



ORIGINALS

Bilingual edition English/Spanish

Analysis of the costs associated with the follow-up of HIV patients discontinuing antiretroviral treatment due to lack of effectiveness or unacceptable toxicity in Spain

Análisis de los costes asociados al seguimiento de pacientes con VIH que discontinúan el tratamiento antirretroviral por falta de eficacia o toxicidad inaceptable en España

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Received 8 March 2022;
Accepted 27 June 2022.
Early Access date (09/30/2022).
DOI: 10.7399/fh.13038

Abstract

Objective: To assess the use of resources and the costs associated with following up patients infected with the human immunodeficiency virus after discontinuation of an antiretroviral treatment and initiation of a new one due to a lack of effectiveness or unacceptable toxicity, as compared to the costs involved in the routine follow-up of patients on antiretroviral treatment, from the Spanish National Health System perspective.

Method: The use of resources (clinical tests, medical visits, and hospital pharmacy visits) associated with following three profiles of patients infected with the human immunodeficiency virus (stable ones, those discontinuing an existing antiretroviral treatment and being switched to a new one due to a lack of effectiveness, and those discontinuing an existing antiretroviral treatment and being switched to a new one due to unacceptable toxicity) was identified, based on clinical practice guidelines and the findings of a multidisciplinary expert panel ($n = 5$). The experts agreed on the main adverse events leading to discontinuation, classifying them into gastrointestinal, renal, osseous, musculoskeletal, dermatological, hepatic, lipid profile-related, neuropsychiatric and sexual alterations. Unit costs were identified from official healthcare costs databases. The cost

Resumen

Objetivo: Estimar el uso de recursos y costes asociados al seguimiento de pacientes con infección por el virus de la inmunodeficiencia humana tras discontinuación del tratamiento antirretroviral actual debido a falta de efectividad o toxicidad inaceptable y cambio a un nuevo tratamiento antirretroviral, comparado con el seguimiento habitual de los pacientes con tratamiento antirretroviral, desde la perspectiva del Sistema Nacional de Salud español.

Método: Se identificó el uso de recursos (pruebas clínicas, visitas médicas, visitas a la farmacia hospitalaria) asociado al seguimiento de pacientes con infección por el virus de la inmunodeficiencia humana en tres perfiles de pacientes (estable, discontinuación y cambio por falta de efectividad, discontinuación y cambio por toxicidad inaceptable), a partir de las guías de práctica clínica y un panel de expertos multidisciplinar ($n = 5$). Los expertos consensuaron los principales eventos adversos que conducían a la discontinuación, agrupándolos en: alteraciones gastrointestinales, renales, óseas, musculoesqueléticas, dermatológicas, hepáticas y del perfil lipídico, trastornos neuropsiquiátricos y sexuales. Los costes unitarios se identificaron a partir de bases de datos oficiales

KEYWORDS

HIV; Antiretroviral therapy; Follow-Up Studies;
Pharmacy Service, Hospital; Toxicity; Health Care Costs.

PALABRAS CLAVE

VIH; Tratamiento antirretroviral; Seguimiento;
Servicio de Farmacia Hospital; Toxicidad; Coste sanitario.



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(€, 2020) of following up each patient profile was estimated, excluding the cost of the antiretroviral treatment itself, with a time horizon of two years.

Results: The per-patient cost of following up stable patients over two years was estimated at €4,148 (tests: €2,293; visits: €1,855). Patient follow-up after discontinuation of an existing antiretroviral treatment and initiation of a different one due to a lack of effectiveness was estimated at €5,434 (tests: €2,777; visits: €2,657). The cost of follow-up after discontinuation of an existing regimen and initiation of a new one due to unacceptable toxicity varied according to the adverse event prompting the switch, ranging from €4,690 for lipid profile dysregulation, to €5,304, for musculoskeletal alterations. In this patient profile, the cost of tests ranged from €2,403 to €3,017, and that of visits from €2,287 to €2,842.

Conclusions: The cost associated with following up of patients infected with the human immunodeficiency virus after discontinuation of an existing antiretroviral regimen and initiation of a new one is higher than that of routine follow-up, without taking the cost of drugs into account. The treatment discontinuation rate is a relevant factor when selecting the most appropriate therapy for each patient.

Introduction

A total of 56,758 new cases of infection with the human immunodeficiency virus (HIV) have been reported in Spain since 2003. Annual rates of new diagnoses per 100,000 inhabitants fell from 12.81 in 2008 to 5.94 in 2019, a reduction associated with the use of antiretroviral therapy (ART)¹. According to a recently published study, the implementation of ART in Spain required an investment of €6,185 billion from its introduction in 1987 to 2018. Moreover, the cost of ART in 2019 was estimated at €677 million, which represents 2.86% of the total spend of the National Health System on pharmaceutical and medicinal products². Taking into account the pharmaceutical cost, the cost of the adverse events resulting from treatment and that of resistance studies and of the required HLA B*5710 tests, the total cost of ART typically ranges between €6,788 and €10,649 per patient³.

Implementation of ART has decreased morbidity and mortality as well as HIV infection transmission rates, making it possible for patients to enjoy a life expectancy similar to that of the general population³. According to the recommendations of the AIDS Study Group (GeSIDA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and to the Spanish National AIDS Plan (PNS)⁴, ART should be administered to every HIV patient. Prior to initiation of ART, it is essential to individually determine which agents should be part the initial regimen given their different efficacy, toxicity, resistance, tropism, interactions, etc., profiles. In addition, the selected regimen should be adapted to the patient's lifestyle and comorbidities, with a particular focus on promoting adherence⁴. Currently, the most often recommended initial regimens are aimed at reducing plasma viral load to less than 50 copies/ml and usually comprise a combination of two (double therapy) or three (triple therapy) drugs. The preferred recommended initial triple therapies are as follows: bictegravir/emtricitabine (FTC)/tenofovir alafenamide (TAF); dolutegravir (DTG)/abacavir/lamivudine (3TC); DTG + FTC/TAF; and raltegravir (400 mg twice a day or 1,200 mg once a day) + TAF/TAF. The only double therapy currently recommended is a combination of DTG/3TC (an integrase inhibitor [INI] and a nucleoside/tide reverse transcriptase inhibitor [NRTI]). However, this therapy is associated with a series of restrictions as it is not recommended for patients with a baseline CD4+ count below 200/μL and it cannot be used in subjects with chronic hepatitis B virus (HBV) infection⁴.

Once the patient has been started on a given ART regimen, there are several reasons why it may be necessary to switch them to a different one, including lack of efficacy, poor tolerability, toxicity, comorbidities, drug-drug interactions, the need to reduce the number of daily doses or tablets, dietary requirements, pregnancy, and the cost of ART itself⁵. Although most switches are motivated by a desire to simplify the therapy, factors such as toxicity or therapeutic failure are also frequent reasons for switching ART therapies in Spain^{6,7}.

de costes sanitarios y de la literatura. Se estimó el coste (€, 2020) del seguimiento en cada perfil de paciente, sin incluir el coste derivado del tratamiento antirretroviral, en un horizonte temporal de dos años.

Resultados: El coste por paciente a dos años se estimó en 4.148 € (pruebas: 2.293 €; visitas: 1.855 €) para el seguimiento del paciente estable. El seguimiento del paciente tras discontinuación por falta de efectividad y cambio de tratamiento antirretroviral se estimó en 5.434 € (pruebas: 2.777 €; visitas: 2.657 €). El coste del seguimiento tras la discontinuación por toxicidad inaceptable y cambio de tratamiento antirretroviral varió en función del evento adverso que motivó el cambio, oscilando entre 4.690 € para las alteraciones del perfil lipídico, y 5.304 € para las alteraciones musculoesqueléticas. En este perfil de pacientes, las pruebas variaron entre 2.403 € y 3.017 € y las visitas entre 2.287 € y 2.842 €.

Conclusiones: El coste asociado al seguimiento del paciente con infección por el virus de la inmunodeficiencia humana tras discontinuación y cambio a un nuevo tratamiento antirretroviral es mayor comparado con el seguimiento habitual, sin tener en cuenta el coste farmacológico. La tasa de discontinuación del tratamiento antirretroviral es un factor relevante a la hora de seleccionar la terapia más adecuada para cada paciente.

In this regard, with a view to comparing the real world results of discontinuing INI-based triple therapy as compared with DTG and/or boosted protease inhibitors (bPIs) double therapy in Spain, an analysis was carried out of patients in the VACH group (a prospective cohort comprising over 14,833 HIV patients followed up at 23 Spanish hospitals)⁸. Results showed a higher risk of all-cause discontinuation, as well as a higher risk of discontinuation caused by virologic failure in patients treated with double therapy. Along the same lines, another subanalysis of the same cohort that included patients switched to DTG-based double therapy or to INI-based triple therapy concluded that the risk of discontinuation of double therapy due to treatment failure was 2.3 times higher than that associated with triple therapy⁹.

In an environment of limited resources, judicious management of the resources allocated to ART is paramount⁴. A few pharmacoeconomic studies carried out in Spain^{3,10} have evaluated the cost-effectiveness of the different therapies and the economic impact of the optimization of ART recommended by GeSIDA. However, to the best of our knowledge no studies have focused on the use of resources and the healthcare costs associated with discontinuation of an existing ART regimen and switching to a different one. Such an analysis would provide for more effective decision-making.

The main purpose of this study is to quantify the use of resources and calculate the costs associated with following up HIV patients following discontinuation of an ART regimen and initiation of a new one due to lack of effectiveness or unacceptable toxicity (i.e., an adverse event whose severity outweighs the benefits of treatment), as compared with the usual follow-up of patients on ART, from the perspective of the Spanish National Health System.

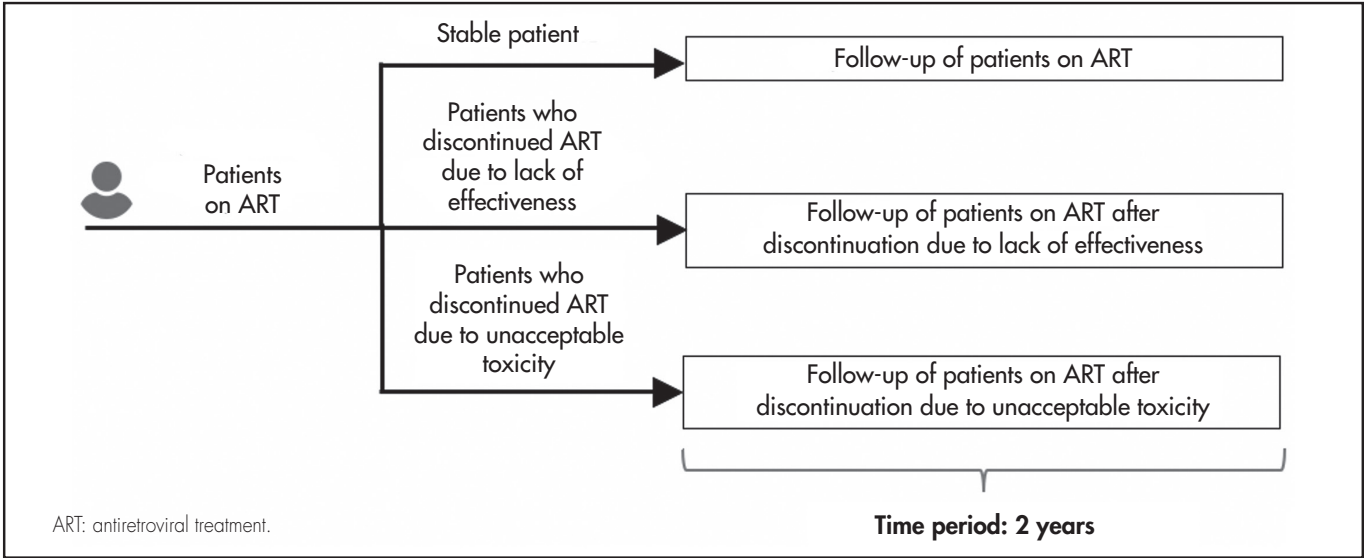
Methods

Drawing on the existing literature, a multidisciplinary expert panel comprising three clinicians specializing in infectious diseases and two hospital pharmacists carried out an estimation of the consumption of resources associated with following up a stable patient and switching their ART regimen as a result of treatment discontinuation. The analysis was based on three hypothetical profiles of HIV patients on ART (Figure 1): stable patient; patient who discontinues their treatment due to lack of effectiveness and is switched to a new ART; and patient who discontinues their treatment due to unacceptable toxicity and is switched to a different ART. Use of resources was calculated over a two-year period from discontinuation.

Resource consumption and costs

The analysis only considered direct healthcare costs, including the costs associated with clinical tests, medical visits and hospital pharmacy visits related to the management of the ART and to the follow-up of adverse events (the cost of the adverse events or of the ART themselves was not taken into consideration). The analysis, based on the patient management recommendations made by GeSIDA^{4,5}, identified the main healthcare resources asso-

Figure 1. Procedure used for the analysis.



ciated with following up the three classes of HIV patients considered (clinical tests and medical visits). The frequency with which these resources were used as well as the amount of resources used, together with the frequency of hospital pharmacy visits over the two-year period, were all estimated by the expert panel (Table 1).

Additionally, for patients who discontinued ART due to unacceptable toxicity, the panel identified the most common adverse events according to their nature: gastrointestinal disorders, renal dysfunction, bone alterations, neuropsychiatric disorders, musculoskeletal alterations, sexual disorders, skin problems, lipid profile dysregulation, and liver dysfunction. They also analyzed the consumption of resources associated with the clinical tests and medical visits required (Table 2). Unit costs were extracted from the eSalud costing database¹¹. The costs of hospital pharmacy visits were obtained from the literature (Table 1)¹².

Cost analysis

For each adverse event considered, a comparison was made between the cost associated with stable patients on ART, the cost of following up patients who discontinued an existing ART and were switched to a new one due to lack of effectiveness and the cost of following up a patient further to

discontinuation of an existing ART and initiation of a new one due to unacceptable toxicity. A distinction was made between the cost of clinical tests and that corresponding to medical visits.

Sensitivity analysis

With a view to determining the potential effect of modifying the level of resource consumption (which could be different across different hospitals depending on individual patient management policies) and the costs included in the assessment, a sensitivity analysis was performed where the total costs of following up stable and discontinuing patients (due to lack of effectiveness or unacceptable toxicity) were made to vary by 25%.

Results

Stable patients

The total cost inherent in following up a stable patient on ART for up to two years was estimated at €4,148, of which €2,293 corresponded to clinical tests, €1,481 to medical visits, and €374 to visits to the hospital's pharmacy (Figure 2).

Figure 2. Cost associated with following up a stable patient as compared with the cost involved in following up a patient after discontinuation due to lack of effectiveness or unacceptable toxicity.

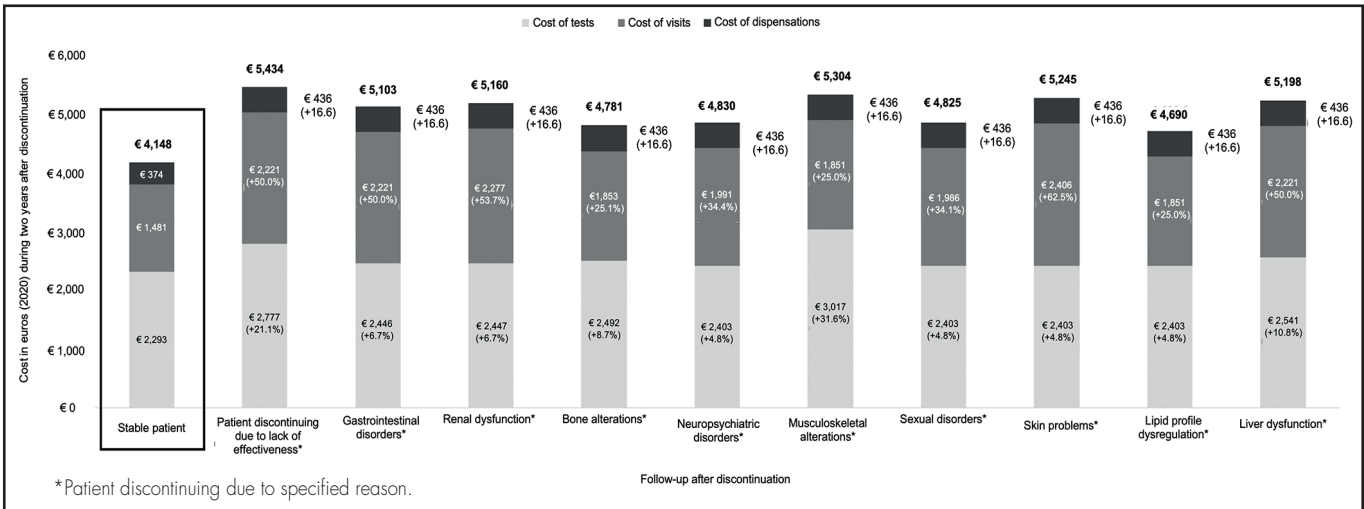


Table 1. Use of resources associated with patient follow-up

Test	Unit cost ^{11,12} (€, 2020)	Percentage of patients	Frequency for stable patients on ART	Frequency for patients on ART after discontinuation due to lack of effectiveness	Frequency for patients on ART after discontinuation due to unacceptable toxicity
CD4+ T cell count (total quantity and percentage)	€17.80	100%	Every 6 months	At 3 months and every 6 months thereafter	Every 6 months
HIV viral load	€110.90	100%	Every 6 months	At one month, at 3 months and every 6 months thereafter	Every 6 months
Hemogram	€6.55	100%	Every 6 months	Every 6 months	At 1 month, at 3 months and every 6 months thereafter
Biochemical blood analysis including determination of liver, kidney (with eGFR) and lipid status	€61.86	100%	Every 6 months	Every 6 months	At 1 month, at 3 months and every 6 months thereafter
Blood sugar	€1.29	100%	Every 6 months	Every 6 months	Every 6 months
Bone metabolic profile (Ca, P & vitamin D)	–		Every 6 months, except for vitamin D which is evaluated on a yearly basis	Every 6 months, except for vitamin D which is evaluated on a yearly basis	Every 6 months, except for vitamin D which is evaluated on a yearly basis
P & Ca	€4.42	100%	Every 6 months	Every 6 months	Every 6 months
Vitamin D	€44.99	100%	Yearly	Yearly	Yearly
Elementary urine and urinary sediment testing and biochemical analysis of an isolated urine sample: proteinuria and protein / creatinine ratio	€41.86	100%	Every 6 months	Every 6 months	At 1 month, at 3 months and every 6 months thereafter
Screening for STD (including HAV & HCV)	€163.12	100%	Every 6 months	Every 6 months	Every 6 months
Anal cytology	€62.40	100%	Yearly	Yearly	Yearly
Smear test (in women)	€42.39	24%* (women with HIV)	Yearly	Yearly	Yearly
Liver ultrasound in subjects also infected with HCV	€67.76	29.9%* (coinfected with HCV) 17.1%* (coinfected with HCV and with a diagnosis of cirrhosis)	Yearly for patients coinfected with HCV (2 tests) Every 6 months for patients coinfectd with HCV and with a diagnosis of cirrhosis (4 tests)	Yearly for patients coinfected with HCV Every 6 months for patients coinfectd with HCV and with a diagnosis of cirrhosis	Yearly for patients coinfected with HCV Every 6 months for patients coinfectd with HCV and with a diagnosis of cirrhosis
Abdominal ultrasound	€69.59	100%	Every 2 years	Every 2 years	Every 2 years
DEXA scan	€68.49	55%* (patients > 50 years)	Every 2 years	Every 2 years	Every 2 years
CD8+ T cell count and CD4+/ CD8+ratio calculation	€66.11	100%	Every 6 months	At 3 months and every 6 months thereafter	Every 6 months
Genotypic resistance testing	€173.11	100%	Not performed	Only once (when failure is detected)	Not performed
HLA B*5701	€116.02	100%	Not performed	Performed only if it was not performed before	Not performed
Clinical examination	€370.13	100%	Every 6 months	Every 6 months	Every 6 months
Visit to an HIV specialist	€370.13	100%	Not performed	At 1 and at 3 months	Depends on AE
Visit to the hospital's pharmacy	€31.17	100%	Every 2 months	On switching, at 1 month, at 2 months and every 2 months thereafter	On switching, at 1 month, at 2 months and every 2 months thereafter

ART: antiretroviral treatment; Ca: calcium; gGFR: estimated glomerular filtration rate; HAV: hepatitis A virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; P: phosphorus; STD: sexually transmitted disease.

*The percentage of patients has been extracted from a hospital-based survey of patients infected with HIV¹⁸.

Table 2. Use of resources associated with adverse event follow-up

Adverse event	Frequency of the adverse event	Follow-up tests required	Unit cost ¹¹ (€,2020)	Frequency
Gastrointestinal disorders				
Diarrhea	15%	Fecal culture	€34.38	Only once
Dyspepsia	60%	<i>Helicobacter pylori</i> test	€34.01	Only once
Nausea	15%	<i>Helicobacter pylori</i> test	€34.01	Only once
Vomiting	5%	<i>Helicobacter pylori</i> test	€34.01	Only once
Persistent epigastric pain	5%	Endoscopy	€218.05	Only once
Additional visits to the HIV specialist (all patients with gastrointestinal disorders)			€370.13	Yearly
Renal dysfunction				
Decreased GFR	60%	Renal ultrasound	€59.69	Only once
Renal tubular disorders	25%	24-hour urine creatinine clearance test	€0.14	At one month, at 3 months and every 6 months thereafter
		Referral to nephrologist	€186.93	
Lithiasis	5%	Uric acid blood test	€1.17€	Only once
		Referral to nephrologist	€186.93	Only once
Proteinuria	5%	24-hour urine analysis	€26.07	Only once
Phosphaturia	5%	Tubular phosphate and vitamin D reabsorption	€70.49	Yearly
Additional visits to HIV specialist (all patients with renal dysfunction)			€370.13	Yearly
Bone alterations				
Osteopenia	10%	DEXA scan	€68.49	Only once
Osteoporosis	4%	DEXA scan	€68.49	Yearly
Vitamin D deficiency	85%	Vitamin D levels	€44.99	Every 6 months, vitamin D levels
Fracture	1%	X-ray	€23.59	Only once
		Referral to orthopedic surgeon	€151.20	Only once
Additional visits to HIV specialist (all patients with bone alterations)			€370.13	Only once
Neuropsychiatric disorders				
Insomnia	35%	Referral to psychiatrist	€138.27	Only once
Headache	20%	Referral to neurologist	€148.44	Only once
Anxiety	25%	Referral to psychiatrist	€138.27	Only once
Depression	10%	Referral to psychiatrist	€138.27	Only once
Irritability	10%	Referral to psychiatrist	€138.27	Only once
Additional visits to HIV specialist (all patients with neuropsychiatric disorders)			€370.13	Only once
Musculoskeletal alterations				
Muscle cramps	100%	Electrophysiological study	€613.97	Only once
Additional visits to HIV specialist (all patients with musculoskeletal alterations)			€370.13	Only once
Sexual disorders				
Sexual dysfunction	100%	Referral to urologist	€135.48	Only once
Additional visits to HIV specialist (all patients with sexual disorders)			€370.13	Only once
Skin problems				
Exanthema	40%	Referral to dermatologist	€92.69	Yearly
Itching	60%	Referral to dermatologist	€92.69	Yearly
Additional visits to HIV specialist (all patients with skin problems)			€370.13	Yearly
Lipid profile dysregulation				
Dyslipidemia	100%	Additional visits to the HIV specialist	€370.13	Only once
Liver dysfunction				
Hypertransaminasemia	75%	Liver ultrasound	€67.76	Only once
		HBV and HCV testing	€94.08	Only once
Liver steatosis	25%	Liver ultrasound	€67.76	Only once
Additional visits to HIV specialist (all patients with liver dysfunction)			€370.13	Yearly

GFR: glomerular filtration rate; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus.

Patients discontinuing ART due to lack of effectiveness

The total cost of following up a patient on ART for up to two years from discontinuation of one regimen and initiation of a new one due to lack of effectiveness was found to be 31.0% higher than the usual cost of following up a stable patient on ART. The cost was calculated to be €5,434, of which €2,777 corresponded to clinical tests (21.1% more than for stable patients), €2,221 to medical visits (50.0% more than for stable patients), and €436 to visits to the hospital's pharmacy (16.6% more than for stable patients) (Figure 2).

Patients discontinuing ART due to unacceptable toxicity

The total cost of following up a patient for up to two years after toxicity-related discontinuation and initiation of a new ART varied depending on the nature of the adverse event experienced (Figure 2).

The total increase in the cost of following up a patient discontinuing an existing ART regimen and initiating a new one due to unacceptable toxicity as compared with the usual follow-up costs for stable patients ranged between 13.1%, when the adverse event was associated with a lipid profile dysregulation, to 27.9%, when the adverse event was a musculoskeletal alteration.

The total cost of following up a patient on ART following discontinuation of an existing ART and initiation of a new one due to unacceptable toxicity was estimated to stand between €4,690, when the adverse event was a dysregulation of the patient's lipid profile, and €5,304, when the problem was a musculoskeletal alteration. Of the €4,690 spent on lipid profile dysregulations, €2,403 corresponded to clinical tests (4.8% more than for stable patients), €1,851 to medical visits (25.0% more than for stable patients), and €436 to visits to the hospital's pharmacy (16.6% more than for stable patients). Of the €5,304 spent on musculoskeletal alterations, €3,017 corresponded to clinical tests (31.6% more than for stable patients), €1,851 to medical visits (25.0% more than for stable patients), and €436 to visits to the hospital's pharmacy (16.6% more than for stable patients) (Figure 2). Supplementary table 1 provides a detailed account of the additional costs associated with each of the adverse events analyzed, distinguishing between the costs corresponding to the discontinuation and those related to the adverse event itself.

Sensitivity analysis

Varying total follow-up costs by 25% in order to evaluate potential differences in the management of patients by different hospitals showed that the total cost of following a stable patient treated with ART for up to two years ranged between €3,111 and €5,185. In the case of patients switched to a different treatment due to lack of effectiveness, the cost ranged between €4,076 and €6,793. As regards patients who discontinued their treatment due to unacceptable toxicity, the cost ranged from €3,518, when lipid profile dysregulations were present, to €6,630 for musculoskeletal alterations.

Discussion

The results of this analysis demonstrate that the consumption of resources and the costs associated to following up HIV patients after discontinuation of an existing ART and initiation of a new one are higher than those corresponding to stable HIV patients, mainly due to the higher number of medical visits required. In the case of patients discontinuing ART due to lack of effectiveness, the amount spent on medical visits was 50% higher than that for stable patients, whereas in patients discontinuing ART due to unacceptable toxicity, the increase ranged from 25% when patients experienced musculoskeletal alterations and lipid profile dysregulations, and 63% when they experienced skin problems. As far as hospital pharmacy visits are concerned, an increase of nearly 17% was observed across all patient groups. Two additional visits to the hospital's pharmacy were considered to result from the change in treatment.

The sensitivity analysis performed showed that the total costs associated with managing an HIV patient whose ART is switched due to lack of effectiveness or unacceptable toxicity could be twice as high as those correspon-

ding to stable patients (considering that stable patients are usually treated conservatively whereas patients whose treatment regimen is modified tend to be managed more comprehensively).

Although the advent of new ART regimens has resulted in improved efficacy and tolerability, switching ART regimens is not unusual particularly during the first year (around 30% of patients)^{3,14}. Changes in treatment are often motivated by poor tolerability, drug-drug interactions, appearance of new comorbidities, dietary requirements, the patient's wishes, unspecified doctor's decisions, the cost of treatment and virologic failure¹⁵. Given its negative impact on adherence and virologic efficacy, the initial ART regimen should be administered unchanged for a considerable period of time¹⁵. Moreover, when changes are made to an ART regimen a more comprehensive patient follow-up should be made⁴.

The current therapeutic modifications recommended for virologically suppressed patients, take into account the antiretroviral drugs included in the patient's regimen, and are grouped into switch to triple therapies (that include change of the NRTI, switch to regimens based on non-nucleoside reverse transcriptase inhibitors (NNRTIs) or switch to an INI-based regimen), or a change to regimens with less than three antiretrovirals (which may be dual therapies made up of a bPI + 3TC, DGT + rilpivirine (RPV), or DGT+ (3TC)⁴). In the case of virologically suppressed patients, an ART regimen with three, or at least two, active antiretrovirals is recommended including, if possible, a next-generation agent⁴.

Two real-world analyses based on a Spanish cohort found that, when the above recommendations are followed, there is a higher risk of discontinuation due to virologic failure when patients are treated with dual vs. triple therapy (analysis 1: HR = 2.06 [1.54; 2.77] for the entire population, HR = 2.78 [1.71; 4.51] for patients on dual or triple therapy based on DTG, and HR = 1.86 [1.15; 3.02] for virologically suppressed patients at initiation [HIV RNA <50 copies/mL]⁸; analysis 2: patients switched to dual DTG-based therapy or triple INI-based therapy: HR = 2.3 [1.3; 4.1])⁹. These results are in line with those of other international studies including the observational OPERA trial, based on the OPERA database, which contains data from 79,803 HIV patients in the United States gathered between 2010 and 2016). The OPERA trial also found a significantly higher discontinuation rate in patients on double therapy as compared with those on triple therapy (HR = 1.51 [1.41; 1.61])¹⁶.

Although the pharmacological cost is the most significant outlay in the treatment of HIV patients^{3,17}, it should be investigated whether other expenses associated with patient follow-up may be avoided. Taking into consideration that the virologic failure risk of patients switched to dual therapy is twice higher than that of patients switched to triple therapy (HR between 1.86 and 2.78), this study may contribute to more judicious choice of the most appropriate ART regimen as the cost of follow-up after discontinuation of an existing ART and initiation of a new ART due to either lack of effectiveness or unacceptable toxicity is higher than that of following up stable patients. This increased use of resources should be taken into consideration.

This article is not without limitations. These are mainly related to the fact that costs were estimated based on a review of the literature and consultations with experts. Moreover, the analysis is somewhat oversimplified as it did not consider HIV patients on ART who require specific management and follow-up adapted to their needs. Nonetheless, the analysis was based on the resources consumed in the course of treating a standard HIV patient with ART, following the recommendations in the guidelines^{4,5}. Furthermore, no consideration was given to the pharmacological cost of ART as it was hypothesized that the management of stable or discontinuing patient does not vary as a function of the type of treatment administered and, therefore, the analysis could be applied to any of the combinations available. Also, as our goal was to focus our analysis on the cost of tests and visits, the costs associated with the concomitant medication prescribed to address the toxicities observed was not part of the analysis. Finally, the indirect costs related to loss of productivity were ignored as the focus was on taking the perspective of the Spanish National Health System.

In spite of the aforementioned limitations, our analysis provides an approximate idea of the cost associated to discontinuation of ART, which may help make better decisions in routine clinical practice.

In conclusion, our study brings to the fore the importance of considering the rates of discontinuation of ART when electing the most appropriate ART regimen for HIV patients as, apart from the clinical consequences associated with such choices, ART regimen selection is a key factor for the consumption of resources, significantly influencing in many cases the overall cost of ART.

Funding

This study was funded by Gilead Sciences.

Conflict of interest

Ángeles Castro declared no conflict of interest. Pilar Díaz declared to have received financial support from Gilead Sciences for her participation in the present study as well consultancy and speaker's fees, and stipends for participating in conferences, bureaus, educational events and the preparation of manuscripts for Gilead Sciences and MSD. She also declared to have received fees for participating as an expert and financial support for attending meetings and/or travelling to events organized by Gilead Sciences prior to the preparation of this study. Pere Domingo declared to have received grants from Gilead Sciences, Janssen & Cilag, and ViiV Healthcare as well as consultancy and speaker's fees, and stipends for par-

ticipating in conferences, bureaus, educational events and the preparation of manuscripts for Gilead Sciences, Janssen & Cilag, and ViiV Healthcare, MSD, Theratechnologies, and Roche prior to the preparation of this study. Juan E. Losa-García declared no have no conflict of interest. Antonio Castro is a Gilead Sciences staff member. Neus Vidal-Vilar and work for Outcomes'10, an independent research organization, and have received fees for their contribution to the development of this project and to the preparation of the manuscript.

Presentation at congresses

- Organization: International Health Economics Association Congress.
- Venue: Online.
- Date: 12-15 July 2021.

Contribution to the scientific literature

Discontinuation of an existing antiretroviral regimen and initiation of a different one increases resource consumption and costs for the National Health System. This should be taken into consideration every time a given antiretroviral therapy is selected.

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Supplementary table 1. Additional costs (€,2020) associated with discontinuation due to unacceptable toxicity for the different types of adverse event studied over a period of two years from switching

Costs	Gastrointestinal disorders	Renal dysfunction	Bone alterations	Neuropsychiatric disorders	Musculoskeletal alterations	Sexual disorders	Skin problems	Lipid profile dysregulation	Liver dysfunction
Additional tests due to discontinuation	€110	€110	€110	€110	€110	€110	€110	€110	€110
Additional tests due to the AE	€43	€44	€89	€0	€614	€0	€0	€0	€138
Additional visits to the HIV specialist	€740	€740	€370	€370	€370	€370	€740	€370	€740
Additional visits to other specialists	€0	€56	€2	€140	€0	€135	€185	€0	€0
Additional visits to the hospital's pharmacy	€62	€62	€62	€62	€62	€62	€62	€62	€62
Total	€955	€1,012	€633	€682	€1,156	€677	€1,097	€542	€1,050

AE: adverse events; HIV: human immunodeficiency virus.