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ORIGINAL RESEARCH

A cost-effectiveness analysis of E/C/F/TAF vs three boosted regimens in the Italian context

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ABSTRACT

BACKGROUND: Highly Active Antiretroviral Therapy (HAART) has transformed HIV into a lifelong condition. Following the chronicity of the disease, and significant increase in lifespan – the prevalence of comorbidities increased in HIV+ subjects that are exposed both to a higher risk of developing cardiovascular disease, renal disease, osteopenia/osteoporosis and diabetes, and to the risk of developing them early. Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate (E/C/F/TAF), a complete, Single-Tablet antiretroviral Regimen (STR) that combines the effectiveness and tolerability of integrase inhibitors with an innovative backbone was recently introduced in Italy. Compared to Tenofovir Disoproxil Fumarate (TDF), TAF reaches the sites of action more efficiently, reducing tenofovir plasma concentration to more than 90% and the risk of off-target effects.

OBJECTIVE: A patient-level micro-simulation model was adapted to the Italian context to evaluate E/C/F/TAF cost-effectiveness vs three boosted regimens for HIV+ patients treatment.

METHODS: A Markov micro-simulation model was adapted to the Italian context for the evaluation of the cost-effectiveness in patients with HIV. The total cost per patient accounts for drug therapies and the management of adverse events and comorbidities. The quality-adjusted life expectancy (in QALYs) is calculated by weighing the years of life lived by the utility weights. A 70-year time horizon was adopted to simulate a lifetime analysis; shorter time horizons were considered in the sensitivity analyses. 3.5% discount rate was applied both for costs and future benefits. The rate of virologic suppression at 48 weeks with E/C/F/TAF is 92.3%; for the other treatments such proportion is calculated by applying to the reference rate the relative risks, as calculated in a recent network meta-analysis (NMA). Alternative treatments considered in this analysis are three boosted regimens commonly used in Italy: tenofovir disoproxil fumarate/emtricitabine/elvitegravir/cobicistat in STR; tenofovir disoproxil fumarate/emtricitabine + darunavir/ritonavir; tenofovir disoproxil fumarate/emtricitabine + atazanavir/ritonavir.

RESULTS: E/C/F/TAF improves survival and quality of life (20.17 LY and 14.89 QALY), with the lowest total cost (€ 280,528), thus resulting dominant over three comparators considered as starting therapy. The sensitivity analysis confirms the results of the base case: at a willingness-to-pay threshold of € 30,000 per QALY, the E/C/F/TAF strategy is the most cost-effective, with a 90% probability and it is the most cost-effective even with a threshold of € 10,000 per QALY, with a 50% probability.

CONCLUSION: E/C/F/TAF can be a sustainable alternative to currently available treatments, combining the advantage of the STR to lower risks of kidney and bone damage than observed in regimens based on TDF.

Keywords

HIV; HAART; E/C/F/TAF; Cost-effectiveness

INTRODUCTION

The typical natural course of untreated HIV starts from an acute phase of 1-2 weeks, with flu-like symptoms, followed by a clinically silent phase of varying duration, usually up to 5 to 12 years, followed by a worsening series of clinical events, defining the Acquired Immune Deficiency Syndrome (AIDS) [1] and ultimately leading to death. The whole process is characterized by the progressive loss of immune competence, in particular cellular immunity, as evidenced by the decline in phenotype CD4+ T cells.

Today, therapeutic regimens currently used for the treatment of HIV infection, identified with the acronym Highly Active Antiretrovi-

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ral Therapy (HAART) in general are based on the combination of three antiretroviral drugs (a "backbone" of two Nucleoside and/or Nucleotide Reverse Transcriptase Inhibitors – NRTIs, plus a third agent: NRTI, Integrase Inhibitor – INI, or Protease Inhibitors – PI). The HAART introduction and consequent widespread use since 1996 has profoundly changed the clinical course of HIV disease, transforming HIV-positive status from a precursor of AIDS and high mortality into a manageable lifelong condition. Therapeutic success is strongly correlated with continuous administration of AntiRetroviral Therapy (ART) and lifelong high levels of adherence. However – due to the chronicity of the disease, and in particular because of a significant increase in lifespan – the prevalence of Non-AIDS Related Morbidities (NARMs) has increased in HIV-infected individuals. Compared to the general population, HIV infection is associated with a higher [2] risk of developing cardiovascular disease, kidney disease, osteopenia/osteoporosis, diabetes and neuropsychiatric disorders, and to the risk of developing these earlier than seen in the general population [3].

It should also be emphasized that the high impact of the cost of ART itself [4], the risk of developing resistance and the switch between treatments – possibly required by the occurrence of adverse events or by a therapeutic failure – all contribute to exacerbate the burden of the disease for the National Health Service.

An appropriate and informed choice of therapeutic regimens can help improve the effectiveness of the prescription, reduce the risk of virologic failure, and reduce resource burden, including potentially more expensive subsequent ART regimens. From this standpoint, the recent developments in ART have focused on the combination of three active molecules in a single tablet (Single Tablet Regimen – STR), with the objective of simplifying administration and maximizing adherence to treatment. Studies have demonstrated that improved adherence to therapy significantly reduces the risks of treatment failure in its various forms, including a lower risk of developing resistance to the antiretroviral drugs.

A recent introduction in the Italian market is a new once daily fixed combination tablet containing a complete ART regimen E/C/F/TAF: Elvitegravir (E) + Cobicistat (C) + Emtricitabine (F) + Tenofovir Alafenamide Fumarate (TAF).

E/C/F/TAF is presented as a complete STR that combines the effectiveness and tolerability of integrase inhibitors with an innovative backbone containing emtricitabine and Tenofovir Alafenamide Fumarate (TAF). Compared to Tenofovir Disoproxil Fumarate (TDF), the molecules contained in the previously approved therapies, TAF is converted into tenofovir (the active ingredient) at lymphocytic level more efficiently, so that tenofovir concentrates at the site of action, rather than persisting in the plasma. This change allows a reduction of more than 90% in the plasma concentration of tenofovir, whose metabolism is associated with adverse bone and kidney effects.

In summary, TAF-based regimens maintain the same high level of efficacy observed with TDF, with reduced side effects [5]. As a consequence, patient long-term outcomes, including persistence with therapy, may be improved at the same time that the costs associated with treatment failure and of managing off-target effects are reduced.

E/C/F/TAF therefore presents a series of characteristics that potentially have positive effects from a pharmacoeconomic perspective: high intrinsic effectiveness (as measured in RCTs), simple administration regimen (STR), which is known to be associated with improved adherence, and a more tolerable safety profile, all factors that contribute to the high level of effectiveness observed in clinical practice.

The data available so far in the literature corroborate these expectations, with indications of a reduction in the risk of hospitalizations for concomitant HIV, with a higher quality-adjusted life expectancy, compared to multi-tablet regimens [6].

The aim of this work is to assess the Incremental Cost-Effectiveness Ratio (ICER) of E/C/F/TAF compared to TDF regimens containing a booster (ritonavir or cobicistat) since they are the most frequent used in the Italian clinical practice for patients with HIV-1 virus. Ideally E/C/F/TAF is an alternative to Tenofovir Disoproxil Fumarate/emtricitabine/elvitegravir boosted with cobicistat (TDF/FTC-EVG/c) in STR and to Tenofovir Disoproxil Fumarate/emtricitabine + darunavir or atazanavir boosted with ritonavir (TDF/FTC-DRV/r or -ATV/r).

METHODS

A patient-level micro-simulation model developed for United Kingdom [7] was adapted to the Italian context for evaluation of the cost-effectiveness of treatments in patients with HIV. The model was developed in R, with input/output interface in MS Excel®. A cohort of 1,000 patients was simulated using a Markov model over a time horizon of

70 years, discretized into monthly cycles (30 days). A simplified diagram of the model is provided in Figure 1.

The evolution of patients' treatment, between the recommended pharmacological therapies (in accordance with the guidelines for the management of HIV-positive patients [8]), occurred via the likelihood of viral suppression associated with each treatment, CD4 level determined the risk of Opportunistic Infections (OIs) and neoplasms, and placed simulated patients into one of the three categories for the use of outpatient resources.

- Complex Patients (HIV3): Patients with AIDS who need additional management of ARV or patients with persistent viremia.
- New patients (HIV1): patients under combination ART (cART) treatment for less than a year without HIV3.
- Stable Patients (HIV2): Unclassified patients such as HIV1 or HIV3.

The risk of NARM was calculated using published regressions specific for each adverse event (cardiovascular [9], renal [10], diabetes [11], hypertension [12]) or, in the case of risk of fracture, on the base of a cohort analysis of 883 treated PLHIV (People Living with HIV) [13]. According to this model, the risks of Treatment-Related Adverse Events (TRAEs) were independent of the CD4 count, but did depend on the antiretroviral therapy the patient was receiving. Mortality was calculated on the basis of the adverse events simulated in the model (specific for OIs and neoplasms, while for TRAEs, mortality was calculated in accordance with the natural mortality of the Italian population, multiplied by specific relative risks).

Pharmacological treatments could be discontinued due to virological failure, or lack of suppression. In this case the choice of the treatments following the first line (up to the fourth line of treatment) was made through a semi-deterministic algorithm, depending on the previous treatments and their tolerability and resistance (see section 2.4 in the text).

The total cost per patient was calculated by economically valuing the drug therapies and the management of adverse events and comorbidities. The quality of life was calculated by weighing the years of life lived by the utility weights, which are a function of the patients' baseline characteristics and their therapeutic and disease course (see paragraph Progression between therapeutic lines section).

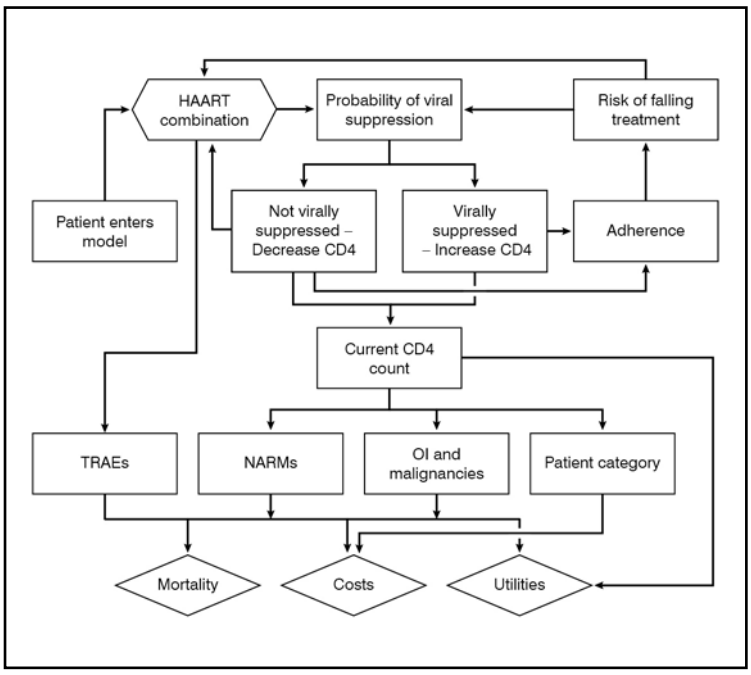

Figure 1. *Simplified diagram of the model*

Comparators

In compliance with published clinical guidelines, patients with newly diagnosed HIV begin a treatment based on a dual NRTI backbone and a third drug chosen from among PIs, INIs or NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors). In this model, the new formulation in the STR E/C/F/TAF was compared with the following three regimens:

- TDF/FTC-EVG/c: Tenofovir Disoproxil Fumarate/emtricitabine/elvitegravir (boosted with cobicistat) in STR.
- TDF/FTC-DRV/r: Tenofovir Disoproxil Fumarate/emtricitabine + darunavir (boosted with ritonavir)
- TDF/FTC-ATV/r: Tenofovir Disoproxil Fumarate/emtricitabine + atazanavir (boosted with ritonavir)

All of these comparator regimens were characterized by the presence of a pharmacokinetic booster, which enhances the absorption of the substrate and reduces its elimination. One of the comparators was a regimen also incorporating EVG (elvitegravir), COBI (cobicistat) booster and FTC (emtricitabine), but differing by containing TDF rather than the newer TAF. In the other two comparators, PIs were associated with RTV (ritonavir) booster. For all comparators, the nucleoside/nucleotide backbone was represented by TDF and FTC. The perspective of this comparison therefore refers to the search for overall differential therapeutic performance elements between a brand new, single-tablet therapeutic formulation – characterized in particular by the presence of TAF – and three TDF-based regimens currently in common usage in Italy (although TDF/FTC-DRV/r and TDF/FTC-ATV/r have been recently recommended for particular conditions only).

	Average	SD[1]	Source	Notes[2]
General characteristics				
Age (years)	36.76	8.24	[19]	N1
Gender (% males)	73.4		[19]	
MSM (%)	31.1		[19]	
IDU (%)	22.4		[19]	
Baseline CD4 count (cells/mm^3)	496.12	288.86	[19]	N1
Viral load (log_{10}copies/ml)	3.85	1.78	[19]	N1
Race (%)			[19]	
• Caucasian	95.6			
• African	4.4			
Initial comorbidities (%)				
Diabetes	2.1		[19]	
CV disease	2.9		[20]	
Bone fractures	2.5		[21]	
Kidney failure	0.7		[20]	
Hypertension	29.4		[22]	
Risk factors				
eGFR (ml/min/1,73 m^2)	100.63	18.19	[19]	N1
Smoker (%)	53.0		[23]	
Former smoker (%)	14.0		[23]	
Total cholesterol (mmol/l)	4.46	1.12	[19]	N1
LDL (mmol/l)	2.75	0.62		N4
HDL (mmol/l)	1.12	0.35	[19]	N1
Triglycerides (mmol/l)	1.68	0.87	[22]	N1
Glycemia (mg/dl)	87.66	11.16	[19]	N1
Systolic pressure (mm Hg)	123.26	14.69	[22]	N2
Diastolic pressure (mm Hg)	78.80	9.81	[22]	N2
BMI (kg/m^2)	23.29	3.15	[20]	N3
Family history of CV disease	9.2		[9]	
HCV co-infection (%)	11.7		[20]	
Family history of hypertension (1 parent)	4.0		[7]	
Family history of hypertension (both parents)	1.0		[7]	
Family history of diabetes	17.0		[11]	

Table I. *Baseline characteristics of the cohort simulated in the model*

[1] If not otherwise specified, standard deviation was calculated to be 10% of the average value

[2] N1: Fitted mean and SD to more accurately fit median and IQR; N2: Mean and SD calculated starting from mean and SD subgroups; N3: Fitted mean and SD to more accurately fit median and %<18.5, %<25; N4: Calculated starting from TC and HDL assuming other components equal to 2/15 of TC according to UK model

BMI = Body Mass Index; eGFR = Estimated Glomerular Filtration Rate; HCV = Hepatitis C Virus; HDL = High Density Lipoproteins; IDU = mode of transmission "Injection Drugs Use"; LDL = Low Density Lipoproteins; MSM = mode of transmission "Man who have Sex with Man"; SD = Standard Deviation

Time horizon, discount rates and perspective analysis

Given the chronic nature of the disease, a 70-year time horizon was adopted to simulate a lifetime analysis; shorter time horizons (5, 10, 20, 40 years) were considered in the sensitivity analysis. The Italian guidelines for healthcare financial assessments issued in 2001 recommended the application of a 3% discount rate for both costs, and future benefits [14]. The same value was indicated in the most recent draft guidelines drawn up and discussed in 2009 by the *Associazione Italiana di Economia Sanitaria* (AIES, Italian Association of Health Economics) [15], while the European Commission proposed an annual rate of 5% [16]. The latter rate has been considered too high by many economists [17], however, and the *Istituto Nazionale per l'Impatto Sociale dell'Economia* (INISE, National Institute for the Social Impact of Economy) recommended a discount rate lower by about 1.5% than the official ones. Based on these considerations, and in line with international publications [18] referring to the Italian context, it was decided to apply a 3.5% discount rate (for costs and benefits).

In order to take into account the Italian and European guidelines, the sensitivity analysis considered the 3% and 5% discount rates.

The analysis was performed from the perspective of the Italian National Health Service (SSN, *Servizio Sanitario Nazionale*); therefore only the direct healthcare costs borne by the health system and its structures were taken into account. Direct non-health-related costs borne by patients, or societal costs due to reduced productivity of patients and their caregivers, were disregarded.

Population

The analysis was conducted in a population of HIV patients, with a mean initial age of 36 years. In the absence of an observational database inclusive of all the characteristics of the population analyzed, necessary for the simulation, input data were obtained from various published studies [8,10,18-22]. These data, and their sources, are summarized in Table I. The cohorts analyzed were comparable as for age, gender, mode of transmission of HIV and baseline CD4 count.

Progression between therapeutic lines

For progression between therapeutic lines, decision-making algorithms based on the opinion of clinical experts were followed. Within the first line treatment a patient began one of the two "paths" considered in the analysis: i.e. PI or INI as third agent. In cases of failure due to tolerability, patients were switched to another therapeutic path (i.e. the class of third agent was changed), or remained on the current path, but changed the drug within the same third agent. The choice of the new drug for each treatment class occurred deterministically, from a list arranged according to the frequency of use in the Ital-

ian clinical practice. Starting from the third line, in case of failure due to resistance, the third drug – besides being replaced – could be "partnered" with another drug of another class (e.g. a PI and an INI), or to maraviroc, in the most critical cases. In addition to the switch for intolerance and resistance, the model assumed that 20% of patients would modify the therapy if they experienced 5 or more TRAEs in the same month. In the limited cases where the patient had exhausted all possible treatments, the model provided for the continuation of treatment with the last assigned sequence of drugs, until death. According to the opinion of clinical experts, changes in the backbone are much rarer than the change of third agent, since the choice is much more limited. As such, switches between backbones, for the given failure reason (resistance, intolerance or non-adherence) were governed by an assumed proportion of 90%, 90% and 20%, respectively.

Any switch to new treatments occurred at follow-up visits; by default, in the first year of treatment, follow up was every 3 months, while from the second year of treatment, if the CD4 count was above 200, follow up was every 6 months.

Clinical inputs

Effectiveness

It was assumed that the percentage of patients with virologic suppression (viral load less than 50 copies per ml) at 12 months corresponds to the proportion of patients successfully treated, derived directly or indirectly to the 48 week data reported in the RCTs; although this hypothesis might not be very precise from a clinical standpoint (patients can take 3 to 6 months to respond), the impact on costs and clinical outcomes is insignificant.

The rate of virologic suppression at 48 weeks with ECF/TAF is 92.3% [24]; for the other treatments, such proportion is calculated by applying to the reference rate the relative risks, as calculated in a recent Network Meta-Analysis (NMA) [25] and reported in Table II (only for the comparators involved in the analysis). Final effectiveness data for all possible treatments in the simulation are reported in Table III.

Second-line treatments were assumed to have the same rates of viral suppression as first-line treatments [expert opinion], while for the subsequent lines, a reduction in effectiveness was applied (-5% in the third line and -10% in the fourth line).

In virological suppression, adherence to treatment crucially affects success [27]. In this model, this trend was incorporated using the rates of adherence in HIV infected patients with, and without, virological failure (36.8% and 89.2%, respectively) [28]. In addition, for patients treated with a STR, a 4.5% increase in adherence was expected [29].

Regimen	RR	95% CI
DRV + FTC/TDF	0.96	0.89-1.02
ATV + FTC/TDF	0.92	0.89-0.97
EVG + FTC/TDF	0.98	0.95-1.01

Table II. *Treatment effectiveness of first line therapeutic options*
RR = Relative Risk

	FTC/TAF	FTC/TDF	ABC/3TC	Other[1]
RPV	NA	0.905	0.905[2]	0.831
ETV [18]	NA	0.759	0.759[2]	0.697
DRV	NA	0.887	0.915	0.814
ATV	NA	0.850	0.868	0.780
EVG	0.923	0.905	0.905[2]	0.831
RAL	NA	0.924	0.933	0.848
DTG	NA	0.952	0.933	0.873
MVC	NA	0.653	0.653[2]	0.599

Table III. *Rate of virological suppression of the treatments for second-line treatments considered in the analysis*
[1] Calculated as 8.25% less than TDF/FTC, in accordance with [26]
[2] Assumed to have same virological suppression rate as the TDF/FTC combination

Causes of failure	PIs	NNRTIs	INIs
Sporadic blip	20.57%	7.06%	15.58%
Intolerance/drug interaction	5.07%	1.74%	3.84%
Poor adherence	73.36%	25.19%	55.57%
Resistance	1.00%	66.00%	25.00%
Loss at follow-up	NA	NA	NA

Table IV. *Causes of virological failure*
INI = integrase inhibitors; NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor; PI = Protease Inhibitor

	Average	SD
Adherence (reference 100%)		
< 100%	1.22	0.2168
≤ 95%	1.51	0.2169
≤ 80%	1.70	0.2781
≤ 65%	1.75	0.3138
Previous failures due to drug resistance (reference 0)		
1	1.39	0.2704
> 1	1.68	0.7730
Drug class (reference NNRTIs)		
PI	1.28	0.1658
Other	0.75	0.2423

Table V. *Risks related to late failure*
NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor; PI = Protease Inhibitor
SD = Standard Deviation

Parameters	Average	SE
α	747.55	6.43
β_{year}	53.68	4.21
β_{CD4} (baseline CD4 count)		
• 500+	-177.92	9.32
• 350-499	-270.35	8.57
• 200-349	-368.46	8.79
• 100-199	-449.20	8.65
• 50-99	-481.46	8.94
• 25-49	-522.19	9.01
$\beta_{CD4year}$ (baseline CD4 count[1])		
• 500+	21.11	6.19
• 350-499	14.37	5.48
• 200-349	20.36	5.65
• 100-199	20.40	5.59
• 50-99	22.56	5.75
• 25-49	32.61	5.91

Table VI. *Coefficients related to the regression of the CD4 count*
[1] Term of interaction between baseline CD4 count and duration of treatment (in years)
SE = Standard Error

Baseline HIV viral load (log_{10})	Reduction in CD4 count
≤ 2.70	3.025
≤ 3.48	3.733
≤ 4.00	4.600
≤ 4.48	5.400
> 4.48	6.375

Table VII. *Correction factor for the CD4 count in patients who do not achieve virological suppression*

OIs and neoplasms	α	λ	R^2
Esophageal candidiasis	2.8952	0.00349	0.94
Kaposi sarcoma	2.5926	0.00359	0.99
Pulmonary tb	3.0467	0.00305	0.96
Non-hodgkins lymphoma	2.7559	0.00333	0.97
Extrapulmonary tuberculosis	2.3084	0.00359	0.95
Bacterial pneumonia	2.5499	0.00323	0.99
Pneumocystus jiroveccii pneumonia	1.0234	0.00472	0.98
Recurrent herpes simplex	2.4731	0.00313	0.97
HIV dementia	2.6290	0.00294	0.88
Cervical cancer[1]	1.7158	0.00242	0.96
Rare ADEs	2.3393	0.00279	0.94
HIV wasting syndrome	1.5530	0.00334	0.95
Progressive multifocal leukoencephalopathy	0.5390	0.00419	0.98
Toxoplasmosis of brain	0.3567	0.00436	0.96
Cytomegalovirus (non-retinitis)	2.6694	0.00173	0.98
Cryptosporidiosis	1.4919	0.00255	0.88
Mycobacterium avium complex	0.1371	0.00365	0.82
Cytomegalovirus retinitis	-0.2564	0.00384	0.95
Cryptococcosis	-0.7088	0.00417	0.96

Table VIII. *Estimation of the exponential curves parameters for each type of infection or neoplasm*
[1] Only for female patients (in this case PYFU = 313,011)

The causes of virological failure were taken from the results of an analysis conducted in Portugal on 187 PLHIV [30]. For simplicity, failures due to intolerance and pharmacokinetic interactions were aggregated into a single cause of virological failure since, it is assumed that they are managed in a similar way. Also, lost to follow-up was not considered a treatment failure, because the simulation model maintained charge of all PLHIV. The rates thus calculated have been scaled down on the basis of the rates of resistance reported for PIs, NNRTIs and INIs (Table IV) [27].
Cambiano et al. [31] have highlighted a risk of late failure for patients who maintain viral suppression after 12 months of treatment, depending on adherence to treatment, on any previous failures due to drug resistance and on the class of the third agent. The relative risks for each risk factor are reported in Table V; the monthly rate of failure used as a reference (corresponding to a 100% adherence) is 0.56%.

Evolution of CD4

The monthly value of the CD4 count is one of the main parameters for determining the risk of diabetes, renal damage, risk of OIs, neoplasms and mortality. The trend over time of the CD4 count for patients in virological suppression was drawn from a cohort of ART-naïve [32] PLHIV, as a function of the CD4 count at the start of treatment, and the duration of treatment. The relation, which is non-linear, is expressed by the formula:

$$p = 1 - e^{\frac{e^{\alpha + \lambda * DC4}}{PYFU/12}}$$

The regression coefficients are reported in Table VI.
For non-suppressed patients, a monthly reduction factor as a function of the baseline viral load [33], was applied to the CD4 value determined by the regression described above (Table VII).

Adverse events

Opportunistic Infections and neoplasms

The risks of OIs and neoplasms were calculated from exponential curves fitted to the data from more than 200,000 adults with HIV, with a Person-Years Follow-Up (PYFU) of 1,154,803, as a function of the CD4 count [34]. The monthly risk p was calculated through the formula:

$$CD4\ count = \alpha + \beta_{year} \ln(year) + \beta_{CD4} + \beta_{CD4*year} \ln(year)$$

where intercept α and shape parameter λ are specific to each of the 19 AIDS-related disorders highlighted in the study (Table VIII).

Treatment Related Adverse Events

Treatment-related adverse events (TRAEs) were divided into the following categories: central nervous system (CNS), gastrointestinal (GI), liver, kidney, metabolic, and cutaneous. The average rate for each event reported in the UK model was detailed for each individual strategy, weighing it using the severity scores devised by a panel of clinicians (0 = no event, 5 = highest frequency). The data were broken down into the relative contributions associated with the backbone and one specific third agent. The effects of the backbone and the third agent are additive in the first line (Table IX). For the subsequent lines when more than one third agent can be combined the assumption is made that the maximum probability for the specific third agents will be used.

Non-AIDS related morbidities

The risks of NARMs are calculated from regressions published in the literature, as a function of the patients' baseline characteristics and any antiretroviral treatments [9-12]; a similar regression for the risk of fractures was not found in the literature, therefore it was decided to act conservatively, using a non-treatment-specific, uniform fractures rate; the data – 10.3% [13] over a median follow-up of 6.19 years – was then converted into a monthly rate.

Mortality

The model considers three possible causes of death: mortality in the general population, NARM-related mortality and mortality for OIs and neoplasms. It was assumed that

Regimen	Monthly frequency (%)					
	CNS	GI	Liver	Kidney	Metabolic	Cutaneous
TDF/FTC + ATV/r	0.1	2.2	0.7	1.3	2.0	0.1
ABC/3TC + ATV/r	0.1	2.2	0.6	0.6	1.0	0.1
TDF/FTC + DRV/r	0.0	2.5	0.6	0.9	1.9	0.3
ABC/3TC + DRV/r	0.0	2.5	0.6	0.1	0.9	0.3
TDF/FTC + RAL	0.0	1.4	0.1	0.8	1.1	0.1
ABC/3TC + RAL	0.0	1.5	0.1	0.0	0.1	0.1
TDF/FTC + DTG	0.7	1.2	0.1	0.8	1.1	0.1
ABC/3TC + DTG	0.7	1.2	0.1	0.0	0.1	0.1
TDF/FTC + EVG/c	0.0	1.3	0.1	1.1	3.1	0.1
E/C/F/TAF/	0.0	1.3	0.1	0.0	3.1	0.1
TDF/FTC + ATV/r + DTG	0.8	2.2	0.7	1.3	2.0	0.2
ABC/3TC + ATV/r + DTG	0.8	2.2	0.6	0.6	1.1	0.2
TDF/FTC + DRV/r + RAL	0.0	2.8	0.6	0.9	2.0	0.3
ABC/3TC + DRV/r + RAL	0.0	2.8	0.6	0.1	1.0	0.3
TDF/FTC + DRV/r + DTG	0.7	2.5	0.6	0.9	2.0	0.3
ABC/3TC + DRV/r + DTG	0.7	2.5	0.6	0.1	1.0	0.3
TDF/FTC + ATV/r + ETV	0.4	2.5	0.7	1.3	2.1	0.7
ABC/3TC + ATV/r + ETV	0.4	2.5	0.7	0.6	1.1	0.7
TDF/FTC + DRV/r + RPV	0.0	2.6	0.9	0.9	1.9	0.3
ABC/3TC + DRV/r + RPV	0.0	2.6	0.9	0.2	0.9	0.3
TDF/FTC + DRV/r + ETV	0.3	2.8	0.7	0.9	2.0	0.9
ABC/3TC + DRV/r + ETV	0.3	2.8	0.6	0.1	1.0	0.8
TDF/FTC + ATV/r + RAL + MVC	0.1	2.4	0.7	1.3	2.1	0.2
ABC/3TC + ATV/r + RAL + MVC	0.1	2.4	0.7	0.6	1.1	0.2
TDF/FTC + ATV/r + DTG + MVC	0.8	2.2	0.7	1.3	2.1	0.2
ABC/3TC + ATV/r + DTG + MVC	0.8	2.2	0.7	0.6	1.1	0.2
TDF/FTC + DRV/r + RAL + MVC	0.0	2.8	0.7	0.9	2.0	0.3
ABC/3TC+DRV/r + RAL + MVC	0.0	2.8	0.6	0.1	1.0	0.3
TDF/FTC + DRV/r + DTG + MVC	0.7	2.5	0.7	0.9	2.0	0.3
ABC/3TC + DRV/r + DTG + MVC	0.7	2.5	0.6	0.1	1.0	0.3

Table IX. *Monthly frequencies of TRAEs for all the regimens simulated in the analysis*
CNS = Central Nervous System; GI = gastrointestinal

NARMs	Gender	SMRs (mean value)	SE
Diabetes [38]	Male	1.31	0.01
	Female	1.39	0.01
CVD [39]	Male	1.36	0.14
	Female	1.34	0.13
CKD [40]	Both	4.70	0.10
Fracture [41]	Both	7.47	0.75

Table X. *Effect of non-AIDS related morbidities on mortality*
CKD = Chronic Kidney Disease; CVD = cardiovascular; NARMs = Non-AIDS Related Morbidities SE = Standard Error; SMRs = Standardized Mortality Ratios

Drugs	Dosage	Monthly cost (€)
III agent		
EFV	600 mg OD	162.90
RPV	25 mg OD	273.60
ETV	200 mg BID	450.00
DRV/r (in non-resistant regimens)	800 mg OD	504.00[1]
DRV/r (in resistant patients)	600 mg BID	743.70[1]
ATV/r	300 mg OD	414.00[1]
RAL	400 mg BID	604.50
DTG (in non-resistant regimens)	50 mg OD	604.80
DTG (in resistant patients)	50 mg BID	1,209.60
MVC	300 mg	900.00
MVC	300 mg BID	1800.00
Backbone		
TDF/FTC	445 mg OD	455
ABC/3TC	900 mg OD	381.00
Other[1]		270.34
STR		
TDF/FTC/EFV	1 TAB OD	664.72
TDF/FTC/RPV	1 TAB OD	728.46
TDF/FTC/EVG/c	1 TAB OD	1,059.50
TAF/FTC/EVG/c	1 TAB OD	1,059.50

Table XI. *Daily dosage and monthly cost for each treatment considered in the model*
[1] Calculated as twice the weighted average of the main backbones for the 2014 UK market quotas [38] (such quotas have been used as a proxy in the absence of data for the Italian market)
BID = *bis in die* (twice a day); CNS = Central Nervous System; GI = gastrointestinal; /r = boosted with ritonavir (100-200 mg OD or BID, ex-factory € 24,00); OD = *semel in die* (once a day); STR = Single-Tablet antiretroviral Regimen

TRAEs are not one of the causes of death, in accordance with the results of Grant et al [35].

Mortality rates in case of opportunistic infections and neoplasms were obtained from an analysis conducted on 30,000 people living with HIV who had initiated HIV antiretroviral therapy [36]; these values are expressed in risk rates in the case of events diagnosed within 6 months of treatment or, in the case of events diagnosed later, as a hazard ratio (HR), adjusted for gender, age, CD4 count, baseline viral load and duration of disease.

In the case of NARMs, however, natural mortality [37] was adjusted for the event-specific Standardized Mortality Ratios (SMRs), which represented the possible increased risk of death in the group under observation in comparison to the general population. When possible, the data were differentiated by gender (Table X). For patients with hypertension, no increase in the risk of death was assumed, because such disease is a risk factor included in other NARMs, such as CVD and diabetes.

Utility

The utility weights for patients with HIV were calculated using a linear regression based on age, gender, race, IDU and CD4 count [42]. To these weights, were then applied the utility decrements related to the development of side effects [43-50] and HIV-related and -unrelated diseases [41,51-55].

Economic inputs

In the analysis, the following cost categories were taken into account:

- Drug therapy for the treatment of HIV.
- Hospitalization for OI/neoplasms.
- Treatment of HIV-unrelated diseases.
- Medical examinations and diagnostic procedures.
- Treatment of side effects.

Drug therapy

The monthly cost of the treatments considered in the model were determined by taking the ex-factory price published in Italian Official Gazette and the dosage recommended in the Summary of Product Characteristics (SPC). Should several packages of the same drug be available, it was decided to consider the one with the lowest cost. Data are summarized in Table XI.

Hospitalizations for OIs/neoplasms

The management of the disease-related events (opportunistic infections and malignant tumors) was valued through the tariffs for Diagnosed Related Group (DRG) 489 (€ 8,186) and 490 (€ 2,458) [56]; specifically, DRG 490 was associated with: cervical cancer, rare adverse events, HIV wasting syndrome, progressive multifocal leukoencephalopathy, cryptosporidiosis and mycobacterium avium complex, while DRG 489 was associated with the remaining events.

HIV-unrelated adverse events

The disease costs for NARMs (diabetes, cardiovascular events, renal damage, bone fractures and hypertension) were calculated starting from observational studies published in

Event	Monthly cost (€)	Description
Diabetes	257.69	Drugs, hospitalizations and specialist visits for the year 2010, updated to 2014 [57]
CVD	172.82	Drugs, hospitalizations and specialist visits for the year 2009, updated to 2014 [58]
Fracture	127.33[1]	Hospitalizations and rehabilitation for fractures (femur/hip and others) [56,59-60]
CKD	146.23	Cost of the resources used, averaged for the distribution of severity stages in Italy [61]
Hypertension	61.09	Average cost of drug therapy [62]

Table XII. *Monthly cost for the management of HIV-unrelated morbidities*
[1] The monthly cost was calculated assuming that the incidence of fractures is not greater than one per year
CKD = Chronic Kidney Disease; CVD = cardiovascular

Patient category	Monthly cost (€)	Description
Category 1 (new patient)	45.76	Viral load (every 4/8 weeks for the first 6 months, then every 3/4 months) + CD4 count (2 consecutive ones at the beginning of therapy, then every 2/4 months) + visits to check the test results
Category 2 (stable patient)	26.65	Viral load + CD4 count (every 3/4 months) + visits to check the test results
Category 3 (critical patient)	65.79	Viral load (every 4/8 weeks) + CD4 count (every 1/2 months) + visits to check the test results

Table XIII. *Cost of management of HIV patients*

the literature (Table XII) and converted into monthly costs.

Disease management

The cost of management of the HIV-positive patient was calculated considering the virology tests and CD4 counts [56], adjusted for the annual frequency indicated by guidelines [8]. For each examination, a specialist visit for the evaluation of the results of the aforementioned tests was also considered (Table XIII).

Management of side effects

Management of adverse events related to drug therapy was valued through the tariff for DRG 490 (HIV associated or not associated to other related conditions) in outpatient care; the cost per event is equal to € 261 [56].

Sensitivity analysis

The uncertainty of the parameters were taken into account by means of a probabilistic sensitivity analysis: 100 simulations were performed, in each of which all input parameters were sampled by appropriate distributions fitted for the average values previously reported, and for the relative standard deviations; for the input data for which variability measures were not available in the literature, a standard deviation – equal to 10% of the average value – was assumed.

Several one-way *Deterministic Sensitivity Analyses* (DSA) were also carried out, in order to assess the impact of certain parameters on the cost-effectiveness of ECF/TAF compared to the comparators considered in this analysis:

- To assess the impact of E/C/F/TAF on the short (5 years)/medium (10-30 years)/ long term (40 years), the time horizon of the simulation was varied from the minimum case up to 40 years.
- Discount rate for costs and benefits equal to 3-5%.
- The cost of disease-related adverse events (OIs, neoplasms and TRAEs) was varied by ± 10%.
- Two alternative adherence scenarios were considered in the sensitivity analysis:
- The increase in adherence due to the STR was set to zero
- For adherence data [1], an alternative source was used for the Italian context: 92.4% for patients in suppression, 38.4% for patients who do not achieve suppression and increase in adherence due to the STRs equal to 6.6 %

RESULTS

Treatment with E/C/F/TAF was dominant over all comparators; in each case, E/C/F/TAF produced better survival and better quality of life (20.17 LY and 14.89 QALY), with the lowest total cost (€ 280,528), (Table XIV and Figure 2). Pharmaceutical costs represent almost 90% of the total cost for the treatment of patients with HIV, followed by NARM costs – 6% of total.

	E/C/F/TAF	TDF/FTC-EVG/c	TDF/FTC+DRV/r	TDF/FTC+ATV/r
Total cost (€)	280,528 ± 7,621	283,908 ± 7,715	296,831 ± 14,759	283,846 ± 15,970
• Drugs	247,011 ± 6,308	249,056 ± 6,376	260,675 ± 13,916	247,606 ± 15,152
• TRAEs	2,983 ± 320	3,532 ± 378	3,753 ± 456	3,796 ± 467
• OIs/neoplasms	7,856 ± 3,818	7,791 ± 3,849	7,812 ± 3,969	7,911 ± 4,028
• NARMs	15,907 ± 1,562	16,835 ± 1,667	17,962 ± 1,757	17,887 ± 1,748
• Disease management	6,771 ± 639	6,692 ± 631	6,628 ± 624	6,646 ± 626
QALY	14.89 ± 0.63	14.75 ± 0.62	14.54 ± 0.62	14.54 ± 0.62
Δ costs (€)	-	3,379 ± 1,116	16,302 ± 15,576	3,318 ± 16,711
Δ QALY	-	-0.14 ± 0.03	-0.35 ± 0.05	-0.35 ± 0.05
ICER per QALY	-	Dominated	Dominated	Dominated

Table XIV. *Results of the cost-effectiveness model: cost and effectiveness increases are calculated compared to E/C/F/TAF (data are reported as average ± SE; standard errors were derived from the results of the probabilistic sensitivity analysis)*
NARMs = Non-AIDS Related Morbidities; OIs = Opportunistic Infections; TRAEs = Treatment-Related Adverse Events

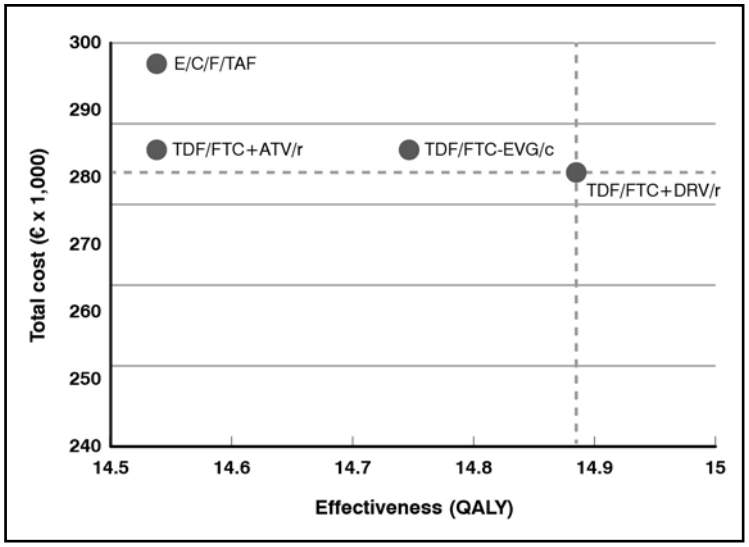

Figure 2. *Total cost and quality of life resulting from the analysis of the base case for E/C/F/TAF and the 3 comparators included in the analysis*

The sensitivity analysis confirmed the results of the base case: at a willingness-to-pay threshold of € 30,000 per QALY, the ECF/TAF strategy was the most cost-effective, with a 90% probability; (Figure 3).
The results were stable under alternative assumptions of discount rates, cost of management of adverse events and adherence to treatment (Table XV). However, when shorter time horizons were taken into account, the only change highlighted was the loss of dominance of E/C/F/TAF vs. TDF/FTC-DRV/r (up to 10 years) and TDF/FTC-ATV/r (up to 20 years) (Figure 4). For the initial drug therapy, in fact, the two treatments have lower acquisition costs, which in the short term are not yet offset by the higher costs due to the switch to subsequent lines, and by the costs of the management of adverse events and comorbidities.

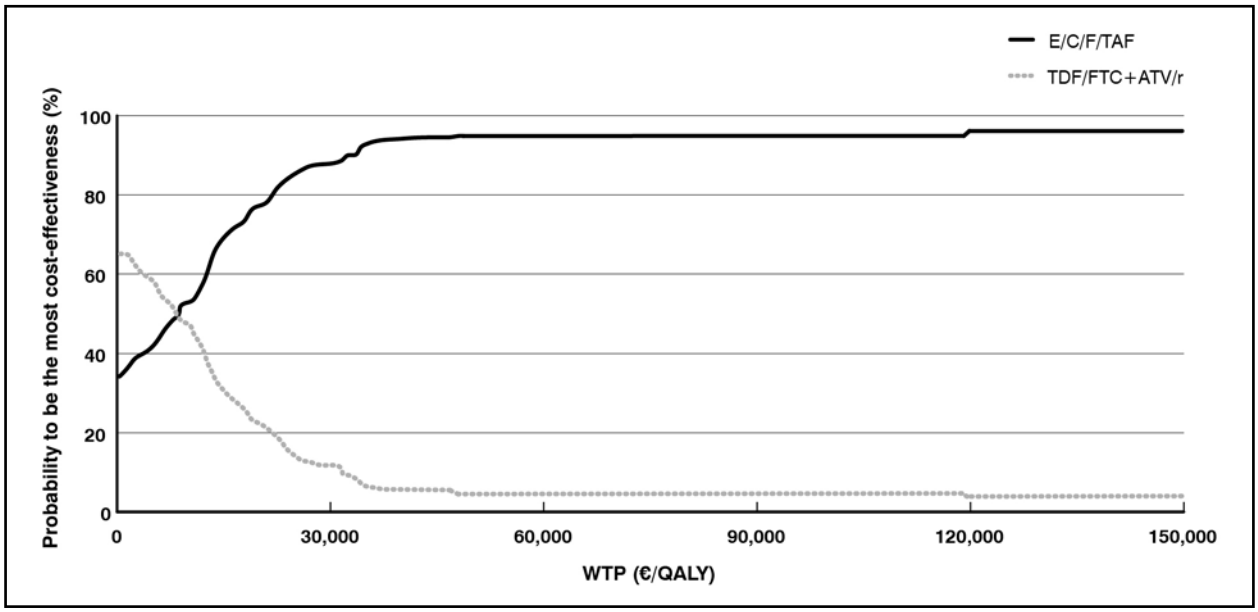

Figure 3. *Cost-effectiveness acceptability curves (CEAC): comparison between E/C/F/TAF and TDF/FTC-ATV/r. TDF/FTC in association with EVG/c or DRV/r does not appear in the comparison, since it wasn't cost-effective for any WTP (Willingness-To-Pay) threshold*

CONCLUSIONS

The introduction of effective combination ART in 1996 significantly changed the clinical course of HIV disease: the progression of the infection is now manageable with therapy, resulting in increased quality of life and much improved patient survival. Since treated HIV is now a lifelong conditions, its treatments need to be increasingly focused on the long-term management of patient NARMs and avoiding/limiting treatment adverse effects. E/C/F/TAF meets these requirements by reducing the side effects associated with antiretroviral therapy, in addition to suppression of viral load. This allows for the optimal management of comorbidities, which are the consequence of a long exposure to virus-related risks, current treatments and advancing age.

Although several therapeutic options are available, the number of usable drugs is limited because of developed resistance, intolerance or high risk of side effect. It is therefore essential to assign the most appropriate therapy to each patient, so as to minimize the risk of failure and maximize the lifespan of each regimen for each patient.

Although it is not possible to develop an actual decision-making algorithm to determine the most appropriate HAART therapy for a treatment-naïve patient, there are guideline recommendations. The Italian Guidelines recommend, without restrictions, certain regimens, including TDF/FTC and TAF/FTC, in association with the integrase inhibitor EVG/c and, under certain conditions, in combination with PIs boosted with ritonavir. Single tablet regimens are recommended by

	E/C/F/TAF	TDF/ FTC-EVG/c	TDF/ FTC+DRV/r	TDF/ FTC+ATV/r
Discount rate (3%)				
Total cost (€)	303,254	306,759	321,651	307,981
QALY	16.02	15.86	15.62	15.62
Δ costs (€)		3,505	18,397	4,727
Δ QALY		-0.16	-0.40	-0.40
ICER		Dominated	Dominated	Dominated
Discount rate (5%)				
Total cost (€)	226,966	229,943	238,553	227,445
QALY	12.19	12.10	11.95	11.96
Δ costs (€)	-	2,978	11,587	479
Δ QALY	-	-0.09	-0.23	-0.23
ICER	-	Dominated	Dominated	Dominated
Cost of management of adverse events (-10%)				
Total cost (€)	279,445	282,775	295,674	282,676
QALY	14.89	14.75	14.54	14.54
Δ costs (€)	-	3,331	16,230	3,231
Δ QALY	-	-0.14	-0.35	-0.35
ICER	-	Dominated	Dominated	Dominated
Cost of management of adverse events (+10%)				
Total cost (€)	281,612	285,040	297,987	285,017
QALY	14.89	14.75	14.54	14.54
Δ costs (€)	-	3,428	16,375	3,405
Δ QALY	-	-0.14	-0.35	-0.35
ICER	-	Dominated	Dominated	Dominated
Alternative source for adherence				
Total cost (€)	281,421	283,664	296,782	283,737
QALY	14.90	14.74	14.54	14.54
Δ costs (€)	-	2,244	15,361	2,316
Δ QALY	-	-0.16	-0.36	-0.36
ICER	-	Dominated	Dominated	Dominated

Table XV. *Results of the sensitivity analysis on discount rate, cost of management of adverse events and adherence to treatment: cost and effectiveness increases were calculated compared to E/C/F/TAF*

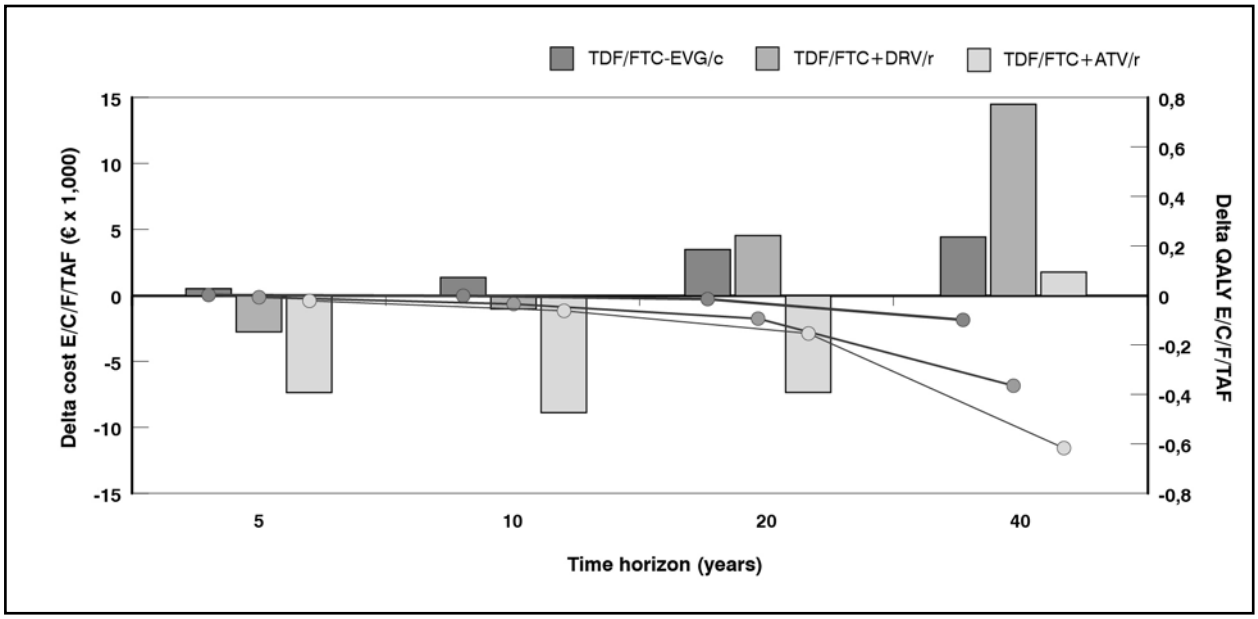

Figura 4. *Results of the sensitivity analysis for different assumptions of time horizon*

the Italian guidelines as a possible tool to simplify treatment, increase adherence to therapy and, consequently, improve the control of the disease.

ECF/TAF is therefore a viable alternative to other currently available treatments, combining the advantage of the STR with improved renal and bone safety than observed in regimens including TDF [24].

The drawback of the success of antiretroviral therapy is the substantial expenditure incurred for lifelong treatment, and the need to resort to second, third and subsequent lines of treatment in case of failure. It is therefore important, for healthcare professionals and decision-makers, to investigate the cost-effectiveness of the new treatment options.

This analysis was aimed at assessing the cost-effectiveness profile of E/C/F/TAF versus TDF/FTC-EVG/c , and versus regimens consisting of TDF/FTC plus boosted darunavir or atazanavir, which in recent years, in Italy, were the most commonly used ART regimens. The patient-level micro-simulation model developed was based on the available evidence derived from high-quality studies: comparative clinical inputs for the effectiveness and tolerability data of ART regimens, national epidemiological characteristics and healthcare profiles, and economic parameters relevant to the NHS and clinical expert opinion. The results indicate that ECF/TAF dominates the alternatives considered: namely, it is associated with better clinical outcomes and with a concomitant saving of resources. This result derives from the highly effective suppression of viral load, greater adherence, thanks also to the STR formulation, combined with improved safety and tolerability associated with TAF , the new component of this fixed-dose combination. This result is consistent with similar finding of a cost-effectiveness analysis performed in the UK setting [7] in which E/C/F/TAF resulted dominant compared to TDF/FTC-EVG/c (£ 192,082 vs £ 195,274 with +0.06 QALY).Therefore use of E/C/F/TAF is a sustainable and cost-saving treatment option that can help to provide a more effective and more efficient management of patients living with HIV.

DRUG NAME ABBREVIATIONS

- 3TC = lamivudine
- ABC = abacavir
- ATV = atazanavir
- DRV = darunavir
- DTG = dolutegravir
- E/C/F/TAF = Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide Fumarate
- EFV = efavirenz
- ETV = etravirine
- EVG = elvitegravir
- FTC = emtricitabine
- MVC = maraviroc
- RAL = raltegravir
- RPV = rilpivirine
- TAF = Tenofovir Alafenamide Fumarate
- TDF = Tenofovir Disoproxil Fumarate
- TDF/FTC-ATV/r = Tenofovir Disoproxil Fumarate/emtricitabine + atazanavir boosted with ritonavir
- TDF/FTC-DRV/r = Tenofovir Disoproxil Fumarate/emtricitabine + darunavir boosted with ritonavir
- TDF/FTC-EVG/c = Tenofovir Disoproxil Fumarate/emtricitabine/elvitegravir boosted with cobicistat
- /c = boosted with cobicistat
- /r = boosted with ritonavir

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Conflict of interest

LP is co-owner and employee of Adres, which has received project funding by Gilead Science Italy for the conduct of the study. LP is an editorial member of Farmeconomia. Health Economics and Therapeutic Pathways.
GDP and GR have received a consulting fee from AdRes, which has received project funding by Gilead Science Italy for the conduct of the study.
EM and SG are employees of Gilead Science Italy.
MP is employee of AdRes, which has received project funding by Gilead Science Italy for the conduct of the study.

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