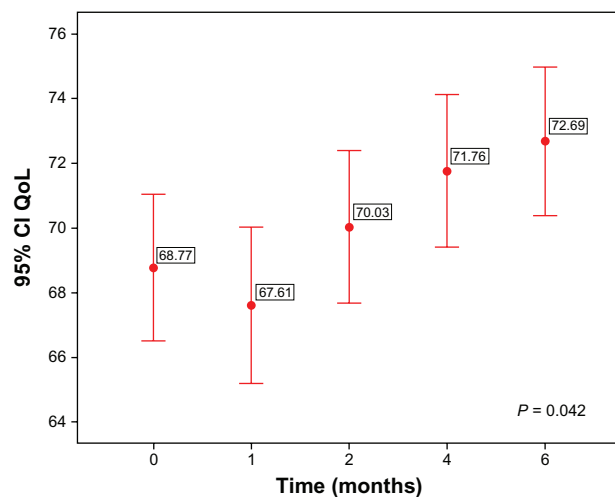


Figure 2 ADONE study.¹³

Note: Variation in quality of life self-reported by patients after switching from the TDF-FTC + EFV multipill regimen to the single-tablet regimen containing the same active ingredients.

Abbreviations: ADONE, ADherence to ONE pill study; CI, confidence interval; EFV, efavirenz; FTC, emtricitabine; QoL, quality of life; TDF, tenofovir.

The sensitivity analysis verified the impact of a series of variations in the base case scenario which had a considerable impact on the results obtained.¹⁵ A series of univariate analyses were carried out on some parameters of the simulation model, including variation in quality of life (utilities) and the cost of the single-tablet regimen, and identifying the threshold value for these parameters. In order to test the improvement in health state perceived by the patient from 68.8% to 72.7% (IC 95%, $P = 0.042$), a probabilistic sensitivity analysis was performed, using a normal distribution to evaluate the improvement in the patient's perceived health state.²⁹ In order to obtain a variability measure of the study parameter, we obtained a bootstrap CI (percentile, bilateral, symmetrical) using the Monte Carlo method. One thousand casual values were extracted from the normal distribution. After determining the 1000 casual values of perceived health state, 1000 de novo utility values were calculated, and from these, the 1000 ICER was generated for the single-tablet regimen. Probabilistic sensitivity analysis was performed using TreeAge version 4.0 software (TreeAge Software Inc, Williamstown, MA).

Results

Table 1 shows the average annual cost and QALYs for a patient with HIV treated with each of the antiretroviral regimens, ie, the TDF-FTC + EFV multipill regimen versus the TDF-FTC-EFV single-tablet regimen. The simulation model shows that the single-tablet regimen (0.755 QALYs/year) resulted in better patient adherence and quality of life, with a higher

number of QALYs than with the daily TDF-FTC + EFV multipill regimen (0.716 QALYs/year). Table 1 shows that the average annual cost of the two treatments is equivalent (€8551.00) and includes the therapeutic regimen cost (the purchase cost for the National Health Service is identical for the two regimens, ie, €7226.00) and other health care costs (hospitalizations, examinations, diagnostic tests). Based on the previously published model,¹⁴ it was finally possible to compare these two strategies with a no-treatment strategy in order to evaluate the contribution of the two therapeutic regimens in terms of ICER, ie, gained year of life weighted for quality (QALYs). After comparing the abovementioned costs and outcomes with the no-treatment strategy in incremental terms (ICER), the single-tablet regimen was shown to be the most cost-effective therapeutic choice, with an ICER of €22,017.00 versus €26,558.00, which is well below the threshold values considered to be acceptable.¹⁸

Therefore, this increment of about 0.039 points in QALY determines a €4541.00 (–17%) improvement in the cost per QALY in favor of the single-tablet regimen. This amount corresponds to the potential economic value of a fixed combination, in terms of patient-reported improvement in quality of life versus the corresponding nonfixed combination regimen.

The sensitivity analysis carried out on the main variables does not highlight significant variations with respect to the base case scenario, as previously reported.¹⁴ However, it is interesting to note the threshold point analysis for the cost of the single-tablet regimen and changes in quality of life parameters. The threshold point analysis allows determination of the maximum values that invert the results for our base case. In Table 2, it is interesting to note that with a 1% increase in the single-tablet regimen cost from the current value, the two strategies are leveled at a single-tablet regimen price of €9317.50, corresponding to a 29% increase in the current market price. In other words, a 10% potential increase in the single-tablet regimen cost corresponds to a 7% increment in cost per QALY. Using a procedure similar to that used for the single-tablet regimen, it is possible to simulate a reduction in cost of the TDF-FTC + EFV multipill regimen to estimate the breakeven point in comparison with the single-tablet regimen. When the daily price of the multipill regimen is decreased by 24%, the two formulations have the same ICER.

Table 3 shows an analysis of the threshold value for the potential increment of utilities (QALYs). For every 1% increase in utility value for the single-tablet regimen, there is a more than proportional increase in the ICER (3.51%).

Table 1 Costs, quality-adjusted life-years, and incremental cost-effectiveness ratio of the base case scenario (10-year horizon)

Treatment	Patient HAART cost per year	Total patient cost per year (HAART + other health cost)	Mean patient QALYs per year	Delta cost	Delta QALYs vs untreated	Diff	ICER QALYs vs untreated	Diff vs STR
Untreated	–	€3,492	0.525					
TDF-FTC – EFV (STR – single-tablet regimen)	€7,226	€8,551	0.755	€5,059	0.230		€22,017	
TDF-FTC + EFV (MPR – multipill regimen)	€7,226	€8,551	0.716	€5,059	0.190	–0.039	€26,558	€4,541

Abbreviations: EFV, efavirenz; HAART, highly active antiretroviral therapy; ICER, incremental cost-effectiveness ratio; MPR, multipill regimen; QALYs, quality-adjusted life-years; STR, single-tablet regimen; TDF, tenofovir, FTC, emtricitabine.

The results of the probabilistic sensitivity analysis were used to determine the cost function per QALY (ICER) by calculating the percentage of the 1000 iterations with the Monte Carlo simulation (shown on the x axis, or abscissa) which are lower than a certain cost per QALY (shown on the y axis, or ordinate). Such a percentage corresponds to the estimated probability that the cost per QALY for the single-tablet regimen is lower than the per QALY cost for the multipill regimen (Figure 2). Figure 3 shows that, for all 1000 simulation values, the ICER generated by the single-tablet regimen is consistently lower in probabilistic terms than the one generated by the daily multipill regimen.

Discussion

Adherence to chronic therapies is a widespread problem in all medical disciplines. In 2003, the World Health Organization reported that 30%–50% of medications prescribed for chronic diseases are not taken according to the instructions given to patients.³⁰ Multiple studies have demonstrated that adherence with antiretroviral therapeutic regimens is one of the most powerful predictors of sustained virologic suppression, reduces the risk of drug resistance, limits disease progression, and improves patient survival and quality of life.^{13,31–33} Analysis of a Swiss cohort³⁴ highlighted that 30% of patients reported omitting one or more drug doses in the preceding weeks and that 7.1% of the same patients reported less than 95% adherence. Among the factors that negatively influenced the levels of adherence, use of a protease inhibitor with a booster was statistically significant. Another study³⁵ found higher adherence in patients treated with non-nucleoside reverse transcriptase inhibitors (93.6%) compared with those who received a regimen based on three nucleoside reverse transcriptase inhibitors (91.7%) or protease inhibitors (89.9%) with or without booster. Finally, in a study using a microelectromechanical monitoring system,³⁶ the investigators observed an adherence rate of 91.5% and 86% in respect of administration timetables for protease inhibitors only. Substantial literature is available in which various authors have analyzed the relationship between adherence and number of pills needing to be taken.^{10,35–39} An evaluation of the impact of this variable on adherence was reported by Maggiolo et al,⁴⁰ showing that “too many pills” was reported by 20% of patients to justify their reduced adherence and how the daily number of pills needed correlated significantly ($P = 0.021$) with adherence. In particular, the simplest therapies, ie, those

Table 2 Results of one-way sensitivity analyses: variation in annual cost of single-tablet regimen and incremental cost-effectiveness ratio (ICER)

STR cost per year	% increase	ICER	% increase	TDF-FTC + EFV (MPR) cost per year	% decrease	ICER	% decrease
€7,226	0%	22,017	0%	7,226	0%	26,558	0%
€7,298	1%	22,173	1%	7,154	-1%	26,366	-1%
€7,371	2%	22,330	1%	7,081	-2%	26,178	-1%
€7,443	3%	22,486	2%	7,009	-3%	25,990	-2%
€7,515	4%	22,642	3%	6,937	-4%	25,801	-3%
€7,587	5%	22,799	4%	6,865	-5%	25,612	-4%
€7,660	6%	22,955	4%	6,792	-6%	25,423	-4%
€7,732	7%	23,111	5%	6,720	-7%	25,234	-5%
€7,804	8%	23,267	6%	6,648	-8%	25,045	-6%
€7,876	9%	23,424	6%	6,576	-9%	24,856	-6%
€7,949	10%	23,580	7%	6,503	-10%	24,667	-7%
€8,021	11%	23,736	8%	6,431	-11%	24,478	-8%
€8,093	12%	23,893	9%	6,359	-12%	24,289	-9%
€8,165	13%	24,049	9%	6,287	-13%	24,100	-9%
€8,238	14%	24,205	10%	6,214	-14%	23,912	-10%
€8,310	15%	24,362	11%	6,142	-15%	23,723	-11%
€8,382	16%	24,518	11%	6,070	-16%	23,534	-11%
€8,454	17%	24,674	12%	5,998	-17%	23,345	-12%
€8,527	18%	24,830	13%	5,925	-18%	23,156	-13%
€8,599	19%	24,987	13%	5,853	-19%	22,967	-14%
€8,671	20%	25,143	14%	5,781	-20%	22,778	-14%
€8,743	21%	25,299	15%	5,709	-21%	22,589	-15%
€8,816	22%	25,456	16%	5,636	-22%	22,400	-16%
€8,888	23%	25,612	16%	5,564	-23%	22,211	-16%
€8,960	24%	25,768	17%	5,492	-24%	22,017	-17%
€9,033	25%	25,925	18%	5,420	-25%	21,834	-18%
€9,105	26%	26,081	18%	5,347	-26%	21,645	-19%
€9,177	27%	26,237	19%	5,275	-27%	21,456	-19%
€9,249	28%	26,393	20%	5,203	-28%	21,267	-20%
€9,322	29%	26,550	21%	5,130	-29%	21,078	-21%
€9,318	29%	26,558	21%	5,058	-30%	20,889	-21%
€9,394	30%	26,706	21%	4,986	-31%	20,700	-22%

Abbreviations: EFV, efavirenz; ICER, incremental cost-effectiveness ratio; MPR, multipill regimen; STR, single-tablet regimen; TDF, tenofovir; FTC, emtricitabine.

that need to be administered only once a day, invariably correlated with significantly ($P = 0.009$) higher adherence levels.³⁵ Finally, several authors have reported a close link between adherence rate and risk of virologic failure.^{41–44} Recent studies have shown that HAART regimens based on only one tablet a day (ie, a single-tablet regimen) are associated with significantly better adherence and a lower hospitalization risk in HIV patients in comparison with patients treated with more complicated regimens involving three or more tablets a day.⁴⁵ In this context, the once-daily TDF-FTC-EFV single-tablet regimen appears to be a reasonable option for individuals with multiple barriers to adherence⁴⁶ and, although new antiretroviral drugs and classes have become available in recent years, the single-tablet regimen continues to show an advantage in

improving adherence in comparison with other combination antiretroviral therapies.⁴⁷

Given that simpler antiretroviral regimens are considered easier to follow and result in improved patient adherence, the trend over the last decade has been to simplify treatment regimens as far as possible.⁴ From this point of view, a multicenter study was carried out in Italy¹³ exploiting the availability of a fixed-dose single-tablet regimen. In this simplification study, patients treated with the individual components of the single-tablet regimen switched to taking the single-tablet regimen itself, thus changing only the number of pills but without modifying the pharmacologic content of the therapeutic regimen. While the patients took the single components, adherence (as a percentage of doses taken) was 96.1% (95% CI 90.4–95.4) but increased to 97.1% (CI 97.0–

Table 3 Results of one-way sensitivity analyses: variation in annual utilities and incremental cost-effectiveness ratio (ICER)

TDF-FTC – EFV	Incremental difference in utilities STR vs MPR	
	No difference in utilities	Incremental difference in utilities STR vs MPR
TDF-FTC – EFV (STR – single-tablet regimen)	€26,558	+0.01 €25,626
TDF-FTC + EFV (MPR – multipill regimen)	–	+0.02 €24,756
Difference	–	+0.03 €23,944
Difference in %	0.00%	+0.04 €23,184
		+0.05 €22,470
		+0.06 €21,931
		+0.07 €21,391
		+0.08 €20,851
		+0.09 €20,311
		+0.10 €19,771
		+0.11 €19,231
		+0.12 €18,691
		+0.13 €18,151
		+0.14 €17,611
		+0.15 €17,071
		+0.16 €16,531
		+0.17 €15,991
		+0.18 €15,451
		+0.19 €14,911
		+0.20 €14,371
		+0.21 €13,831
		+0.22 €13,291
		+0.23 €12,751
		+0.24 €12,211
		+0.25 €11,671
		+0.26 €11,131
		+0.27 €10,591
		+0.28 €10,051
		+0.29 €9,511
		+0.30 €8,971
		+0.31 €8,431
		+0.32 €7,891
		+0.33 €7,351
		+0.34 €6,811
		+0.35 €6,271
		+0.36 €5,731
		+0.37 €5,191
		+0.38 €4,651
		+0.39 €4,111
		+0.40 €3,571
		+0.41 €3,031
		+0.42 €2,491
		+0.43 €1,951
		+0.44 €1,411
		+0.45 €867
		+0.46 €327
		+0.47 €-113
		+0.48 €-573
		+0.49 €-1,013
		+0.50 €-1,453
		+0.51 €-1,893
		+0.52 €-2,333
		+0.53 €-2,773
		+0.54 €-3,213
		+0.55 €-3,653
		+0.56 €-4,093
		+0.57 €-4,533
		+0.58 €-4,973
		+0.59 €-5,413
		+0.60 €-5,853
		+0.61 €-6,293
		+0.62 €-6,733
		+0.63 €-7,173
		+0.64 €-7,613
		+0.65 €-8,053
		+0.66 €-8,493
		+0.67 €-8,933
		+0.68 €-9,373
		+0.69 €-9,813
		+0.70 €-10,253
		+0.71 €-10,693
		+0.72 €-11,133
		+0.73 €-11,573
		+0.74 €-12,013
		+0.75 €-12,453
		+0.76 €-12,893
		+0.77 €-13,333
		+0.78 €-13,773
		+0.79 €-14,213
		+0.80 €-14,653
		+0.81 €-15,093
		+0.82 €-15,533
		+0.83 €-15,973
		+0.84 €-16,413
		+0.85 €-16,853
		+0.86 €-17,293
		+0.87 €-17,733
		+0.88 €-18,173
		+0.89 €-18,613
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		+0.95 €-21,253
		+0.96 €-21,693
		+0.97 €-22,133
		+0.98 €-22,573
		+0.99 €-23,013
		+1.00 €-23,453

Abbreviations: EFV, efavirenz; MPR, multipill regimen; STR, single-tablet regimen; TDF, tenofovir; FTC, emtricitabine.

98.4, $P=0.014$) after the patients switched to the single-tablet regimen. Adding new single-tablet antiretroviral regimens to conventional therapies can help physicians in the choice of the best possible treatment to administer to HIV patients. Because the single-tablet regimen is not the only available therapeutic alternative, it was deemed necessary to carry out a comparison with other antiretroviral regimens containing the same active ingredients, but not in fixed combination, with the aim of highlighting the presence of potential benefits for patients, and ultimately, for the Italian National Health Service. Specifically, an incremental cost-effectiveness analysis of TDF-FTC-EFV in the single-tablet regimen versus the TDF-FTC + EFV multipill regimen was performed in comparison with untreated HIV-infected patients from the point of view of the National Health Service.¹⁴ Using the Markov model, we could identify the economic value of the improved response by patients on the single-tablet regimen versus those on a multipill regimen in terms of quality of life and cost per QALY gained. As a result of the better quality of life perceived by patients, the ICER was more favorable and came to €4541.00 per QALY (–17%). In practice, assessment of the single-tablet regimen in the terms described here may indicate the range of cost reduction possible for a treatment regimen comprising various molecules (some of which may be nearing patent expiration) with a cost-effectiveness ratio equivalent to that of the corresponding single-tablet regimen. In our study, a 24% price decrease for the multipill regimen would make it comparable with that of the single-tablet regimen. Similarly, the results of our study could be used to identify a potential premium price to be assigned to a single-tablet regimen. In the proposed study, the maximum premium price could be about 29% of the corresponding noncombined therapeutic regimen.

Our study has a few limitations, the most important being the quality of data entered into the model, with parameters such as efficacy and utilities scores, for example, being based on studies of relatively short duration, which may be inadequate for modeling the treatment of a chronic disease for a longer period of time. In our analysis, we include results from a visual analog scale (Short Form-36¹³) in order to weight the utility scores for patients treated with the single-tablet regimen. In this case, the best solution would be to weight utilities on the basis of the data measured, eg, with the EQ5D; however, in the absence of these data, we weighted the utilities taking account of some positive relationships between these two assessment tools when used in other diseases.^{48,49} For this reason, changes in the utilities deriving from the switch to a single-tablet regimen were examined using a

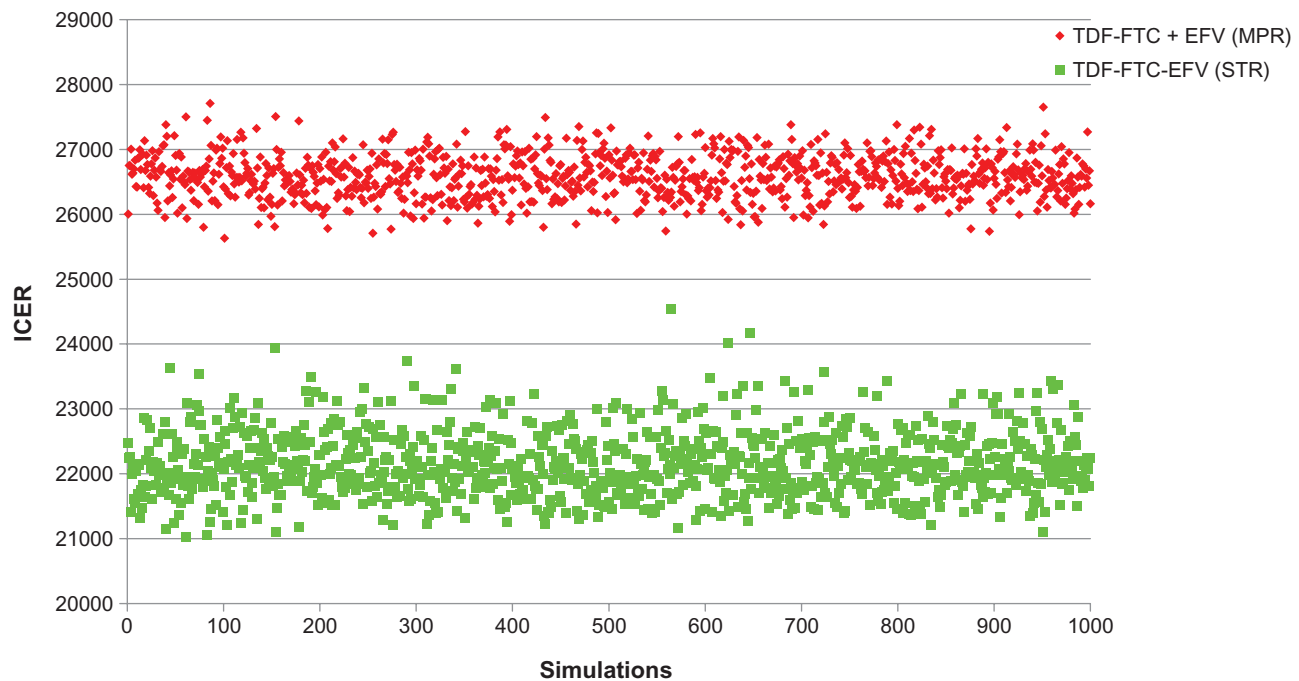


Figure 3 Probabilistic sensitivity analysis: variation in incremental cost-effectiveness ratio for TDF-FTC + EFV multipill regimen versus single-tablet regimen. **Abbreviations:** EFV, efavirenz; FTC, emtricitabine; STR, single-tablet regimen; TDF, tenofovir; ICER, incremental cost-effectiveness ratio.

rigorous probabilistic sensitivity analysis which took into account their limitations and ranges of variation.

Another important limitation is the assumptions on which the analysis is based, that may be necessary to simplify the model or in case of incomplete data. Specifically, transition probabilities were lacking in some cases, and were thus assumed to remain constant over time, and the utilities were derived from different literature sources and considered to be acceptable for an Italian population.¹⁴ Therefore, such models can be used to predict the possible final results, such as in our case, when the clinical trial is incomplete or lacking important data (in this case, the data necessary for the economic evaluation was derived from different and nonhomogeneous sources) and only measures an intermediate result or has a short-period follow-up. For example, the improvement in quality of life seen upon switching from a multipill regimen to a single-tablet regimen was only assessed over a one-year time horizon, whereas the results of our study were extended to 10 years of assessment, for reasons of economic simulation. This hypothesis is based on the assumption that the results of the study by Airoidi et al¹³ were also obtained over longer time periods. However, a recent paper⁴⁸ observes that the once-daily single-tablet regimen showed greater durability than the twice-daily multipill regimen during an observation period of 7 years. For the single-tablet regimen and multipill regimen, the durability, time from initiation of antiretroviral therapy to first

treatment modification, after a reduction of first 48 months, remains constant in this period of observation. Once-daily single-tablet regimens have shown greater durability than twice-daily multipill regimens.⁵⁰

Acknowledging the abovementioned limitations, the results of this study allow us to propose a pharmacoeconomic pathway for assigning a value to combination HIV therapies aimed at simplifying daily treatment into a single-tablet regimen. This pathway runs through the development of a series of epidemiologic and cost-of-illness studies, as well as simulation models, which are necessary when obtaining a picture of patients, costs, their evolution over time, and clinical studies to assess and compare the various treatment options, including quality of life. The information contained in this type of study should be summarized in pharmacoeconomic simulation models to provide constant support to policy-makers, because decisions about resource allocation (price and drug reimbursement) must be made before introduction of new treatments on the market and, therefore, are based on hypotheses and simulations that can only be validated by the presence of the drug on the market. In spite of the limitations of pharmacoeconomic models, these tools play a fundamental role when it is necessary to establish priorities in allocation of resources. Indeed, they supply decision-makers within health care systems with useful tools to make more rational and effective decisions. By collecting appropriate data and integrating them into the

abovementioned models, it is possible to obtain more accurate estimates for the cost-effectiveness ratios of the various strategies used in the treatment of immunocompromised patients and to supply significant evidence for use in future prospective pharmacoeconomic evaluations.

Disclosure

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