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ORIGINALES

Cost-utility analysis of the fixed-dose combination of dolutegravir/abacavir/lamivudine as initial treatment of HIV+ patients in Spain

Análisis de coste-utilidad de la combinación a dosis fijas de dolutegravir/abacavir/lamivudina como tratamiento inicial de pacientes con VIH + en España

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Abstract

Objective: Fixed-dose combinations of antiretroviral drugs have meant an important step forward in simplifying treatment and improving compliance and has led to an increased effectiveness of therapy, a viral load decrease and improving the quality of life of patients.

The single-tablet formulation of dolutegravir with abacavir and lamivudine (DTG/ABC/3TC) is a highly efficacious and well-tolerated once-daily regimen for HIV-infected patients. The objective of the study was to assess the incremental cost-utility ratio of the fixed-dose combination of (DTG/ABC/3TC) versus the combinations emtricitabine/tenofovir/efavirenz (FTC/TDF/EFV), and darunavir/r (DRV/r) or raltegravir (RAL) with emtricitabine/tenofovir (FTC/TDF) or abacavir/lamivudine (ABC/3TC) as initial antiretroviral therapy in patients infected with HIV-1 from the perspective of the Spanish National Health System.

Method: The ARAMIS model, which uses a microsimulation approach to simulate the individual changes in each patient from the start of treatment to death through a Markov chain of descriptive health states of the disease, was adapted to Spain. The alternatives used for comparison were the fixed-dose combination of emtricitabine/tenofovir/efavirenz (FTC/TDF/EFV), and the fixed-dose combinations of emtricitabine/tenofovir (FTC/

Resumen

Objetivo: Las combinaciones a dosis fijas de medicamentos antirretrovirales han significado un importante paso adelante en la simplificación del tratamiento y la mejora del cumplimiento, así como hacia una mayor eficacia de la terapia, una disminución de la carga viral y una mejora de la calidad de vida de los pacientes.

La formulación de un comprimido único una vez al día con dosis fijas de dolutegravir, abacavir y lamivudina (DTG/ABC/3TC) para pacientes infectados con VIH es un régimen altamente eficaz y bien tolerado. El objetivo del estudio fue evaluar la relación coste-utilidad incremental de la combinación de dosis fija de (DTG/ABC/3TC) versus las combinaciones de emtricitabina/tenofovir/efavirenz (TDF/FTC/EFV) y darunavir/r (DRV/r) o raltegravir (RAL) con emtricitabina/tenofovir (FTC/TDF) o abacavir/lamivudina (ABC/3TC) como tratamiento antirretroviral inicial en pacientes infectados con VIH-1 desde la perspectiva del Sistema Nacional de Salud Español.

Método: Se adaptó en España el modelo ARAMIS. Este utiliza un enfoque de microsimulación para emular los cambios individuales en cada paciente desde el inicio del tratamiento hasta su muerte mediante una cadena de Markov de estados de salud descriptivos de la enfermedad. Las alternativas empleadas para la comparación fueron la combinación de dosis fijas de emtricitabina/tenofovir/efavirenz (TDF/FTC/EFV) y las combinaciones de dosis fijas de emtricitabina/tenofovir (FTC/TDF) o abacavir/lamivudina (ABC/3TC) con darunavir/r (DRV/r) o raltegravir (RAL). La

KEYWORDS

HIV treatment; Computer simulation; Cost-Utility analysis.

PALABRAS CLAVE

Tratamiento del VIH; Simulación por ordenador; Análisis coste-utilidad.



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TDF) or abacavir/lamivudine (ABC/3TC) with darunavir/r (DRV/r) or raltegravir (RAL). The probability of achieving virological suppression by the treatments included in the model was obtained from clinical trials SINGLE, SPRING-2 and FLAMINGO and the costs were expressed in € (2015). The model use the perspective of the Spanish National Health System, with a lifetime horizon and a discount rate of 3% was applied to cost and effectiveness.

Results: Treatment initiation with DTG/ABC/3TC was dominant when it was compared with treatment initiation with all the comparators: vs. FTC/TDF/EFV (-67 210.71€/QALY), vs. DRV/r + FTC/TDF or ABC/3TC (-1 787 341.44€/QALY), and vs. RAL + FTC/TDF or ABC/3TC (-1 005 117.13€/QALY). All the sensitivity analyses performed showed the consistency of these findings.

Conclusions: With the premises considered, treatment initiation with DTG/ABC/3TC STR appears to be the most cost-effective option in ART-naïve HIV infected patients from the Spanish Health System perspective.

Introduction

The natural history of infection by human immunodeficiency virus (HIV) is characterized by a progressive decrease of CD4+ cells and immune function, promoting the occurrence of infections and AIDS-defining malignancies. It is estimated that there are 36.7 million HIV-infected people worldwide and that 1.1 million deaths occur annually from the disease¹. In Spain, it affects about 148,785 people² and its estimated annual mortality is approximately 845 deaths per year³.

Since the introduction of highly active antiretroviral therapy (HAART) as a combination of three antiretroviral drugs, control and maintenance of the disease has been achieved in HIV-infected patients and morbidity and mortality have markedly decreased, converting HIV infection into a chronic disease⁴.

Although Spanish guidelines have been recommending an initial treatment including two nucleoside reverse transcriptase inhibitors (NRTIs) combined with an integrase inhibitor (INI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor boosted with ritonavir (PI/r), currently only INI-based regimens are preferentially recommended⁵.

Fixed-dose combinations of antiretroviral drugs have meant an important step forward in simplifying treatment and improving compliance. Better compliance has led to a lower risk of treatment errors and decreased resistance selection, which results in an increased effectiveness of therapy with the consequent decrease in viral load and improvement in quality of life of patients⁶.

Dolutegravir (DTG) is an integrase inhibitor whose clinical development has shown good tolerability and safety, a high barrier to resistance and a lack of relevant drug interactions. The single-tablet formulation with abacavir and lamivudine (DTG/ABC/3TC) obtained European approval in September 2014 and has been marketed in Spain since May 2015.

To assist in the inclusion of the drug on the formulary, the study objective was to assess the incremental cost-utility ratio (ICUR) in €/QALY of the fixed-dose combination of (DTG/ABC/3TC) versus the combinations Emtricitabine/Tenofovir/Efavirenz (FTC/TDF/EFV), and darunavir/r (DRV/r) or Raltegravir (RAL) with Emtricitabine/Tenofovir (FTC/TDF) or Abacavir/Lamivudine (ABC/3TC) as initial antiretroviral therapy in patients infected with HIV-1 from the perspective of the Spanish National Health System.

Methods

Description of the model

The study consisted of adaptation to Spain of the Anti-Retroviral Analysis by Monte Carlo Individual Simulation (ARAMIS) model^{7,8}, which uses a microsimulation approach to simulate the individual changes in each patient from the start of treatment to death through a chain of descriptive health states of the disease that are mutually exclusive (the patient can only be in one state). Thus, by including the behaviour of each individual generated with baseline characteristics of patients from clinical trials of DTG in naïve patients (SINGLE, FLAMINGO and SPRING-2 trials), the model is able to show the biological variability of the responses that may occur, which is an advantage over typical aggregate approaches such as the Markov models in which the aggregate variables only represent the behaviour of the population mean.

probabilidad de lograr la supresión virológica mediante los tratamientos incluidos en el modelo se ha obtenido de ensayos clínicos individuales, SPRING2 y FLAMINGO, y los costes fueron expresados en € (2015). El uso del modelo de la perspectiva del Sistema Nacional de Salud español, con un horizonte de vida útil y una tasa de descuento del 3% se, aplicó a coste y efectividad.

Resultados: El inicio de tratamiento con DTG/ABC/3TC fue dominante cuando se comparó con el inicio del tratamiento con el resto de comparadores: frente a TDF/FTC/EFV (-67.210,710 € / AVAC) vs DRV/r FTC/TDF o ABC/3TC (-1,787,341.44 € / AVAC) y vs RAL FTC/TDF o ABC/3TC (-1,005,117.13 € / AVAC). Todos los análisis de sensibilidad realizados demostraron la consistencia de estos hallazgos.

Conclusiones: Con las premisas consideradas, el inicio del tratamiento con la combinación a dosis fijas de DTG/ABC/3TC parece ser la opción más rentable para el tratamiento de pacientes infectados con el VIH desde la perspectiva del Sistema Nacional de Salud español.

The alternatives used for comparison were the fixed-dose combination of Emtricitabine/Tenofovir/Efavirenz (FTC/TDF/EFV), and the fixed-dose combinations of Emtricitabine/Tenofovir (FTC/TDF) or Abacavir/Lamivudine (ABC/3TC) with Darunavir/r (DRV/r) or Raltegravir (RAL). Thus was obtained the comparing of DTG/ABC/3TC versus standard treatments with NRTIs, INI and a PI/r as a third agent.

As shown in figure 1, the model defined the following health states: HIV infection without chronic disease as first-line treatment, HIV infection without chronic disease as second-line or subsequent treatment, HIV infection for chronic disease non-related to AIDS (second-line or subsequent treatment), opportunistic disease (viral, bacterial, fungal, protozoan or other), adverse event to the treatment and death (absorbing state).

Each month throughout the simulation and depending on the treatment received, the changes in patient characteristics are determined and if these changes cause the individual to remain in the initial state or change to a new one. These changes are determined by the probability of disease progression, occurrence of opportunistic infections and/or adverse effects, and occurrence of long-term chronic diseases and death. All these probabilities are determined by the CD4+ count the patient has at the start of each cycle.

Thus, depending on the treatment received, the individual will show a given probability of achieving viral suppression (defined as viral load suppression below 50 copies/mL at 48 weeks). This leads to an increase in the CD4+ count that is more marked in the first two months of treatment but which is maintained if viral suppression persists, reaching a maximum values of 1,200 cells/ μ L. If virological suppression is not achieved with treatment initially, or if it is lost subsequently, the individual moves on the next line of treatment and so on. Once treatment options have been exhausted, the individual experiences a decrease in the CD4+ count as described in previously published models⁹.

The model includes nine categories of adverse events that individuals may experience during treatment (diarrhoea, nausea, dizziness, vomiting, rash, sleep disturbances, insomnia, depression and other). The probability of experiencing these events in grade 2 or higher and of discontinuing treatment due to the events was obtained from their clinical trials.

The occurrence of opportunistic infections was modelled as a probability dependent on the CD4+ count as described in the literature⁷.

Cardiovascular disease was modelled as a monthly risk determined by a Framingham equation¹⁰ for prediction of coronary heart disease and stroke.

In addition to mortalities due to opportunistic infections and cardiovascular diseases, all-cause mortality and HIV mortality were modelled based on Spanish data from interactive consultation of the National Health System Statistical Portal¹¹.

Thus, at the end of each cycle, a specific effectiveness is obtained and the corresponding allocation of costs generated in the period. These are cumulative throughout the life of each simulated individual and finally allow for obtaining the incremental cost-effectiveness ratio (ICER) of DTG/ABC/3TC versus other treatment options using the formula:

$$\text{ICER} = \frac{(\text{Cost Triumeq} - \text{Cost alternative})}{(\text{Effectiveness Triumeq} - \text{Effectiveness alternative})}$$

The model was developed in Microsoft Excel 2007 and Microsoft Visual Basic for Applications as embedded code. The results shown corres-

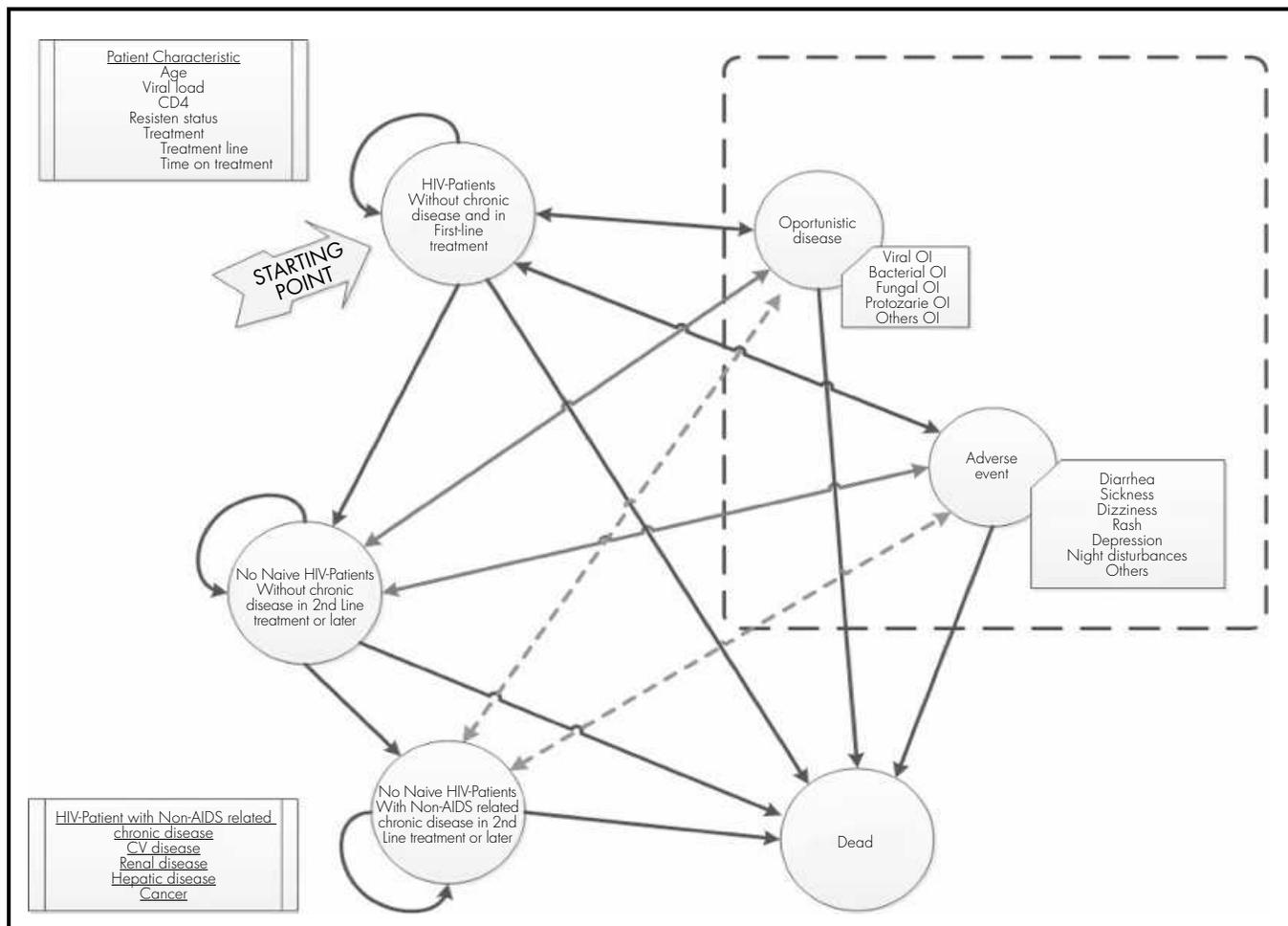


Figure 1. Patient flow

pond to 1 million simulated individuals, from the perspective of the Spanish national health system. The base case was performed for a time horizon of the patient’s whole lifetime and applying a discount rate of 3%.

Model parameters

Study population

Initially patients were described with demographic variables (age, sex), disease defining parameters (plasma viral load, CD4+ cell count), and co-variables used for measuring cardiovascular risk in the Framingham equation

(systolic pressure, total cholesterol, high-density lipoprotein [HDL] cholesterol, history of smoking, diabetes and left ventricular hypertrophy).

Table 1 shows a summary of the baseline characteristics used in the model. These were obtained from patients participating in the SINGLE, SPRING-2 and FLAMINGO clinical trials of DTG in treatment-naive patients.

Treatment algorithms

As shown in figure 2, an expert panel determined the four treatment algorithms, one for each initial treatment. The choice of treatment in the

Table 1. Baseline characteristics of the patients included in the model

Characteristic	SINGLE (n= 833)	SPRING-2 (n= 822)	FLAMINGO (n= 484)	Cohort model (n= 2.139)
Age (mean)	36.4	37.0	36.0	36.5
Sex – women (%)	15.6	14.5	14.9	15.0
HIV-1 RNA (log ₁₀ copies/mL) (mean)	4.7	4.6	4.50	4.59
CD4 + count (cells/μL) (mean)	350	377	412	374
Total cholesterol (mmol/L) (mean)	4.12	4.16	4.13	4.13
HDL (mmol/L) (mean)	1.12	1.14	1.13	1.13
Systolic blood pressure (mm Hg) (mean)	122.71	123.08	123.32	122.99
Diabetes (%)	4.9	3.5	2.7	3.88
History of smoking (%)	52.8	58.6	60.3	56.76
Left ventricle hypertrophy (%)	0.5	0.1	0.2	0.28

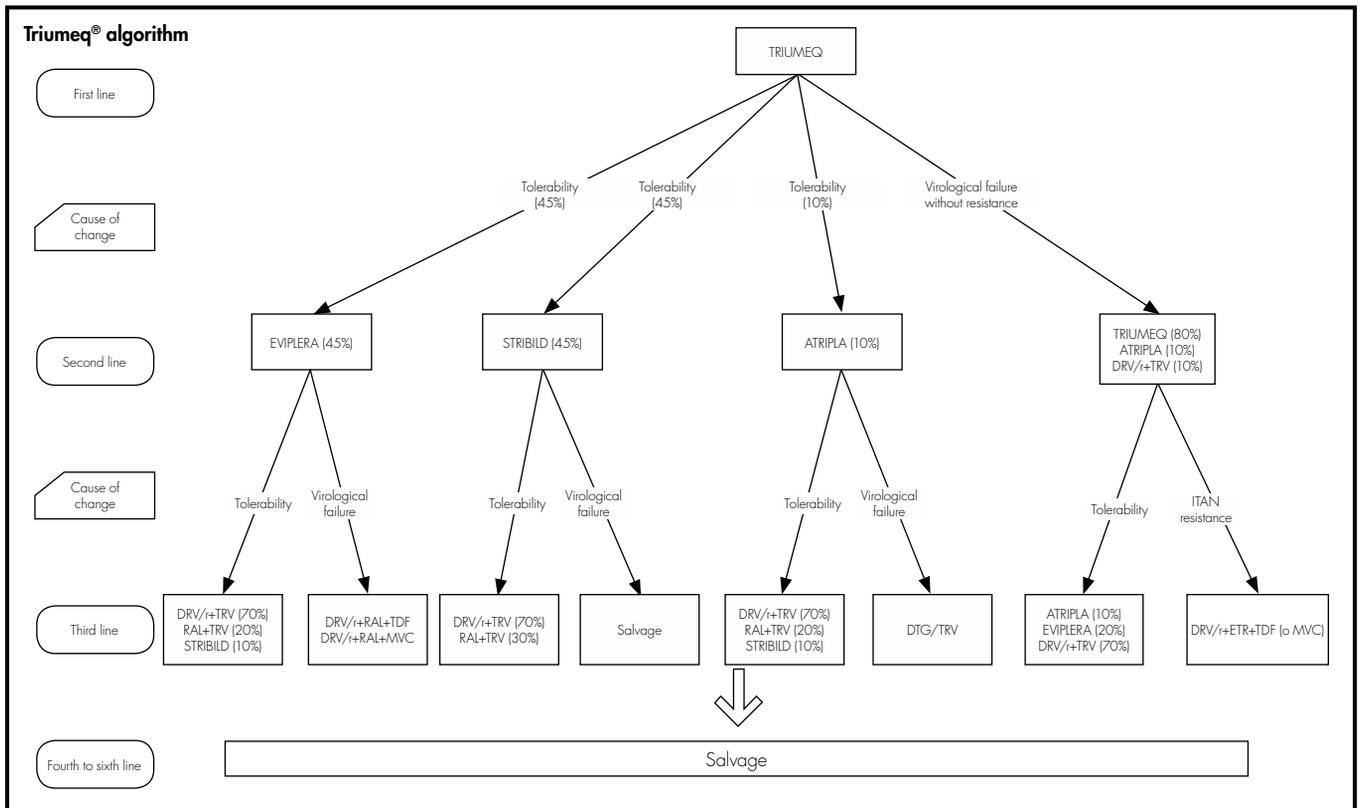


Figure 2a. Treatment algorithms

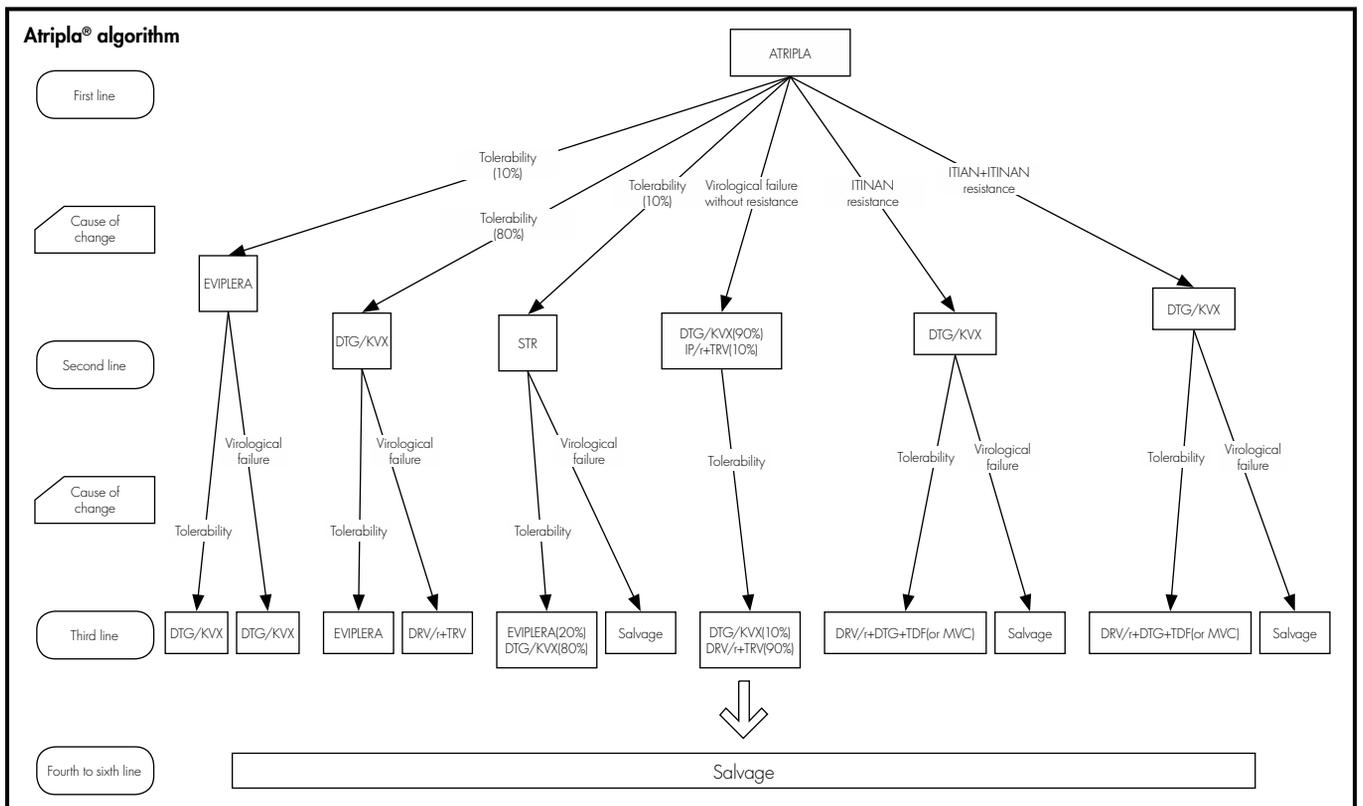


Figure 2b. Treatment algorithms

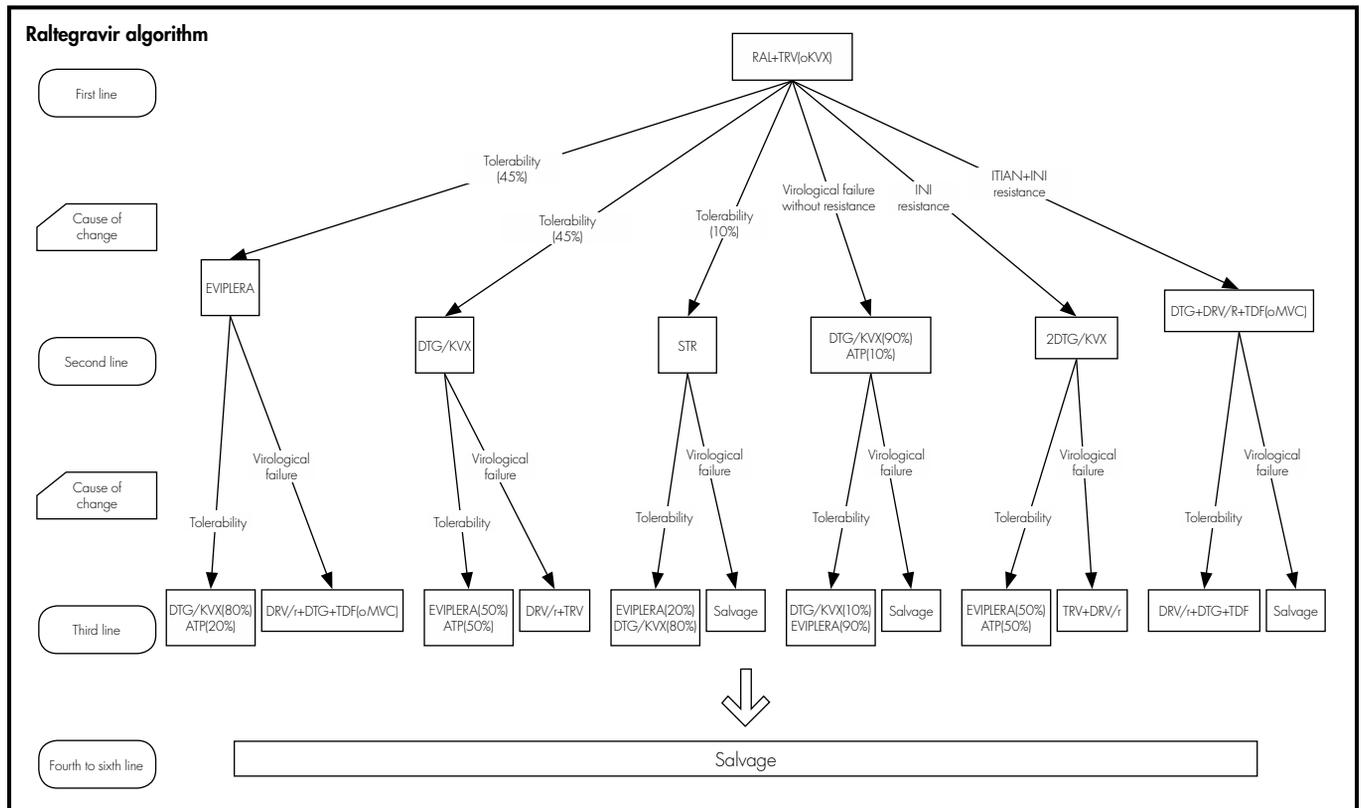


Figure 2c. Treatment algorithms

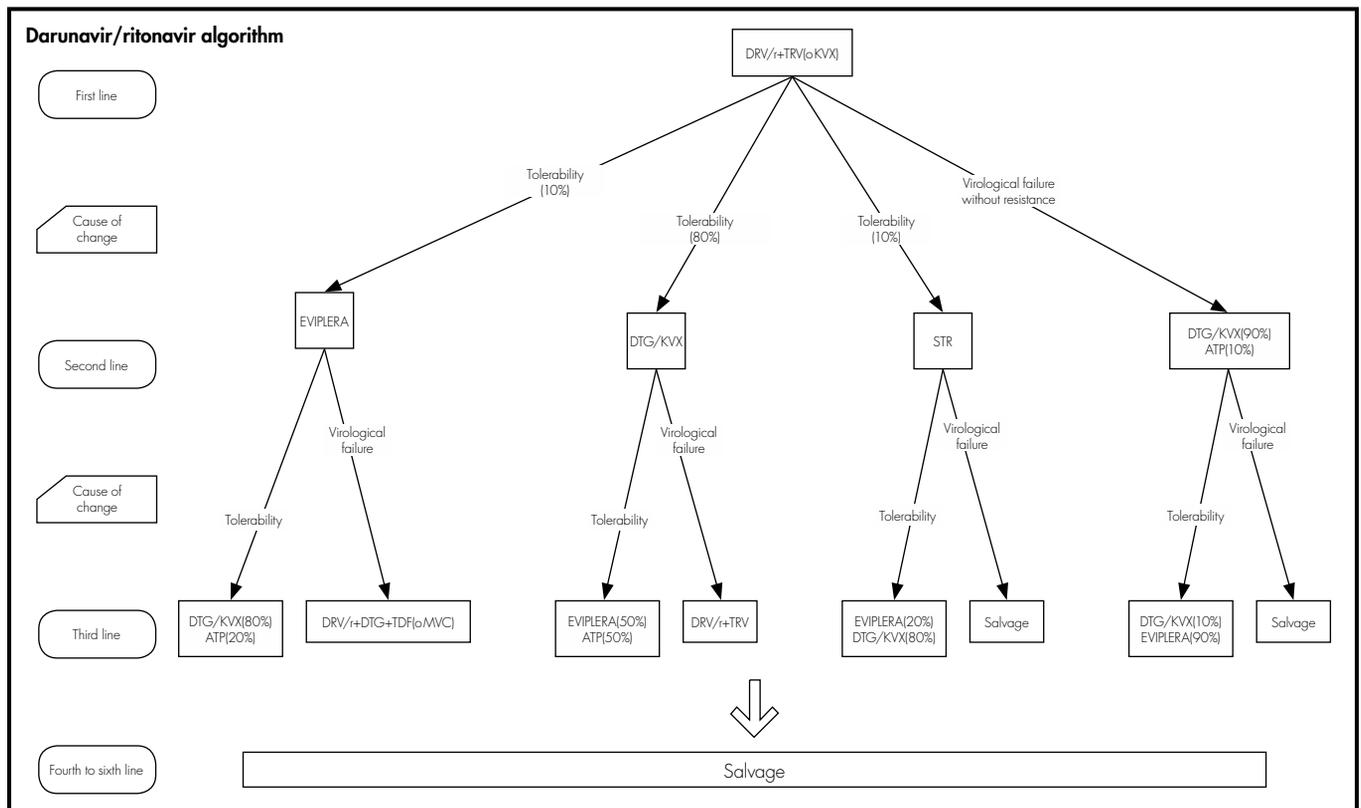


Figure 2d. Treatment algorithms

second and subsequent lines was made attempting to prevent problems of tolerability and resistance that could compromise efficacy. The model took into account resistance to NRTIs, NNRTIs, and INI.

Estimation of effectiveness

The probability of achieving virological suppression by the treatments included in the model was obtained from clinical trials comparing DTG/ABC/3TC versus the other alternatives, SINGLE trial for FTC/TDF/EFV^{12,13}, SPRING-2 trial^{14,15} for RAL + (FTC/TDF) or + (ABC/3TC) and FLAMINGO trial^{16,17} for DRV/r + (FTC/TDF) or + (ABC/3TC). Based on their clinical practice, the expert panel considered that the proportions for applying FTC/TDF and ABC/3TC in these two alternatives are 80 and 20, respectively. Since there are no direct trials of DTG/ABC/3TC versus Rilpivirine/Emtricitabine/Tenofovir (RPV/FTC/TDF) and Emtricitabine/Tenofovir/ Elvitegravir/Cobicistat (FTC/TDF/EVG/cob), the results used for comparison of these regimens were obtained by a network meta-analysis¹⁸. The evidence used for showing the long-term efficacy of all treatments was the STARTMRK trial^{19,20} and assumptions validated by the expert panel.

The efficacy of treatment alternatives was measured as life years gained (LYG) and quality-adjusted life years (QALYs) by applying the corresponding utilities associated with CD4+ level, having an opportunistic infection and its sequelae, having an adverse event and those associated with chronic diseases not related to AIDS. These utilities shown in table 2 were obtained from the literature^{7,21-24}.

While quality of life stratified by CD4 was calculated in each cycle in which the patient was in the health state, in the case of opportunistic infections, it was calculated in three cycles, assuming that this opportunistic infection had a duration of three months. The effect of adverse events was

Table 2. Utilities used in the model

Item	Utility Value	Source
CD4+ level		
> 500	0.946	Simpson 2004 ⁽²⁷⁾
350-500	0.933	
200-350	0.931	
100-200	0.853	
50-100	0.853	
0-50	0.781	
Opportunistic infection		
Bacterial	0.561	Paltiel 1998 ⁽²⁶⁾
Fungal	0.652	
Protozoan	0.561	
Viral	0.652	
Other	0.561	
Chronic disease not related to AIDS		
Cardiovascular disease	0.902	Brown 2010 ⁽²⁵⁾
Adverse events (disutilities)		
AE grade ≥ 2	- 0.012	Elvira Martínez 2005 ⁽²³⁾
Diarrhoea	- 0.009	
Nausea	- 0.008	
Vomiting	- 0.005	
Rash	- 0.01	
Sleep disturbances	- 0.019	
Dizziness/Vertigo	- 0.033	
Depression	- 0.054	
Insomnia	0	
Other AE	- 0.012	

applied in the cycle in which they occurred, except for cases of depression, whose disutility was imputed over a period of three cycles (3 months).

Resources and costs

As the model uses the perspective of the Spanish National Health System, only direct health care costs expressed in € (2015) were considered.

Thus, standard patient care costs were considered such as those derived from medical visits, diagnostic tests, management of adverse events, care of chronic diseases and drug costs of antiretroviral therapy and prophylaxis and treatment of opportunistic infections.

Table 3 shows the costs attributable to each event and health state from the official rates and were calculated from the clinical trial protocols and stratified by CD4+ levels²². The costs of diagnostic tests come from the rates of the Instituto de Salud Carlos III. The costs derived from treatment of adverse events for Spain were obtained from the literature²⁵ and the costs derived from the prophylaxis and treatment of opportunistic infections from the BotPlus-Portsalharma database 2.0 of the General Council of Offi-

TABLE 3. Monthly costs

Item	Cost (€ 2015)	Source
Routine patient care according to CD4+ level		
> 500	132.91	Brown 2010 ⁽²⁵⁾
350-500	196.39	
201-350	723.77	
101-200	990.45	
51-100	990.45	
0-50	2,550.89	
Treatment of opportunistic infection		
Bacterial	2,557	Elvira Martínez 2005 ⁽²³⁾
Fungal	287	
Protozoan	1,905	
Viral	3,512	
Other	7,067	
Prophylaxis of opportunistic infection		
CMV	1.07	GESIDA 2008 ⁽²⁹⁾
PCP	197.11	
Visit cost		
Outpatient clinic	72.60	Mean autonomous community rates (*)
Diagnostic tests		
Tropism (Maraviroc)	106.00	ISCarlosIII rates (*)
Genotype	93.00	
CD4	40.00	
Viral load	50.00	
HLA-B5701 (ABC/3TC)	18.95	Hospital San Cecilio Granada 2012 (*)
Treatment of adverse events		
Diarrhoea	37.61	Brown 2007 ⁽²⁸⁾
Nausea	9.10	
Vomiting	26.24	
Rash	0.00	
Sleep disturbances	0.00	
Other	334.86	

(*) Costs updated to 2015. CMV, cytomegalovirus; PCP, pneumonia by *Pneumocystis jirovecii*; ABC, abacavir; 3TC, lamivudine.

cial Pharmacists Associations (<https://botplusweb.portalfarma.com>)^{21,26}. The drug acquisition costs of the different antiretroviral therapies by the National Health System were obtained from the SESCAM²⁷.

Sensitivity analysis

In order to assess the consistency of the model and the effect on its results of the relative efficacy of DTG/ABC/3TC versus its alternatives, the time horizon and discount rate applied, as recommended by the proposed Spanish guidelines for economic evaluation²⁸, the following sensitivity analyses were performed:

Model using a time horizon of 5 and 10 years.

Application of higher relative and lower efficacy using the maximum and minimum values of the confidence intervals of clinical trials^{21,17}.

Model without application of a discount rate and using a rate of 5%.

Results

Base case

Of all the initial treatment regimens studied, DTG/ABC/3TC was the dominant combination by achieving greater effectiveness at a lower cost (Table 4). The incremental cost-effectiveness plane is shown in figure 3. Table 5 shows the duration and average monthly cost of each strategy evaluated.

Sensitivity analysis

Table 6 presents the results of the comparisons used in sensitivity analyses. In these comparisons, DTG/ABC/3TC was the dominant combination (representing a lower cost and greater effectiveness) in all cases versus FTC/TDF/EFV.

Identical behaviour was shown in the comparison with RAL + (FTC/TDF) or + (ABC/3TC), except in cases of without discounting in which DTG/ABC/3TC represented a saving of 24,415.86 € for a lower effectiveness of 0.0396 QALYs, and when the lower limit of efficacy was considered for DTG/ABC/3TC, a saving of 19,454.97 € for a lower effectiveness of 0.0511 QALYs. In both cases, the strategy was found to be cost-effective.

Similar results occurred with DRV/r + (FTC/TDF) or + (ABC/3TC), which were shown to be cost-effective in the non-discounted analyses (saving of 9,646.16 € and lower efficacy of 0.036 QALYs) and in the lower limit of

Table 4. Cost-effectiveness results of comparisons analyzed

Comparison DTG/ABC/3TC vs. EFV/FTC/TDF		
Therapy	Effectiveness (QALYs)	Cost (€)
DTG/ABC/3TC	18.0026	237,363.44
EFV/FTC/TDF	17.6986	257,795.31
ICER (€/QALY)	-67,210.71	
Comparison DTG/ABC/3TC vs. RAL + (FTC/TDF) or + (ABC/3TC)		
Therapy	Effectiveness (QALYs)	Cost (€)
DTG/ABC/3TC	18.0058	234,470.45
RAL + (FTC/TDF) or + (ABC/3TC)	17.9846	255,754.37
ICER (€/QALY)	-1,005,117.13	
Comparison DTG/ABC/3TC vs. DRV/r + (FTC/TDF) or + (ABC/3TC)		
Therapy	Effectiveness (QALYs)	Cost (€)
DTG/ABC/3TC	18.0269	235,376.30
DRV/r + (FTC/TDF) or + (ABC/3TC)	18.0205	246,767.62
ICER (€/QALY)	-1,787,341.44	

QALYs, Quality-Adjusted Life Year; ICER, Incremental Cost-Effectiveness Ratio.

efficacy of DTG/ABC/3TC (saving of 8,698.67 € and lower efficacy of 0.049 QALYs). In the rest of the cases, DTG/ABC/3TC was shown to be the dominant alternative.

Discussion

Since the introduction of HAART, control and maintenance of HIV infection has been achieved, decreasing its morbidity and reducing costs associated with its medical care. However, the increased survival produced causes costs of treatment and patient care to occur over a much longer time

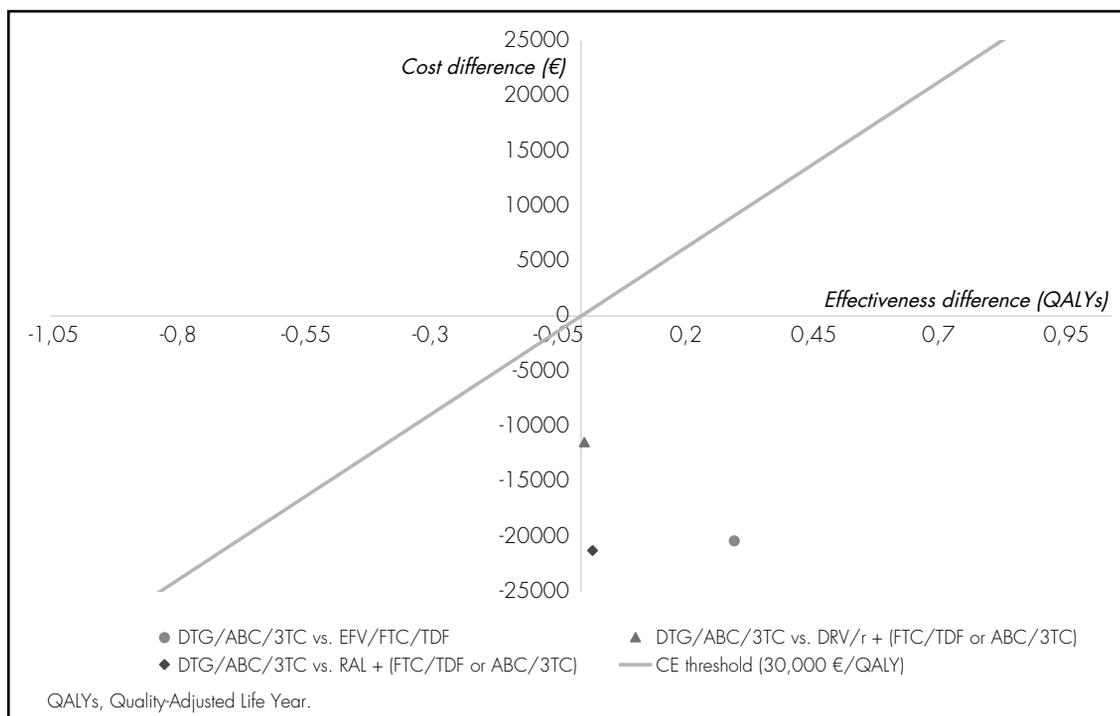


FIGURE 3. Incremental cost-effectiveness plane.

Table 5. Duration and average monthly cost per treatment line

		DTG/ABC/3TC	EFV/FTC/TDF	RAL+ (FTC/TDF) or (ABC/3TC)	DRV/r+ (FTC/TDF) or (ABC/3TC)
1L	Months	126	105	124	122
	Cost	595.38€	586.19€	754.75€	718.28€
2L	Months	93	69	92	99
	Cost	458.52€	590.71€	542.53€	530.70€
3L	Months	39	54	54	55
	Cost	541.39€	623.50€	466.71€	457.24€
4L	Months	12	25	13	11
	Cost	928.35€	937.06€	913.29€	903.08€
5L	Months	36	74	39	30
	Cost	810.23€	888.25€	828.07€	807.14€
6L	Months	77	45	61	67
	Cost	726.18€	743.24€	715.41€	711.34€

L, treatment line.

period, normally causing overall costs to become larger than other treatment alternatives and making it necessary to evaluate its cost-effectiveness.

The ARAMIS model used for this adaptation has been verified and previously used in several studies⁷⁸. This is the first research that uses microsimulation to assess the cost-utility of a VIH fixed dose combination in Spain. The stochastic approach used in this study enabled us to show the biological variability and to determine that the fixed-dose combination DTG/ABC/3TC

is the most efficient alternative among the initial treatment regimens evaluated. It was to be the dominant strategy in the comparisons considered as the base case and in 14 of 18 sensitivity analyses, and was cost-effective in the remaining four.

This greater efficiency is determined by the savings derived from starting treatment with DTG/ABC/3TC and because this alternative was the most efficient in all cases, except in the sensitivity analyses without discounting

Table 6. Results of sensitivity analyses

Sensitivity analysis	Increases		ICER (€/QALY)	RESULT
	Cost (€)	QALYs		
Comparison DTG/ABC/3TC vs. EFV/FTC/TDF				
Horizon 5 years	-2,248.61	0.009224	-243,786.29	Dominant
Horizon 10 years	-6,886.16	0.015022	-458,403.99	Dominant
Maximum efficacy threshold	-21,677.90	0.332017	-65,291.52	Dominant
Minimum efficacy threshold	-18,038.80	0.230343	-78,312.71	Dominant
Discount 0%	-27,023.63	0.939241	-28,771.77	Dominant
Discount 5%	-16,323.15	0.15629	-104,441.31	Dominant
Comparison DTG/ABC/3TC vs. RAL+ (FTC/TDF) or + (ABC/3TC)				
Horizon 5 years	-10,291.40	0.000985	-10,450,123.22	Dominant
Horizon 10 years	-16,824.92	0.004571	-3,680,909.56	Dominant
Maximum efficacy threshold	-22,928.71	0.02417	-948,625.45	Dominant
Minimum efficacy threshold	-19,454.97	-0.04917	395,668.21	Cost-effective
Discount 0%	-24,415.86	-0.03634	671,837.48	Cost-effective
Discount 5%	-19,266.14	0.018724	-1,028,979.77	Dominant
Comparison DTG/ABC/3TC vs. DRV/r+ (FTC/TDF) or + (ABC/3TC)				
Horizon 5 years	-7,474.85	0.004915	-1,520,681.62	Dominant
Horizon 10 years	-11,731.11	0.005504	-2,131,418.50	Dominant
Maximum efficacy threshold	-12,979.35	0.072724	-178,473.05	Dominant
Minimum efficacy threshold	-8,698.67	-0.04312	201,716.49	Cost-effective
Discount 0%	-9,646.16	-0.03124	308,794.36	Cost-effective
Discount 5%	-11,248.35	0.008914	-1,261,845.60	Dominant

and using the lower efficacy level of the trials with dolutegravir (DTG) when compared to the alternatives RAL and DRV. In these cases, the lower efficacy of the alternative to starting with DTG/ABC/3TC was shown to be marginal with values between -0.04 and 0.03 QALYs, which over the lifetime of the patient are equivalent to a lifetime benefit of between 10 days and two weeks. This marginality of the unprovided benefit causes the savings produced to make the alternative appear cost-effective with respect to the compared alternatives.

This effectiveness is consistent with the proposed treatment algorithms since all alternatives are favoured by having treatments including DTG in subsequent lines. Thus, the effectiveness shown in the first lines of treatments is consistent with the efficacy results of the comparative clinical trials of the treatments evaluated²¹⁷. And this dominance is consistent with the results of previous research comparing DTG with ABC/3TC or FTC/TDF in Canada²⁹.

As shown in Table 5, this efficiency of the first lines of the alternative to starting with DTG/ABC/3TC is boosted by a lower mean monthly cost of treatment than the other compared strategies. Furthermore, it can be seen how other alternatives are benefited by the use of DTG/ABC/3TC in the second lines of treatment.

Although the model has limitations due to the lack of data on the efficacy of subsequent treatment lines and the costs derived from visits in actual clinical practice, these have been treated conservatively. Thus,

the high efficacy applied to treatments after the first failure will mean that patients continue with high CD4+ levels. Hence, the benefit of postponing the change of initial treatment shown in the alternative to starting with DTG/ABC/3TC is masked by the effect of subsequent lines. With regard to the case to imputing only protocol visits, this is also a consequence of a conservative approach because it does not consider unexpected visits occurring in actual clinical practice as a result of adverse effects and interactions, regardless of whether or not it involves discontinuation. It is considered that this assumption could penalize the strategy of starting with DTG/ABC/3TC since its safety profile, tolerability and interactions suggests that this treatment generates a lower number of these visits, which leads to underestimating the costs attributable to the other compared strategies. Finally, another limitation has been that the study has not taken into account the subsequent introduction of the generic ABC/3TC.

Cost-utility analyses of these alternatives based on real World data of their clinical effectiveness and associated resource consumption will be recommended in the future.

Since the results obtained with this model are favourable to the strategy of starting with DTG/ABC/3TC, it may be concluded that, this is the most efficient option of the alternatives evaluated for the Spanish National Health System. This result could assist informed decision-making about inclusion of the fixed-dose combination DTG/ABC/3TC into the hospital formularies.

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