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ORIGINAL ARTICLE

Costs and adherence to antiretroviral treatment

J.M. Ventura-Cerdá,* D. Ayago-Flores, E. Vicente-Escrig, S. Mollá-Cantavella, and M. Alós-Almiñana

Servicio de Farmacia, Hospital General de Castellón, Castellón, Spain

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Abstract
Objective: To develop a system of data management that allows us to estimate the comparative effectiveness of the various antiretroviral treatment (ART) regimens.
Method: Restrospective observational study in patients infected with HIV with stable ART. Adherence to treatment and unit cost for each patient's treatment was determined. The cost/patient/day was calculated and, multiplying by an adherence factor (f_{ADH}), the (cost/patient/day)$_{ADH}$. The comparison of both allowed us to obtain the $\Delta_{cost/patient}$, which estimates the additional costs caused by lack of adherence. The incremental cost-effectiveness (iCER), grouping the results by the various coformulated drugs ("combos"). A study of the budgetary impact of these combos was carried out.
Results: 468 patients were evaluated (62%adherent). Average adherence was 88±18%. The average value of (cost/patient/day)$_{ADH}$ was significantly higher than the cost/patient/day (27.3±9.8 € compared to 24.3±7.6 €, $P<.001$). Just as with the f_{ADH}, no differences were found in the $\Delta_{cost/patient}$ between the different ART combinations. The combo with the least deviation from the cost/patient/day due to lack of adherence was that composed of abacavir/zedovudine/lamivudine (ABC/AZT/3TC, $\Delta_{cost/patient}$=8.72±14.18%), and that with the greatest deviation AZT/3TC ($\Delta_{cost/patient}$=13.52±17.68%). No significant differences were found in the iCER calcluated for any combo. The ART that included abacavir/lamivudine (ABC/3TC) obtained the least budgetary impact.
Conclusions: The greatest cost and percentage of adherent patients associated with the combos composed of Tenovovir/Emtricitabine(TDF/FTC) and ABC/3TC, and the least cost and effectiveness of those composed of AZT/3TC and ABC/AZT/3TC, does not allow us to identify any option as significantly dominant. The regimens with ABC/3TC were shown to be the most favourable from the combined point of view of cost and adherence.

*Corresponding author.
E-mail address: ventura_jma@gva.es (J.M. Ventura-Cerdá).

PALABRAS CLAVE
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Adherencia;
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Síndrome de la inmunodeficiencia humana adquirida;
VIH;
Investigación de resultados

Costes y adherencia del tratamiento antirretroviral

Resumen

Objetivo: Desarrollar una sistemática de manejo de datos que permita estimar comparativamente la eficiencia de los diferentes esquemas de tratamiento antirretroviral (TAR).

Método: Estudio observacional retrospectivo en pacientes infectados por el VIH con TAR estable. Se determinó para cada paciente su adherencia y el coste unitario de su tratamiento. Se calculó el coste/paciente/día y, multiplicando por un factor de adherencia (f_{ADH}), el (coste/paciente/día)$_{ADH}$. La comparación de ambos permitió obtener el $\Delta_{coste/paciente}$, que estima la desviación de costes originada por la falta de adherencia. Se calculó el coste-efectividad-incremental (CEI) agrupando los resultados en los diferentes fármacos coformulados (combos). Se realizó un estudio de impacto presupuestario de dichos combos.

Resultados: Se evaluaron 468 pacientes (62%adherentes). La adherencia media fue de 88 ± 18%. El valor medio del (coste/paciente/día)$_{ADH}$ fue significativamente superior al coste/paciente/día (27,3 ± 9,8 € frente 24,3 ± 7,6 €, $p < 0,001$). Al igual que para el f_{ADH}, no se encontraron diferencias en el $\Delta_{coste/paciente}$ entre las diferentes combinaciones de TAR. El combo con menor desviación del coste/paciente/día debida a la falta de adherencia fue el constituido por abacavir/zidovudina/lamivudina (ABC/AZT/3TC, $\Delta_{coste/paciente}$=8,72±14,18%), y el de mayor desviación el AZT/3TC ($\Delta_{coste/paciente}$=13,52±17,68%). No se encontraron diferencias significativas en los CEI calculados para ningún combo. Los esquemas de TAR que incluyeron abacavir/lamivudina(ABC/3TC) obtuvieron el menor impacto presupuestario.

Conclusiones: El mayor coste y porcentaje de pacientes adherentes asociados a los combos compuestos por tenofovir/emtricitabina (TDF/FTC) y ABC/3TC, y el menor coste y efectividad de los compuestos por AZT/3TC y ABC/AZT/3TC no permiten identificar ninguna opción significativamente dominante. Los esquemas con ABC/3TC se muestran como los más favorables desde el punto de vista combinado del coste y la adherencia.

Introduction

Since it was discovered over 20 years ago, human immunodeficiency virus (HIV) has become a pandemic, with over 30 million people throughout the world infected in 2007. With the arrival of the first antivirals, especially protease inhibitors (PI) during the mid-nineties, the evolution of the disease could be drastically modified, reducing morbidity and mortality.[1,2] Later progress with antiretroviral treatment (ART) have contributed to maintaining and improving survival and clinical control of the infection, and have especially increased patients' quality of life.[3] The staggered introduction of antiretroviral drugs (ARV) determined that, at a given moment for a given patient, the possible antiretroviral treatment combinations could be limited (mainly due to selecting the resistances and intolerance), therefore, personalisation was completely justified. Currently, in countries which have access to ART, chronic HIV infection is clinically controllable, although its epidemiology is still an important issue for public health, and it continues to hold an important social, economic and media impact.[4-6]

The Spanish AIDS plan (PNS) and the Spanish AIDS study group (GESIDA) gave preference to the combination of three drugs in the latest recommendations update on antiretroviral treatment in adults.[7] They recommend starting with two nucleotide or nucleoside analogue reverse transcriptase inhibitors (NtARTI or NARTI) and efavirenz (EFV: non-nucleoside reverse transcriptase inhibitor [NNRTI]), or two NARTI/NtARTI and a ritonavir-boosted PI (PI/r). Coformulated drugs, usually called 'combos' are recommended for combinations of two NARTI/NtARTI. For the first time since ARV were first introduced and regardless of different possible treatment scenarios, there are several combinations available that are capable of make up active ART regimens thanks to the recent arrival of new active drugs against resistant strains. This quantitative and qualitative change has meant that the general recommendations recognise that there are likely to be several ART regimens of similar antiretroviral potency and that, selecting a given regimen would therefore depend on, among other factors, the cost of the drugs.[7]

Controlling and treating HIV/AIDS involves a high economic cost, both in terms of direct (antiretroviral treatment, health costs) and indirect costs.[5,8-10] The annual cost for HIV patients has been estimated at €10,000 for asymptomatic patients and €15,000 for symptomatic patients.[9] Health expenses have been changing over the past 15 years, and drug treatment costs is currently greater than patient healthcare costs.[10,11]

Adherence to ART, fundamentally due to its role in virological response and in selecting resistant strains, is one of the main factors which determine whether therapy is to be successful or not. Lack of adherence is related with an increase in hospital admissions, progression from HIV to AIDS, and patient mortality, leading to an inefficient use of healthcare resources.[11-14] Despite there being numerous AIDS research groups and despite the abundance of specific

publications and their overwhelming bibliographic impact (203,432 references retrieved using search criteria 'HIV or antiretroviral therapy'), it is seemingly absurd that there are so few pharmacoeconomic studies considering the significant economic impact that HIV treatment has (93 references retrieved using the search criteria '*pharmacoeconomics and antiretroviral therapy*'). Both searches were performed on 5 September 2009 from *www.ncbi.nlm.nih.gov/pubmed*.

The purpose of this study is to develop and establish a systematic data and indicator management system that allows us to estimate the comparative effectiveness of the various antiretroviral treatment (ART) regimens. To do so, we have set the clinical data to one side, and have combined economical and drug use data with adherence.

Methods

We conducted a retrospective, observational study which included adult HIV patients being treated with stable ART for at least the last six months, and who were only attended to in the pharmacy department at our hospital during 2008. We estimated each patient's adherence using the Spanish version of the Simplified Medication Adherence Questionnaire (SMAQ),[15] which classifies the patients as adherent or non-adherent. We also used the dispensing records (DR), allowing us to estimate adherence as a continuous variable. A patient was considered adherent when the SMAQ indicated adherence and DR≥90%.

Daily cost of the patient's ART regimen was also calculated (€), using the average prescription cost (APC) for December 2008, with the following formula:

$$\text{cost/patient/day} = \sum \left[\frac{N \times PMFi}{Days} \right]$$

where *Ni* is the number of units dispensed of a drug *i*, *APCi* is the average unitary prescription cost and *Days* are the days treated in accordance with the quantity dispensed and the administration regimen. We only included for ≥180 days.

We also calculated the adherence factor *(f_{ADH})* for each patient, using the following formula:

$$f_{ADH} = 1 + (1 - DR)$$

where *DR* is the value taken for the dispensing record average for the drugs which form part of the patient's regimen, expressed as parts per unit.

Using both formulae, we calculated each patient's normalised daily cost for adherence (*[cost/patient/day]$_{ADH}$*):

$$(\text{cost/patient/day})_{ADH} = (\text{cost/patient/day}) \times f_{ADH}$$

The variable $\Delta_{cost/patient}$ estimates the deviation due to a lack of adherence, with regard to the baseline cost of the treatment regimen. The difference between the variables cost/patient/day and $(\text{cost/patient/day})_{ADH}$ has been expressed as a percentage with regard to the first variable value using the following formula:

$$\Delta_{cost/patient} = \frac{(\text{cost/patient/day})_{ADH} - (\text{cost/patient/day})}{(\text{cost/patient/day})} \times 100$$

A greater $\Delta_{cost/patient}$ value indicates that the ART regimen is less effective, with regard to its use in relation to the adherence calculated as DR.

We analysed ART regimens separately. They included coformulated active ingredients in fixed combinations or 'combos', considered as first-line treatment in accordance with ART recommendations that were in force until 2008, devised by the GESIDA and PNS[16]: zidovudine 300 mg+lamivudine 150 mg (AZT/3TC), tenofovir 245 mg+emtricitabine 200 mg (TDF/FTC), abacavir 600 mg+lamivudine 300 mg (ABC/3TC). We also included combos consisting of abacavir 300 mg+zidovudine 300 mg+lamivudine 150 mg in the analysis (ABC/AZT/3TC). We calculated the percentage of adherent patients and the mean cost/patient/day for each combo. We compared them with the mean values for patients that were not administered such combo, allowing us to calculate the absolute risk reduction (ARR), understood as the 'risk' of being adherent with a given combo. We also determined the incremental cost-effectiveness (iCER), which defined the over-cost necessary

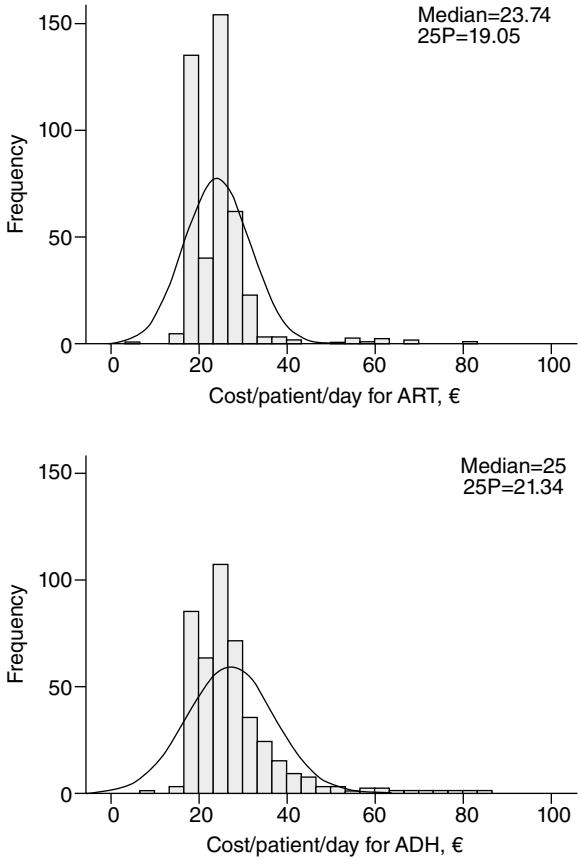

Figure 1 Distribution histograms for cost/patient/day and $(\text{cost/patient/day})_{ADH}$. ADH indicates adherence; ART, antiretroviral treatment.

to obtain an adherent patient with a given combo. Cost analysis allowed us to analyse the budgetary impact (BI), which estimated the additional cost for all of the patients to be treated with the same combo for 1 year. We only calculated the BI for dominant combos in terms of effectiveness, considered as the percentage of adherent patients, i.e. those with mean ARR above 0.

$$ARR_i = [(\%patsADH)_{patientswthcomboi} - (\%patsADH)_{remainingpatientswithcombos}] \times \frac{1}{100}$$

$$CER_i = \frac{(cost/patient/day)_{comboi} - (cost/patient/day)_{remainingcombos}}{ARR_i}$$

$$BI_{comboi} = [(cost/patient/day)_{comboi} - (cost/patient/day)_{remainingcombos}] \times n_{not\,i} \times 365$$

where BI_{comboi} is the budgetary impact calculated for a given combo i and $n_{not\,i}$ is the number of patients that do not take combo i.

The continuous variables have been reported using their mean value and standard deviation (SD) and the categorical values as percentage (%), calculating 95% confidence interval (CI: 95%) when necessary. Frequency distribution of the continuous variable was presented as the median (50th percentile) and 25th (25P) and 75th (75P) percentiles. We estimated continuous variable distribution using the Kolmogorov-Smirnov test. When distribution did not adjust to normality, we used non-parametric hypothesis tests (Kruskal-Wallis). When the data did adjust to normal distribution, we used parametric tests (student's t test) to compare averages. We compared the possible differences between the categorical variables using the chi-square test (χ^2). We examined the continuous variables depending on the different categories, using single factor analysis of variance (ANOVA).

Results

We assessed a total of 468 patients, they were 42±7 years old and mainly male (72%). 62% were estimated as being adherent, combining SMAQ and DR. Only considering SMAQ, 72% of patients were adherent, and 66% of patients obtained DR>90%. Adherence measured as a continuous variable with the DR values obtained a mean of 88±18%

Table 1 Cost per patient and day, with and without adjustment to adherence, for each of the ART regimes that include combos*

	No.	Cost/patient/day, €	f_{ADH}	(Cost/patient/day)ADH, €
AZT/3TC/EFV	79	19.05	1.09 (0.14)	20.70 (4.20)
AZT/3TC/LPV$_r$	35	*23.74*	1.20 (0.22)	**28.56 (5.24)**
AZT/3TC/ATV[a]	25[a]	**25.00/26.28**	1.20 (0.20)/1.21 (0.21)	***30.11 (4.88)/32.12 (6.69)***
AZT/3TC/SQV$_r$	3	*21.94*	1.00 (0.00)	21.94 (0.00)
AZT/3TC/FPV$_r$	1	*22.40*	1.36	***30.46***
AZT/3TC/NVP	12	16.78	1.11 (0.14)	*18.78 (2.39)*
TDF/FTC/EFV	57	**23.88**	1.10 (0.17)	**26.2 (4.2)**
TDF/FTC/LPV$_r$	30	***28.57***	1.13 (0.21)	***32.33 (6.20)***
TDF/FTC/ATV[a]	17[a]	***30.61/29.83***	1.15 (0.21)/1.23 (0.28)	***34.30 (6.32)/37.87 (8.73)***
TDF/FTC/SQV$_r$	4	***26.77***	1.14 (0.29)	***30.65 (7.76)***
TDF/FTC/FPV$_r$	7	***27.23***	1.10 (0.15)	***30.11 (4.24)***
TDF/FTC/NVP	7	*21.61*	1.09 (0.15)	*23.62 (3.45)*
ABC/3TC/EFV	20	*21.52*	1.08 (0.11)	*23.26 (2.49)*
ABC/3TC/LPV$_r$	7	**26.21**	1.04 (0.11)	**27.37 (3.07)**
ABC/3TC/ATV$_r$	5	***28.25***	1.30 (0.28)	***36.78 (8.03)***
ABC/3TC/SQV$_r$	6	**24.41**	1.01 (0.02)	*24.69 (0.69)*
ABC/3TC/FPV$_r$	2	**24.87**	1.35 (0.21)	***33.57 (5.27)***
ABC/3TC/NVP	2	*19.25*	1.11 (0.16)	*21.46 (3.13)*
ABC/AZT/3TC	22	17.00	1.08 (0.14)	18.48 (2.41)

3TC indicates lamivudine; ABC, abacavir; ADH, adherence; ATV, atazanavir; AZT, zidovudine; EFV, efavirenz; fADH, adherence factor; FPV, fosamprenavir; FTC, emtricitabine; LPV, lopinavir; NVP, nevirapine; SQV, saquinavir; TDF, tenofovir.

[a]Data for ATV/ATVr are shown.

*The type of letter shows the value position between the percentiles shown in Figure 1; normal character: value less than 25P; character in italics: value between 25P and the median (50P); character in bold: value between the median and 75P, character in bold-italics: value above 75P.

Table 2 Comparison between different combos

	AZT/3TC	TDF/FTC	ABC/3TC		ABC/AZT/3TC	
Age, years		44 (8)	41 (7)	42 (9)	42 (6)	NS
Dispensing record (DR, %)		87 (18)	88 (20)	89 (17)	91 (14)	NS
Cost/patient/day, €		21.04 (2.87)	26.11 (2.80)	23.57 (2.65)	17.00	
		P<.001				
		P<.001				
		P<.001				
			P<.001			
			P<.001			
				P<.001		
$(\text{Cost/patient/day})_{ADH}$		24.02 (5.78)	29.48 (6.91)	26.17 (5.81)	18.48 (2.41)	(€)
		P<.001				
		P=.250				
		P<.001				
			P<.001			
			P<.001			
				P<.001		

Mean and standard deviation.
NS indicates not significant.
3TC indicates lamivudine; ABC, abacavir; ADH, adherence; AZT, zidovudine; DR, dispensing records; FTC, emtricitabine; TDF: tenofovir.

The mean indicator value $(\text{cost/patient/day})_{ADH}$ was significantly higher than cost/patient/day (€27.3±€9.8 compared with €24.3±€7.6 respectively; $P<0.001$). Figure 1 shows the distribution histograms for both variables including their respective median values, 25P and 75P. The range of both indicators fluctuated between 16.2 (zidovudine-didanosine-efavirenz; ATZ/ddI/EFV) and 80.3 (darunavir-ritonavir-raltegravir-maraviroc; DRVr/RGV/MRV) €/patient/day and between 16.2 (ATZ/ddI/EFV) and 80.3 (darunavir-ritonavir-raltegravir-tenofovir-emtricitabine; DRVr/RGV/TDF/FTC) $(€/\text{patient/day})_{ADH}$.

Of the 468 patients, 341 (73%) were administered a combo-based ART regimen. The most frequent combo was AZT/3TC (155 patients, without including the combination AZT/3TC/TDF), then TDF/FTC (122 patients), ABC/3TC (42 patients) and ABC/AZT/3TC (22 patients). Table 1 shows the values of the main variables for each of the ART regimens which included a combo. Table 2 shows the comparative values among the different combos. We did not find any significant differences between the combos grouped for age or adherence (measured as DR). The cost/patient/day was significantly different for all possible combo comparisons ($P<.001$). The $(\text{cost/patient/day})_{ADH}$ was also different except when comparing AZT/3TC and ABC/3TC ($P=.250$)

Five out of the 6 combinations with AZT/3TC had a lower cost/patient/day than the median value calculated for all of the possible ART regimens. One was greater than the 75P, zidovudine (lamivudine/atazanavir-ritonavir [AZT/3TC/ATVr]), see Table 1. The anterior distribution for $(\text{cost/patient/day})_{ADH}$ was substantially adjusted: it was less than the median for 3 out of 6 combinations, although the other 3 combinations were above this value. Two of them were even above the 75P value (AZT/3TC/ATV and zidovudine/lamivudine/fosamprenavir-ritonavir; AZT/3TC/FPVr). Four out of the six combinations which include TDF/FTC were above the 75P value for cost/patient/day, one combination (TDF/FTC/EFV) remained between the median and the 75P value, and the other was less than the median (tenofovir/emtricitabine/nevirapine; TDF/FTC/NVP). The anterior distribution was maintained for $(\text{cost/patient/day})_{ADH}$. Of the 6 ABC/3TC combinations, 2 did not reach the median value and 2 were greater than the 75P value for cost/patient/day. For $(\text{cost/patient/day})_{ADH}$ only the combination abacavir/lamivudine/saquinavir-ritonavir (ABC/3TC/SQVr) did not maintain the anterior distribution, whose value changed to less than the median, and ABC/3TC/FPVr, whose value, which was initially between the median and the 75P value, was greater than the 75P for $(\text{cost/patient/day})_{ADH}$ Finally, the combination ABC/AZT/3TC remained below 25P for every case.

Similarly to f_{ADH}, no significant differences were found for the variable $\Delta_{cost/patient}$ among the different ART combinations, considering each one of the regimens and combo-based

regimens (Table 3). Nor did we find any differences when comparing all regimens that included the same combo (Figure 2). The combo with the lowest deviation from its cost/patient/day baseline value was ABC/AZT/3TC, due to the lack of adherence. It had a $\Delta_{cost/patient}$ of 8.72±14.18%. The highest deviation was for AZT/3TC combinations ($\Delta_{cost/patient}$=13.52±17.68%).

Table 4 shows the iCER estimate for each of the combos examined, including ARR and CI 95%. In all cases, CI 95% for ARR included the value 0, and therefore none of the options was significantly associated with an increase in the number of adherent patients compared with the others. With regard to absolute value, the most favourable regimens, given their higher percentage of adherent patients, are formed by TDF/FTC and ABC/3TC, having mean ARR values greater than 0. Figure 3 shows the relative position of each combo compared with mean values. The most favourable absolute value combination (ABC/3TC) is in the right lower quadrant, considering cost and percentage of adherent patients, and in relation to the patient cohort's mean values. The impact from treating 341 patients which use a combo with combinations TDF/FTC or ABC/3TC equals an outlay of €398,875 and €82,943/year, respectively.

Discussion

Twenty years since antiretroviral therapy was introduced, ART regimens can now be formulated in accordance with potency.[7] However, study strategies on ARV drug use still has not been sufficiently developed within the field of effectiveness-based medicine, which, in short, attempt to find the most efficient option to obtain maximum benefits for the population's health and for individual patients. Many HIV patients have limited possibilities to take on an active ART regimen, due to virological aspects, tolerance or their personal preferences or convenience. However, there are other scenarios in which a given patient (e.g. some naïve patients, many patients with first ART change...) can be put forward to receive different ART regimens *a priori* equivalent regarding potency, tolerance and convenience. As with other drugs and/or pharmacotherapeutic protocols usually used in the hospital, adequate examination and selection is necessary, bearing in mind the subsequent therapeutic positioning of each drug or regimen to ensure that they are not used arbitrarily and that the best interest of the patient and society are served (i.e. the best possible alternative is used).

Use of ARV in medical practice should be reflected upon, as their overall cost is increasing due to the introduction of progressively more active, yet more expensive, drugs. If we were to only limit the study to cost analysis and not consider aspects related to their adequate use, we would not be providing a complete and comparative view of the situation. The main limitation in our study was its design. The most recommended framework for evaluating and comparing different ART regimens is probably an economic assessment of cost-effectiveness, including surrogate clinical variables to make the study more effective (CD4 T helper cells and plasma viral load [VL]). However, such analysis would also have important limitations for comparing regimens, due precisely to its substitutive nature. Another limitation is that the study was developed in a specific hospital with determined purchasing costs, meaning that it is difficult to extrapolate the results and conclusions obtained. Moreover, given the limited population, some of the subgroup samples were too small, which explains the extensive variability observed. Another of the methodological problems was that the bias resulting from measuring adherence as a continuous variable (DR) and its tendency to over-estimate.[14,17,18] Furthermore, using DR as a drug 'use'-related variable is also an approximation, given that dispensing does not necessarily represent drug use. However, although the possible over-estimation can determine the results' absolute values, comparing the various ART regimens compensates the bias, given that it was applied to all of the patients and applied in the same way. However, adherence, with all its bias, is a clinical variable surrogate of final results, i.e. it is associated with HIV infection morbidity and mortality[12-14] and could therefore be used in the cost-effectiveness analysis. ART durability should also be considered, given that, regardless of the estimated effectiveness such as CD4 T helper cells, VL or adherence, it is an objective piece of information used to assess the actual usefulness of a given combination. It also makes it is easier to compare different ART, and is especially applied to the economic assessment.[19,20] Our cross sectional design does

Table 3 $\Delta_{cost/patient}$ for each of the ART regimens which include any type of combo

ART regimen	No.	$\Delta_{cost/patient}$ (%)
AZT/3TC/EFV	79	8.73 (17.47)
AZT/3TC/LPV$_r$	35	20.31 (22.09)
AZT/3TC/ATV[a]	25[a]	20.42 (19.55)
AZT/3TC/SQV$_r$	3	0.00 (0.00)
AZT/3TC/FPV$_r$	1	36.00 (0.00)
AZT/3TC/NVP	12	11.91 (14.28)
TDF/FTC/EFV	57	9.74 (17.47)
TDF/FTC/LPV$_r$	30	13.17 (21.72)
TDF/FTC/ATV[a]	17[a]	23.73 (28.54)
TDF/FTC/SQV$_r$	4	14.50 (29.00)
TDF/FTC/FPV$_r$	7	10.57 (15.60)
TDF/FTC/NVP	7	9.29 (15.99)
ABC/3TC/EFV	20	8.10 (11.58)
ABC/3TC/LPV$_r$	7	4.43 (11.72)
ABC/3TC/ATV[a]	5[a]	30.20 (28.45)
ABC/3TC/SQV$_r$	6	1.17 (2.86)
ABC/3TC/FPV$_r$	2	35.00 (21.21)
ABC/3TC/NVP	2	11.50 (16.26)
ABC/AZT/3TC	22	8.73 (14.18)

3TC indicates lamivudine; ABC, abacavir; ART, antiretroviral treatment; ATV, atazanavir; AZT, zidovudine; EFV, efavirenz; FPV, fosamprenavir; FTC, emtricitabine; LPV, lopinavir; NVP, nevirapine; SQV, saquinavir; TDF, tenofovir.

[a]Includes ATV and ATVr.

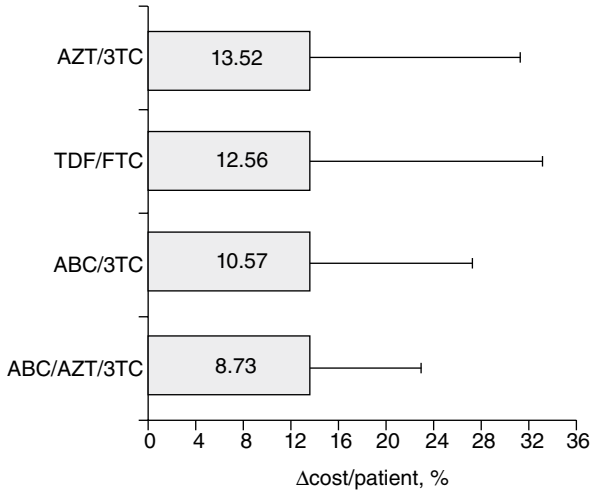

Figure 2 $\Delta_{cost/patient}$ grouped mean (%) of the ART regimens formed by each of the combos. The bars represent the mean value and the lines standard deviation for each case. No significant differences are observed between them. 3TC indicates lamivudine; ABC, abacavir; AZT, zidovudine; FTC, emtricitabine; TDF, tenofovir.

Table 4 Incremental cost-effectiveness (iCER: €/patient/day to obtain an additional adherent patient) estimated for each of the combos in relation to the given comparative for mean values cost/patient/day and percentage of adherent patients obtained from patients not taking the combo being researched

		No.	%patients ADH	ARR (CI 95%)	Cost/patient/day	Δcost (€/patient/day)	iCER (€/day/patient ADH)
AZT/3TC	Yes	155	57.8	−0.065 (−0.17;0.038)	21.04 (2.87)	−3.42	52.6
	No	186	64.3		24.46 (3.91)		
TDF/FTC	Yes	122	65.3	0.061 (−0.048;0.165)	26.11 (2.80)	4.99	81.8
	No	219	59.2		21.12 (3.16)		
ABC/3TC	Yes	42	64.3	0.034 (−0.118;0.193)	23.57 (2.65)	0.76	22.4
	No	299	60.9		22.81 (4.01)		
ABC/AZT/3TC	Yes	22	59.1	−0.024 (−0.233;0.192)	17	−6.31	262.9
	No	319	61.5		23.31 (3.66)		

3TC indicates lamivudine; ABC, abacavir; ADH, adherence; ARR, absolute risk reduction; AZT, zidovudine; CI, confidence interval; iCER, incremental cost-effectiveness; FTC, emtricitabine; TDF, tenofovir.

not provide information about the possible changes or causes, assuming that all regimens are similar in duration.

We divided the study into two main sections: one section assessed the cost/patient/day for each of the patients, and their adjustment (absolute and relative), determined by adherence as a continuous variable (DR). In section 2, we compared the cost/patient/day and the percentage of adherent patients for each of the regimens based on a specific combo compared with the regimens that did not include such combo. In the first case, we observed that most of the ART regimens still had a relative distribution after applying the adherence factor (only four regimens are penalised due to poor adherence, and only one regimen improved). This means that drug cost is the main factor for a given regimen to have values higher or lower than the median or a given percentile. In relative terms, we observed that regimens containing the combo AZT/3TC had a higher, but not significant $\Delta_{cost/patient}$, therefore suggesting that their adherence is lower. This finding can be explained using the reverse correlation between adherence and time under ART, given that AZT/3TC is the combination that has been the longest on the market of those studied.[14,21] By contrast, the combination ABC/AZT/3TC, despite being older than other combos, has the most favourable $\Delta_{cost/patient}$, probably because it is used on fewer patients, with a good clinical control and has a high adherence rate.

The iCER attempts to determine the cost of increasing patient adherence for an ART regimen based on a given

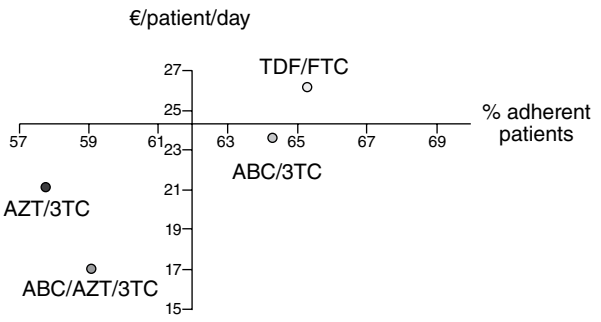

Figure 3 Representation of mean value pairs for cost/patient/day and adherence for each of the combos. The axis corresponds with the reference mean values (62% adherent patients [SMAQ=ADH and DR>90%]; cost/patient/day=€24.3). 3TC indicates lamivudine; ABC, abacavir; AZT, zidovudine; FTC, emtricitabine; TDF, tenofovir.

combo compared with remaining regimens. Its main limitation is that it has not been validated externally, given that the comparison has not been performed using a standard ART. The highest percentage of adherent patients was found for TDF/FTC and ABC/3TC based regimens, although the ARR was never significantly above 0. As such, we are not able to conclude that any given combo has a greater percentage of adherent patients. TDF/FTC had a higher iCER value than ABC/3TC, mainly because cost increase was higher. This also determines a much higher BI, as treating 341 patients with TDF/FTC instead of ABC/3TC costs over €300,000/year. These findings show that, in absolute value, ABC/3TC-based regimens are the most favourable option, with the lowest iCER, and within a cost-effectiveness dominant quadrant compared with the mean values (Figure 3). We did not however identify any significant differences with regard to the remaining combinations.

To conclude, we would like to highlight the differences found for the two analysis sections. With regard to the impact of adherence on cost/patient/day, AZT/3TC-based regimens are less preferred given the lower adherence associated with them. However their favourable cost allows an acceptable iCER. By contrast, the ABC/AZT/3TC regimen has a good adherence in terms of DR and a lower cost, although its therapeutical use is not comparable with other combos. However, it does not have a favourable iCER. When comparing the combos of choice at present, TDF/FTC-based regimens are those which obtain a less favourable cost-effectiveness, mainly because it is more expensive than ABC/3TC. Despite the implicit interest of the results shown, a consensus must be agreed on concerning which ART regimens can be used as the comparable standard, so that the results can be deemed valid. Consensus must consider costs, adherence and clinical effectiveness, so that, in view of new ARV, assessment and selection strategies introduced it in the most efficient position within HIV pharmacotherapy.

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