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Original article

Costs and cost-efficacy analysis of the 2014 GESIDA/Spanish National AIDS Plan recommended guidelines for initial antiretroviral therapy in HIV-infected adults

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ABSTRACT

Introduction: GESIDA and the National AIDS Plan panel of experts suggest preferred (PR) and alternative (AR) regimens of antiretroviral treatment (ART) as initial therapy in HIV-infected patients for 2014. The objective of this study is to evaluate the costs and the efficiency of initiating treatment with these regimens.

Methods: An economic assessment was made of costs and efficiency (cost/efficacy) based on decision tree analyses. Efficacy was defined as the probability of reporting a viral load <50 copies/mL at week 48, in an intention-to-treat analysis. Cost of initiating treatment with an ART regimen was defined as the costs of ART and its consequences (adverse effects, changes of ART regimen, and drug resistance studies) during the first 48 weeks. The payer perspective (National Health System) was applied by considering only differential direct costs: ART (official prices), management of adverse effects, studies of resistance, and HLA B*5701 testing. The setting is Spain and costs correspond to those of 2014. A sensitivity deterministic analysis was conducted, building three scenarios for each regimen: base case, most favourable and least favourable.

Results: In the base case scenario, the cost of initiating treatment ranges from 5133 Euros for ABC/3TC + EFV to 11,949 Euros for TDF/FTC + RAL. The efficacy varies between 0.66 for ABC/3TC + LPV/r and ABC/3TC + ATV/r, and 0.89 for TDF/FTC/EVG/COBI. Efficiency, in terms of cost/efficacy, ranges from 7546 to 13,802 Euros per responder at 48 weeks, for ABC/3TC + EFV and TDF/FTC + RAL respectively.

Conclusion: Considering ART official prices, the most efficient regimen was ABC/3TC + EFV (AR), followed by the non-nucleoside containing PR (TDF/FTC/RPV and TDF/FTC/EFV). The sensitivity analysis confirms the robustness of these findings.

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Análisis de costes y de coste/eficacia de las pautas recomendadas por GESIDA/Plan Nacional sobre el Sida en 2014 para el tratamiento antirretroviral inicial en adultos infectados por el VIH

Palabras clave:
Costes
Eficacia
Eficiencia
VIH
Sida
Antirretrovirales
Tratamiento

R E S U M E N

Introducción: El panel de expertos de GESIDA/Plan Nacional del Sida ha recomendado pautas preferentes (PP) y alternativas (PA) de tratamiento antirretroviral (TARV) como terapia de inicio en pacientes infectados por VIH para 2014. El objetivo de este estudio es evaluar los costes y la eficiencia de iniciar tratamiento con estas pautas.
Métodos: Evaluación económica de costes y eficiencia (coste/eficacia) mediante construcción de árboles de decisión. Se definió eficacia como la probabilidad de tener carga viral <50 copias/mL en la semana 48 en análisis por intención de tratar. Se definió coste de iniciar tratamiento con una pauta como los costes del TARV y de todas sus consecuencias (efectos adversos, cambios de pauta y estudio de resistencias) que se producen en las siguientes 48 semanas. Se utilizó la perspectiva del Sistema Nacional de Salud, considerando sólo costes directos diferenciales: fármacos (a precio oficial), manejo de efectos adversos, estudios de resistencias y determinación de HLA B*5701. El ámbito es España, con costes de 2014. Se realizó análisis de sensibilidad determinista construyendo tres escenarios para cada pauta: basal, más favorable y más desfavorable.
Resultados: En el escenario basal, los costes de iniciar tratamiento oscilaron entre 5.133 euros para ABC/3TC + EFV y 11.949 euros para TDF/FTC + RAL. La eficacia osciló entre 0,66 para ABC/3TC + LPV/r y ABC/3TC + ATV/r, y 0,89 para TDF/FTC/EVG/COBI. La eficiencia, en términos de coste/eficacia, osciló entre 7.546 y 13.802 euros por respondedor a las 48 semanas, para ABC/3TC + EFV y TDF/FTC + RAL, respectivamente.
Conclusión: Considerando el precio oficial del TARV, la pauta más eficiente fue ABC/3TC + EFV (PA), seguida de las PP que contienen no nucleósidos (TDF/FTC/RPV y TDF/FTC/EFV). El análisis de sensibilidad confirmó la robustez de estos hallazgos.

Introduction

Antiretroviral treatment (ART) has drastically reduced human immunodeficiency virus (HIV)-related morbidity/mortality. In fact, ART has changed the disease's natural course,[1,2] and has made it possible for patients' life expectancy to approach that of the general population.[3,4] ART is usually based on a three-drug approach with the goal of lowering the plasma viral load to undetectable levels, i.e., below a threshold of less than 50 copies/mL, and keep it suppressed as long as possible. In most cases, current ART regimens lead to a partial restoration of the immune system, both in quantity and quality, depending in part on the degree of baseline immunodeficiency levels.[5–8] Thus, as a whole, ART is considered one of the top medical interventions in medical history in terms of cost/efficacy ratios, including developing countries.[9–16]

Expert panels from the AIDS Study Group (GESIDA for its Spanish acronym) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC for its Spanish acronym) and the (Spanish) AIDS National Plan (PNS for its Spanish acronym) have issued their 2014 treatment guidelines. Their recommendations include several preferred (PR) and alternative regimens (AR) supported by randomized clinical trials (RCT) and the expert panel's opinion.[17] However, in the context of limited resources any therapeutic intervention must be applied efficiently. Thus, both costs incurred and the results obtained by the different ART must be examined to identify the most efficient regimens within those recommended by the GESIDA/PNS guidelines as PR or AR. Evidently, in addition to the drugs, there are other costs to consider including those incurred while managing adverse effects (AE) or the costs of drug-resistance studies, among others. Studies published between 2011 and 2013 evaluated the efficiency of ART preferred regimens according to GESIDA/PNS.[18–20] Regimens recommended for 2014 as PR differ from those recommended in 2013 and the recommendations now include AR in the list. In addition, new scientific evidence and substantial changes in costs very likely rendered the 2013 study results obsolete.[20]

Consequently, the need for this new cost evaluation arose. The purpose of this study is to evaluate the costs and the efficiency (cost/efficacy) of the ART regimens proposed by the GESIDA/PNS 2014 guidelines as recommended initial therapies for HIV-infected patients who have not received previous ART, i.e., treatment-naïve patients.

Methods

The first step was to form a scientific committee (SC) of 18 Spanish experts identified by GESIDA (this paper's authors except AJB and PL) with experience in the clinical management of HIV-infected patients. SC's tasks included providing general advice, validating the assumptions made as part of the economic evaluation, supplying the RCT studies used as scientific evidence, and providing expert opinion when the scientific evidence was insufficient.

Design

The design is an economic assessment of the costs and efficiency (cost/efficacy) by building decision trees with deterministic sensitivity analysis. The decision trees were built for the calculation of costs, efficacy, and efficiency for each of the PR and AR recommended by GESIDA/PNS (Table 1). The analysis is performed from the payer's perspective: the Spanish National Health System (NHS) and, thus, only direct costs are considered. The setting is Spain and the model's time horizon is 48 weeks. This is a cost and cost/efficacy study because ART outcomes are based on CT findings (efficacy).

Models of economic evaluation

The model of economic analysis consists of as many decision trees as recommended regimens there are. Each decision tree is built based on the data from the CT assessing the corresponding regimen and it reproduces the regimen's characteristics in terms of efficacy, AE, and reasons for withdrawal (Table 1 and Fig. 1).

Table 1
Regimens included in the evaluation, clinical trials used in the models, and regimen costs.

Regimen	Dose (mg/day)	Trials	Cost[a] (Euros)
TDF/FTC/EFV (PR)	300/200/600	STARTMRK[23], GS-934[24], ECHO[33], ACTG 5202[37], GS-US-236-0102[38], SINGLE[41], STAR[44,45]	6515
ABC/3TC + EFV (AR)	600/300 + 600	CNA30024[32], ACTG 5202[37]	5015[b]
TDF/FTC/RPV (PR)	245/200/25	ECHO[33], STAR[44,45]	6765
TDF/FTC + NVP (AR)	300/200 + 400	ARTEN[27], VERxVE[35]	6513[c]
TDF/FTC + ATV/r (PR)	300/200 + 300/100	CASTLE[26], ARTEN[27], ACTG 5202[37], GS-US-236-0103[39], GS-US-216-0114[40]	9469
TDF/FTC + DRV/r (PR)	300/200 + 800/100	ARTEMIS[23], FLAMINGO[46]	9368
TDF/FTC + LPV/r (AR)	300/200 + 800/200	ARTEMIS[25], ABT730[28], CASTLE[26], GEMINI[29], HEAT[30], PROGRESS[36]	8833
ABC/3TC + ATV/r (PR)	600/300 + 300/100	ACTG 5202[37]	8109
ABC/3TC + DRV/r (AR)	600/300 + 800/100	FLAMINGO[46]	8008
ABC/3TC + LPV/r (AR)	600/300 + 800/200	KLEAN[31], HEAT[30]	7473
TDF/FTC + RAL (PR)	300/200 + 800	STARTMRK[23], QDMRK[d,34] SPRING-2[42,43]	11,957
ABC/3TC + RAL (PR)	600/300 + 800	SPRING-2[42,43]	10,597
TDF/FTC/EVG/COBI (PR)	245/200/150/150	GS-US-236-0102[38], GS-US-236-0103[39]	9072

ABC: abacavir; ATV: atazanavir; COBI: cobicistat; DRV: darunavir; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; LPV: lopinavir; NVP: nevirapine; /r: ritonavir-boosted; RAL: raltegravir; RPV: rilpivirine; TDF: tenofovir DF; 3TC: lamivudine.
PR: Regimen designated as "Preferred" by the expert panel of GESIDA and the 2014 AIDS National Plan.[17]
AR: Regimen designated as "Alternative" by the expert panel of GESIDA and the 2014 AIDS National Plan.[17]
[a] Cost at 48 weeks, laboratory sale price (LSP) plus 4% VAT minus the 7.5% obligatory reduction, based on the combinations Atripla®, Truvada®, Kivexa®, Eviplera® and Stribild®.[17]
[b] Using the price of generic EFV.
[c] Using the price of Viramune®, extended-release NVP.
[d] Considering only the arm where patients are treated with 400 mg of RAL every 12 h.

Sources providing data on efficacy, AE, and withdrawals

The SC provided the studies reporting the CT data potentially useful for the economic evaluation models of the different regimens under evaluation. To be included in the study RCTs had to: (1) assess at least one of the regimens under evaluation; (2) provide or allow the calculation of the proportion of patients with undetectable viral loads (<50 copies/mL) at 48 weeks; (3) follow patients for at least 48 weeks; (4) report patient withdrawal rates and reasons; and (5) report AE. CT studies provided by the SC were reviewed for inclusion by two investigators (PL and AJB) independently. Differences were resolved by consensus. Studies found eligible were included as source of scientific evidence for the evaluation model. Study inclusions and exclusions were reviewed and validated by the SC.

Sources of information in the absence of scientific evidence: the use of expert opinion

When scientific evidence on certain variables in the evaluation model was not available, the SC expert opinion was used. Two investigators (PL and AJB) composed data collection sheets for the variables of interest. These sheets were then sent to each expert.

To insure the experts' responses were independent from each other, contact among SC members was not allowed. Regarding continuous variables (e.g., duration in days of an itching episode, or number of visits to a specialist in case of renal failure), the mean of the experts' estimates was calculated. For dichotomous variables (e.g., regarding serious/moderate AE, etc. is it ART-related vs. not, or is it chronic vs. an isolated occurrence) the majority opinion was chosen. Resulting summary estimates were reviewed and approved by all SC members.

Efficacy definition and measurement

Efficacy was defined as the quotient of the number of patients with undetectable viral load at week 48 post-ART (i.e., responders) (numerator) and the number of patients initiated on ART (denominator). Efficacy was estimated based on an intention-to-treat analysis of the exposed ("*Intent-to-treat exposed" [ITT-E])* and missing or incomplete follow-ups were designated as failures

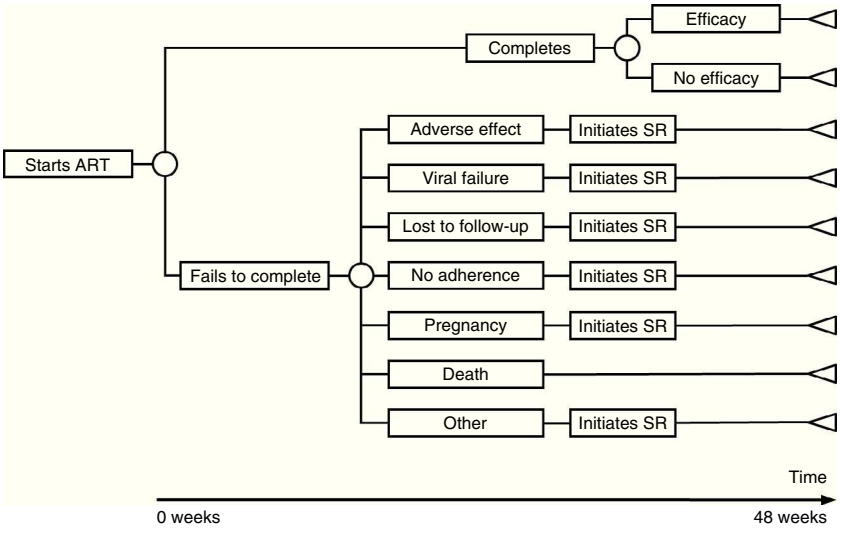

Fig. 1. Structure of the economic evaluation model for each regimen of antiretroviral treatment (ART). SR, substitution regimen.

Table 2
Substitution regimens for each initial regimen by reason for change (scientific committee consensus).

Initial regimen	Substitution regimens for each initial regimen and reason for switching					
	Viral failure	Pregnancy	Adverse effect	Lost to follow-up	Lack of adherence	Other
1. TDF/FTC/EFV	6	7	3	1	6	1
2. ABC/3TC + EFV	6	10	3	2	6	2
3. TDF/FTC/RPV	6	7	1	3	6	3
4. TDF/FTC + NVP	6	4	3	4	6	4
5. TDF/FTC + ATV/r	6	5	6	5	5	5
6. TDF/FTC + DRV/r	11	6	11	6	6	6
7. TDF/FTC + LPV/r	6	7	6	7	6	7
8. ABC/3TC + ATV/r	6	8	6	8	6	8
9. ABC/3TC + DRV/r	6	9	3	9	6	9
10. ABC/3TC + LPV/r	6	10	6	10	6	10
11. TDF/FTC + RAL	6	11	12	11	6	11
12. ABC/3TC + RAL	6	12	6	12	6	12
13. TDF/FTC/EVG/COBI	6	13	12	13	6	13

ABC: abacavir; ATV: atazanavir; COBI: cobicistat; DRV: darunavir; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; LPV: lopinavir; NVP: nevirapine; /r: ritonavir-boosted; RAL: raltegravir; RPV: rilpivirine; TDF: tenofovir DF; 3TC: lamivudine.

("*missing or non-completer = failure*"). Although this may not have been one of the main endpoints in the CTs examined, it could be calculated from all studies under review. In the event that more than one CT assessed the same regimen, efficacy was calculated as the quotient of the sum of responders (numerator) and sum of patients initiated on ART in the CTs (denominator).

Definition and calculation of costs

Based on a payer's perspective, this study only considers direct costs, i.e., the use of NHS resources. Within these costs, however, only differential costs are taken into account, i.e., non-identical costs across all regimens under study: ART, AE management, genotypic study of drug resistance, and HLA B*5701 testing. Direct costs were calculated multiplying the amount of resources used by the unit cost of each resource. The cost of initiating a regimen comprises the cost of ART and all the consequences (e.g., AE or need to switch regimens) incurred in 48 weeks due to the decision of initiating ART with that regimen.

Use of resources

ART

Patients completing treatment during the trial are assigned the costs of 48 weeks of the initial regimen. For those who do not complete the treatment, it was assumed that the initial regimen was discontinued at 24 weeks, on average. Thus, they are assigned the costs of 24 weeks of the initial regimen plus the costs of 24 weeks of the substitution regimen. This substitution regimen was chosen based on the reason for discontinuation of the initial regimen, according to the opinion of the 15 SC experts (Table 2).

AE management

AE were defined as those effects identified by the CT as ART-related. When the CT reported a list of AE without identifying the ART-related ones, the SC opinion was applied. Since CT usually reports AE affecting over 2% of patients under the treatments assessed, only these AE were considered and classified into chronic and isolated according to expert opinion. Chronic AE are those that last as long as the treatment (e.g., dyslipidaemia), whereas isolated AE are those occurring sporadically (e.g., skin rash).

The resources considered for the management of EA have been: drug treatment, emergency room visits, additional visits to the HIV specialist, visits to other specialists, diagnostic tests, and hospital admissions. To the patients completing treatment during the trial, the costs of managing the AE occurring within the 48 weeks of their initial regimen were assigned. For those who do not complete the treatment, and following the aforementioned assumptions, the costs of 24 weeks of AE management related to the initial regimen and 24 weeks of AE management related to the substitution regimen were assigned (Table 2). Further, because chronic AE were assumed to occur for half of ART duration on average, the cost allocated for chronic AE management corresponds to half the period the patient received the corresponding ART. Compared to the 2013 study, there are no new AE to be considered, and thus, the use of resources estimates are those estimated by the SC in the 2013 study.[20]

*Genotypic study of drug resistance and HLA B*5701 testing*

Genotypic studies of drug resistance considered as differential costs include: (1) conventional drug resistance study (in case of virologic failure); and (2) integrase resistance study (when virologic failure occurs in a regimen containing an integrase inhibitor such as raltegravir [RAL] or elvitegravir [EVG]). When a regimen involved abacavir (ABC), HLA B*5701 testing was considered before initiating treatment.

Estimation of the unit costs of resources considered

ART

The cost of each ART was calculated based on the costs of the drugs involved. In the case of Spain, this means that regimen costs were calculated based on the laboratory sale price (LSP) plus 4% VAT minus the 7.5% reduction required by the Spanish government as one of the extraordinary measures to reduce public deficit (not applicable to generic drugs).[21] Specifically, the following drugs were assigned the following prices: (1) the ABC and lamivudina (3TC) combination was priced as Kivexa®; (2) emtricitabine (FTC) and tenofovir DF (TDF) was priced as Truvada®; (3) for the TDF/FTC/efavirenz (EFV) regimen, the price of Atripla® was applied; (4) the regimen comprised of TDF/FTC/rilpivirina (RPV) was priced as Eviplera®; (5) the regimen TDF/FTC/EVG/cobicistat (COBI) was priced as Stribild®; (6) for nevirapine (NPV) the price of extended-release NVP (Viramune®) was applied; and (7) for EFV the price of the generic drug was used. Prices were obtained from the 2014 GESIDA/PNS consensus paper[17] (Table 1).

AE-related costs

The costs of the drugs used to manage AE were estimated based on the drugs' retail price plus VAT.[22] When more than one commercial preparation was available, the least expensive one was chosen. Estimating the costs of the other resources involved in AE management (emergency room visits, additional visits to the HIV

Table 3
Unit cost of resources.

Resource	Euros	Units
Drug resistance studies		
Conventional	328.00	Study
Integrase	328.00	Study
*HLA B*5701*	151.00	Test
Visit to specialist		
First visit	144.84	Visit
Following visits	80.34	Visit
Emergency oom		
Emergency room visit	191.21	Visit
Hospitalization		
Hospital ward admission	527.08	Day
Diagnostics		
Ultrasound	71.31	Unit
Routine blood work	64.71	Unit
Transaminases	6.94	Unit
Coagulation	7.10	Unit
Stool culture	23.96	Unit
Insulinaemia	9.27	Unit
Glycemic curve	31.28	Unit
Treatments		
Atorvastatine	0.16	10 mg
Bezafibrate	0.32	400 mg
Glibenclamide	0.06	5 mg
Insuline	9.39	300 U
Paracetamol	0.03	500 mg
Lormetazepam	0.07	1 mg
Metoclopramide	0.08	10 mg
Loperamide	0.30	2 mg
Loratadine	0.16	10 mg
Prednisone	0.08	10 mg

specialist, visits to other specialists, diagnostic tests, and hospital admissions) was a bit more involved due to the structure of the Spanish health care system. In Spain, health care falls under the competence of the Autonomic Communities (AC) and, thus, prices vary by AC. Resources were priced using the official fees in each AC. The cost of each unit of resource has been estimated as the average of the prices to the general public, defined as the price applied to third parties responsible for payment or to patients not eligible for coverage of health care services corresponding to those services offered by the Health Services of the Departments of Health of each AC (Table 3).

*Genotypic study of drug resistance and HLA B*5701 testing*

Due to lack of official data on the costs of drug resistance studies and HLA B*5701 testing, the costs provided by the Hospital Clínico of Barcelona were used (Table 3). HLA B*5701 testing is considered amortized in 5 years, thus, first year's amortization is 20%.

Definition and calculation of efficiency

Efficiency (cost/efficacy) for each regimen was calculated as the quotient of the cost of initiating treatment with that regimen (numerator) and efficacy (denominator). The result represents the cost of achieving a responder by week 48.

Sensitivity analysis

Deterministic sensitivity analysis was performed for each of the models to assess the uncertainty level introduced by the estimators (e.g., estimators of efficacy, AE, or costs). These analyses provide the potential range within which to find the cost/efficacy ratios for each ART regimen. To this end, three scenarios were created: base case, most favourable, and least favourable for each initial ART regimen. The base case scenario is defined as the ratio of the central cost estimator (numerator) and the central efficacy estimator (denominator). The most favourable scenario is defined similarly where the numerator is the most favourable cost estimator and the denominator is the most favourable efficacy estimator. Finally, the least favourable scenario uses the least favourable estimators for both costs and efficacy for numerator and denominator, respectively.

The central cost estimator is calculated based on the central estimator of the AE probability and the average costs of AE management, drug resistance studies, and HLA B*5701 testing. The most favourable cost estimator is computed applying the 95% confidence interval (95% CI) lower limit of AE probability, and a 15% cut in the average costs of AE management, drug resistance studies, and HLA B*5701 testing. The least favourable cost estimator is computed applying the 95% CI upper limit of AE probability, and an additional 15% over the average costs of AE management, drug resistance studies, and HLA B*5701 testing. All scenarios include the same cost for each ART regimen since those costs do not involve any uncertainty. Finally, the 95% CI upper and lower limits are used to calculate the most and least favourable estimators of efficacy, respectively.

Software application

Since local cost of a specific hospital may be different to the costs used in the model, a software application that facilitates the assignment of local costs was designed for allowing the calculation of ART costs, regimen initiation costs, efficiency (cost/efficacy), and relative efficiency of initiating treatment with the different regimens at each individual hospital setting. The application is available free of charge at: http://www.gesida-seimc.org/contenidos/utilidades/aplicacion-tarv-vih-gesida-2014.exe or https://dl.dropboxusercontent.com/u/35731022/coste-eficacia-2014/aplicacion-tarv-vih-gesida-2014.exe.

Results

In addition to the 20 CT included in the 2013 study[20] (STARTMRK,[23] GS-934,[24] ARTEMIS,[25] CASTLE,[26] ARTEN,[27] ABT730,[28] GEMINI,[29] HEAT,[30] KLEAN,[31] CNA30024,[32] ECHO,[33] QDMRK,[34] VERxVE,[35] PROGRESS,[36] ACTG5202,[37] GS-US-236-0102,[38] GS-US-236-0103,[39] GS-US-216-0114,[40] SINGLE,[41] SPRING-2[42,43]), the SC selected 2 additional CT that evaluate the efficacy of the regimens recommended in the 2014 GESIDA/PNS consensus paper[17]: STAR[44,45] and FLAMINGO.[46] With the available scientific evidence all recommended regimens could be evaluated (Table 1).

Costs of the different ART regimens at 48 weeks varied between 5015 and 11,957 Euros, corresponding to ABC/3TC + EFV and TDF/FTC + RAL, respectively (Table 1). The cost of initiating ART in the base case varied between 5133 Euros for ABC/3TC + EFV and 11,949 Euros for TDF/FTC + RAL. Of the regimens involving a ritonavir-boosted protease inhibitor (PI/r), ABC/3TC + lopinavir (LPV)/r had the lowest cost. Within the most favourable scenario, costs varied between 5098 and 11,941 Euros for ABC/3TC + EFV and TDF/FTC + RAL, respectively. Within the least favourable scenario, costs fluctuated between 5174 and 11,961 Euros for ABC/3TC + EFV and TDF/FTC + RAL, respectively (Table 4 and Fig. 2A and B).

Efficacy in base case scenario ranged between 0.66 (66% response rate at 48 weeks) for ABC/3TC + LPV/r and ABC/3TC + atazanavir (ATV)/r, and 0.89 for TDF/FTC/EVG/COBI. Within the most favourable scenario, efficacy varied between 0.70 for ABC/3TC + LPV/r and ABC/3TC + ATV/r, and 0.92 for ABC/3TC + RAL. The least favourable scenario saw a variation in efficacy ranging from 0.61 for ABC/3TC + ATV/r and 0.86 for TDF/FTC/EVG/COBI (Table 4 and Fig. 2A).

Regarding the efficiency (cost/efficacy), the base case scenario varied between 7546 and 13,802 Euros per responder for ABC/3TC + EFV and TDF/FTC + RAL, respectively. Efficiency

Table 4
Cost, efficacy, efficiency (cost/efficacy) and relative efficiency of initiating treatment with each regimen (using regimen ABC/3TC + EFV as the reference). Sensitivity Analysis.

Initial regimen	Baseline scenario				Most favourable scenario				Least favourable scenario			
	Cost[a] (Euros)	Efficacy	C/E[b]	Relative C/E	Cost[a] (Euros)	Efficacy	C/E[b]	Relative C/E	Cost[a] (Euros)	Efficacy	C/E[b]	Relative C/E
TDF/FTC/EFV (PR)	6650	0.80	8280	1.097	6620	0.82	8086	1.131	6684	0.79	8488	1.062
ABC/3TC + EFV (AR)	5133	0.68	7546	1.000	5098	0.71	7152	1.000	5174	0.65	7989	1.000
TDF/FTC/RPV (PR)	6892	0.84	8161	1.082	6860	0.87	7879	1.102	6929	0.82	8466	1.060
TDF/FTC + NVP (AR)	6567	0.73	8972	1.189	6558	0.75	8688	1.215	6578	0.71	9276	1.161
TDF/FTC + ATV/r (PR)	9540	0.79	12,003	1.591	9519	0.81	11,702	1.636	9565	0.78	12,324	1.543
TDF/FTC + DRV/r (PR)	9499	0.83	11,421	1.514	9456	0.86	10,940	1.530	9549	0.80	11,951	1.496
TDF/FTC + LPV/r (AR)	8887	0.75	11,907	1.578	8873	0.77	11,596	1.621	8904	0.73	12,236	1.532
ABC/3TC + ATV/r (PR)	8108	0.66	12,322	1.633	8108	0.70	11,563	1.617	8108	0.61	13,190	1.651
ABC/3TC + DRV/r (AR)	8193	0.85	9639	1.277	8103	0.93	8729	1.221	8304	0.77	10,760	1.347
ABC/3TC + LPV/r (AR)	7654	0.66	11,561	1.532	7615	0.70	10,956	1.532	7698	0.63	12,239	1.532
TDF/FTC + RAL (PR)	11,949	0.87	13,802	1.829	11,941	0.89	13,450	1.881	11,961	0.84	14,178	1.775
ABC/3TC + RAL (PR)	10,646	0.87	12,295	1.629	10,622	0.92	11,570	1.618	10,680	0.81	13,125	1.643
TDF/FTC/EVG/COBI (PR)	9227	0.89	10,416	1.380	9180	0.91	10,095	1.412	9282	0.86	10,763	1.347

ABC: abacavir; ATV: atazanavir; COBI: cobicistat; DRV: darunavir; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; LPV: lopinavir; NVP: nevirapine; /r: ritonavir-boosted; RAL: raltegravir; RPV: rilpivirine; TDF: tenofovir DF; 3TC: lamivudine.
PR: Regimen designated as "Preferred" by the expert panel of GESIDA and the 2014 AIDS National Plan.[17]
AR: Regimen designated as "Alternative" by the expert panel of GESIDA and the 2014 AIDS National Plan.[17]
[a] Cost of initiating a regimen including all potential consequences of deciding to initiate ART with that regimen (adverse effects and changes to other regimens) that may occur within 48 weeks.
[b] Efficiency or cost/efficacy. Cost (Euros) of achieving one responder for the NHS (<50 copies of RNA of HIV per mL of plasma by week 48; *ITT-E missing or NC = failure*).

estimates for the most favourable scenario ranged between 7152 and 13,450 Euros per responder for ABC/3TC + EFV and TDF/FTC + RAL, respectively. Within the least favourable scenario these same estimates varied between 7989 and 14,178 Euros per responder for ABC/3TC + EFV and TDF/FTC + RAL, respectively. In comparison, when initiating ART with the regimen TDF/FTC + RAL, each responder was 82.9% more expensive than with the regimen ABC/3TC + EFV if using the base case scenario, 88.1% more expensive in the most favourable scenario, and 77.5% more expensive in the least favourable scenario (Table 4 and Fig. 2A and B).

Among the regimens containing non-nucleoside reverse transcriptase inhibitors, the most efficient was ABC/3TC + EFV, followed by TDF/FTC/RPV, TDF/FTC/EFV and TDF/FTC + NVP. Using this last regimen, achieving a responder is 18.9% more expensive than ABC/3TC + EFV, varying between 21.5 and 16.1% within the least and most favourable scenarios, respectively. Among the regimens including PI/r, the most efficient was ABC/3TC + DRV/r, and the least efficient was ABC/3TC + ATV/r. With this last regimen, achieving a responder was 27.8% costlier than with ABC/3TC + DRV/r, with this percentage oscillating between 32.5 and 22.3% depending on the scenario (Table 4 and Fig. 2A and B).

Among the regimens considered PR by GESIDA/PNS, the most efficient were TDF/FTC/RPV and TDF/FTC/EFV.

Discussion

Of all the ART regimens recommended by GESIDA/PNS in their January 2014 consensus paper[17] as PR for naïve patients, TDF/FTC/EFV emerged as the least expensive whether considering the ART cost alone or considering all the additional costs derived from the decision of initiating treatment with an ART regimen (AE management, drug resistance tests, HLA B*5701 test, and regimen change). Regimens TDF/FTC/RPV and TDF/FTC/EFV turned out to be the most efficient ones in terms of cost/efficacy. Considering also regimens recommended as AR, ABC/3TC + EFV was the least expensive and the most efficient in terms of cost/efficacy despite being one of the regimens presenting the lowest efficacy in the CTs. Regimens including integrase-inhibitors (EVG and RAL) presented the most efficacy, but the regimens containing RAL are also the least efficient due to their high cost. Another low efficient regimen is ABC/3TC + ATV/r due to its low efficacy.

The cost of initiating treatment with a certain regimen is what the decision to initiate treatment with a certain regimen really costs to the NHS, because it includes ART costs and the costs of the consequences (e.g., AE management or switching regimen); whereas for the hospital's pharmacy the cost consists of only the ART. The ratio cost/efficacy represents the NHS cost of achieving one responder (at 48 weeks in our particular case). In certain cases, the physician and/or the patient may prefer a regimen with a non-nucleoside, with a PI/r, or with a integrase-inhibitor for clinical reasons or personal preferences. In such cases, the costs of initiating treatment, its efficacy, and the cost/efficacy ratio would have to be considered within each of these three regimen types.[47]

For all regimens, the main cost of initiating treatment is the ART due to its high price. In contrast, the costs related to managing AE are low since not only a very small percentage of patients present AE but also the costs involved are low.

The study results should be interpreted in the context of its limitations. A potential limitation is that the analyses are based on CTs performed in different countries, during different periods of time, with different inclusion and exclusion criteria, and even with different presentations for the same drug in regimens with LPV (capsules and pills) or NVP (normal formula or extended-release). Thus, results may have differed if all regimens had been administered in similar populations and time periods. For instance, more recent studies include lower percentages of patients with poor prognosis, i.e., those with low CD4 counts (<100/200 cells/μL) and elevated plasma viral load (>100,000 copies/mL). This leads to results with higher levels of efficacy than those reported in previous studies and may offer an advantage to drugs assessed recently for the first time. In addition, there are drugs with restricted use. For instance, NVP should only be initiated on women with CD4 < 250 cells/μL or on men with CD4 < 400 cells/μL. Also, RPV is only approved for individuals with baseline plasma viral loads <100,000 copies/mL, and TDF/FTC/EVG/COBI is only approved for patients with estimated glomerular filtration rate 70 mL/min. RPV efficacy results in patients with plasma viral load <100,000 copies/mL are better than the average efficacy from the CTs included in this analysis. However, these studies included patients similar to those participating in studies of the other drugs, thus, efficacy data refer to comparable patient groups.

Further, NVP studies reviewed (ARTEN[27] and VERxVE[35]) included only patients with low CD4 counts (<250 cells/μL in women and <400 cells/μL in men) which may explain the poorer results regarding efficacy compared to other regimens. However, because those are the drug label's approved criteria, such trials were

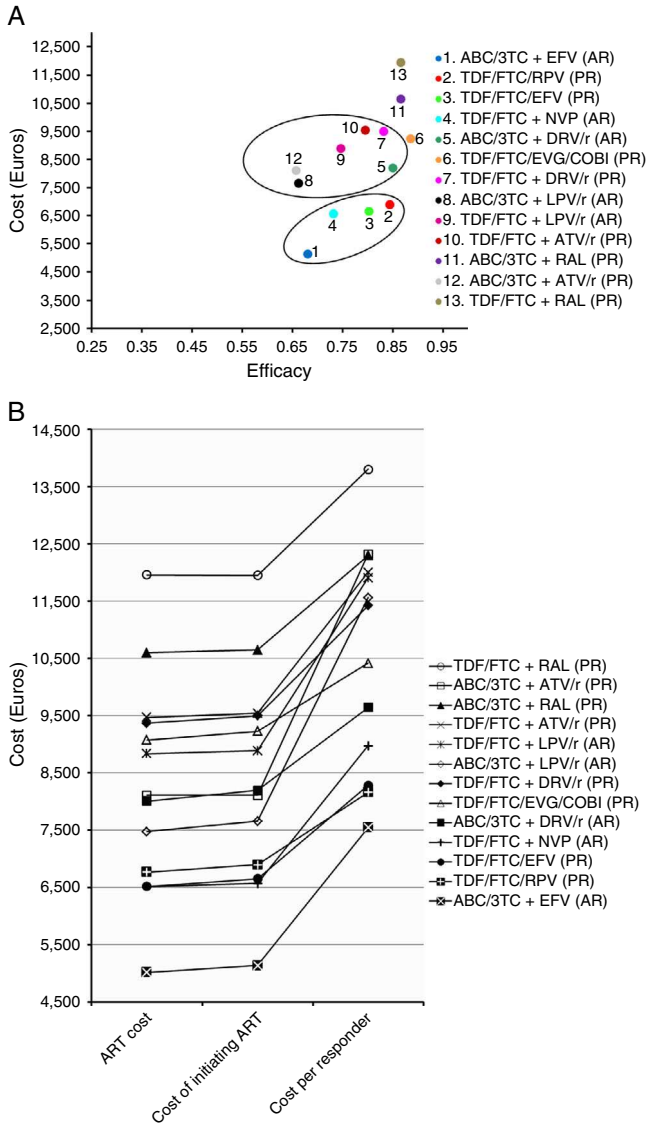

Fig. 2. Representation of the base case scenario. (A) Cost: cost of initiating a regimen including all potential consequences of initiating ART with that regimen (adverse effects [AE] and changes to other regimens) that may occur within 48 weeks. Efficacy: proportion of patients with undetectable plasma viral load (<50 copies of RNA of HIV/mL) at 48 weeks. The slope between the *y*-intercept and the coordinates for each regimen represents efficiency (cost/efficacy), and it reflects the cost of achieving one responder by week 48 for the National Health Service (NHS). (B) ART Cost: Drug costs for each regimen for 48 weeks (laboratory sale price (LSP) + 4% VAT – 7.5% reduction). Cost of initiating ART: cost of initiating a regimen including all potential consequences of initiating ART with that regimen (adverse effects [AE] and changes to other regimens) that may occur within 48 weeks. Cost per Responder: Cost of achieving one responder (<50 copies of RNA of HIV per mL of plasma) by week 48 for the NHS. This is calculated as the cost of initiating ART divided by efficacy. ABC: abacavir; ATV: atazanavir; COBI: cobicistat; DRV: darunavir; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; LPV: lopinavir; NVP: nevirapine; /r: ritonavir-boosted; RAL: raltegravir; RPV: rilpivirine; TDF: tenofovir DF; 3TC: lamivudine. PR: Regimen designated as "Preferred" by the expert panel of GESIDA and the 2014 AIDS National Plan.[17]
AR: Regimen designated as "Alternative" by the expert panel of GESIDA and the 2014 AIDS National Plan.[17]

included in the analysis. Also, study ACTG 5202[37] did not provide AE data at 48 weeks so data at 96 weeks were included instead under the assumption that most AE do occur during the first 48 weeks. Another limitation is that some CTs failed to specify which AE were ART-related, data gaps that were filled with the experts' opinion. Similarly, for lack of other scientific evidence, resources needed for AE management and the substitution regimens used when the initial regimen was suspended were estimated based on experts' opinion. Additionally, although the study's methodology ensures agreement at a national level, calculations may differ in other countries. Finally, regimens' efficacy were evaluated using the ITT-E analytical approach assigning missing or incomplete follow-ups as failures ("*missing or non-completer = failure*"). This method of evaluation may not coincide with the main end-point in some of the studies, though the data published in the reports do allow for the necessary calculations. In other words, results may have differed if other analytical methods of measuring efficacy had been used instead. Also, when more than one CT assessed the same regimen, a metanalysis could not be performed because of the absence of a common comparator. Finally, another limitation would be that these findings are applicable only to Spain and taking into account the Spanish official drug prices in January 2014, not considering potential local discounts even when they could be substantial and not uncommon as in the case of RAL. Thus, results should be interpreted cautiously especially in environments where prices differ substantially from the Spanish average.

Major strengths of this study include using the best scientific evidence available and performing sensitivity analyses for each of the models to best capture the underlining uncertainty in costs and outcomes. Further, the models use efficacy estimators, with universal validity, which, added to the fact that the methodology is applicable to any environment, would make the results valid in other contexts as long as local costs could be entered into the models.

In order to facilitate the use of this methodology in other centres or countries with different ART- or HIV management-related costs or to take into account the potential future use of generic drugs,[48] a software application was developed and made available free of charge at: http://www.gesida-seimc.org/contenidos/utilidades/aplicacion-tarv-vih-gesida-2014.exe. This application allows the calculations of ART costs, initiating ART costs, efficiency (cost/efficacy), and the relative efficiency of initiating treatment with the different regimens based on local costs. This application will aid any centre interested in computing its own estimates based on the model developed here.

The ideal study design to determine ART efficiency in regular clinical practice would be a prospective cohort cost/effectiveness study with a long follow-up period, but these studies are unlikely to be carried out. For lack of such studies, cost/efficacy models provide a very useful tool to examine costs and ART efficiency based on the best scientific evidence available.

Current study findings are relevant because the mission of any health care system is to maximize its population's health outcomes in a context of inherently limited resources. In such context, guaranteeing the system's sustainability requires an efficient use of resources.[49,50] Periodic economic evaluation studies such as this one have the potential of facilitating the decision making process of health professionals, managers, and political decision-makers in the field of HIV-infection management.

Conflict of interest

Antonio Javier Blasco has no potential conflicts of interest related to this study.

Josep M. Llibre has received research funding, consultancy fees, and lecture sponsorships from or has served on advisory boards for Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, and ViiV Healthcare.

Juan Berenguer has performed consulting work for laboratories Abbvie, Boehringer Ingelheim, BMS, Gilead Sciences, Janssen, Merck, and ViiV Healthcare, he has enjoyed grants for clinical research from BMS, MSD and ViiV Healthcare, and has received

compensation for talks from Abbvie, BMS, Gilead Sciences, Janssen, MSD and ViiV Healthcare.

Juan González-García has received advisories and speaker fees from Abbott Laboratories, Bristol-Myers Squibb, Gilead-Sciences, Janssen-Cilag, Merck Sharp & Dohme and ViiV Healthcare.

Hernando Knobel has done consultancy work for Abbott Laboratories, Abbvie Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp Done and ViiV Healthcare and has received compensation for lectures from Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, Janssen and ViiV Healthcare.

Fernando Lozano has disclosed that he has served as an advisor or consultant for Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithkline, Gilead Sciences, Jansen-Cilag, MSD, Roche Pharmaceuticals and ViiV Healthcare, and has also served on the speaker's bureaus for, as well as received support for educational activities from Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithkline, Gilead Sciences, Jansen-Cilag, MSD, Roche Pharmaceuticals and ViiV Healthcare.

Daniel Podzamczer has received research grants and/or honoraria for advisories and/or conferences from Boehringer Ingelheim, GSK, Viiv, Pfizer, BMS, Abbott, Gilead, Janssen and Merck.

Federico Pulido has received consultancy and lecture fees from Abbvie, Bristol-Myers-Squibb, Janssen, Gilead Sciences, MSD and ViiV Healthcare.

Antonio Rivero has received consultancy fees from Abbott Laboratories, Bristol-Myers Squibb, Boehringer Ingelheim, ViiV Healthcare, Gilead Sciences, GlaxoSmithKline,

Janssen-Cilag and Roche Pharmaceuticals, and speaker fees from Abbott Laboratories, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, ViiV Healthcare, Janssen-Cilag, Merck-Sharp & Dohme and Roche Pharmaceuticals.

Montserrat Tuset has received grants from Bristol-Myers Squibb, Gilead Sciences, Merck, and Janssen and speaker fees from Janssen, Merck, and ViiV Healthcare.

Pablo Lázaro has no potential conflicts of interest related to this study.

Josep M. Gatell has received honoraria for speaking or participating in Advisory Boards and/or research grants from BMS, MSD, Tobira, Gilead, BI, Janssen, ViiV and Abbvie.

José Ramón Arribas receives advisory fees, speaker's fees, or grant support from Viiv, Tibotec, Janssen, Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Inc, and Tobira.

Vicente Boix has disclosed that he has served as an advisor or consultant for Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithkline, Gilead Sciences, Jansen-Cilag, MSD, Roche Pharmaceuticals and ViiV Healthcare, and has also served on the speaker's bureaus for, as well as received support for educational activities from Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithkline, Gilead Sciences, Jansen-Cilag, MSD, Roche Pharmaceuticals and ViiV Healthcare.

Bonaventura Clotet has served as a consultant on advisory boards or participated in speakers' bureaus or conducted clinical trials with Abbott Laboratories, BMS, Boehringer Ingelheim, Gilead Sciences, Janssen, Merck (MSD), Shionogy, Tibotec and ViiV Healthcare.

Pere Domingo has received honoraria for consultancy from Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, Janssen & Cilag, and ViiV Healthcare. He has also received research grants (money for Institution) from Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen & Cilag, Pfizer Inc and ViiV Healthcare. He had also received honoraria for speech from Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp& Dohme, Gilead Sciences, Janssen and ViiV Healthcare. Dr. Domingo is recipient of a grant from the Programa de Intensificación from FIS in the year 2013 (INT12/383).

Juan Carlos López has served as an advisor or consultant for Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, Jansen-Cilag, and MSD, and has also served on the speaker's bureaus or received support for educational activities from Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, Jansen-Cilag, MSD, Roche Pharmaceuticals and ViiV Healthcare.

José M. Miró has received honoraria for consultancy from Abbott Laboratories, Bristol- Myers Squibb, Cubist, Gilead Sciences, Merck, Novartis, Pfizer and Theravance. He has also received research grants from Cubist, Novartis, Fondo de Investigaciones Sanitarias (FIS) from Instituto de Salud Carlos III (Madrid), Fundación para la Investigación y Prevención del Sida en España (FIPSE, Madrid), Ministerio de Sanidad, Política Social e Igualdad (MSPSI, Madrid), National Institutes of Health (NIH, Bethesda, MA, EE, UU.) He had also received honoraria for speech from Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Cubist, GlaxoSmithKline, Gilead Sciences, Janssen, Merck, Novartis, Pfizer, Roche, Schering-Plough, Theravance y ViiV Healthcare. Dr. Miró is recipient of a grant in the year 2011 (INT 10/219) from the Programa de Intensificación de la Actividad Investigadora del Sistema Nacional de Salud and from Departamento de Salud de la Generalitat de Cataluña (Programs I3 SNS and PRICS).

Juan Miguel Santamaría has received honoraria for consultancy from Janssen-Cilag and Merck Sharp & Dohme Laboratories and has received research grants from Abbott and Merck. He has participated in lectures or symposia sponsored by Janssen-Cilag, Merck Sharp & Dohme, Gilead and Abbott.

Laura Zamora has no conflicts of interest.

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Appendix A.

The GESIDA ART Cost-efficacy Study Group is composed by the authors of the manuscript (except AJB and PLM) plus the following members:

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