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Clinical and economic benefit of 32 years of antiretroviral treatment for people living with HIV in Spain: Has it been an efficient intervention? ☆



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ABSTRACT

Introduction: Although antiretroviral therapy (ART) for HIV/AIDS was introduced in 1987, improvement in disease progression and reduction in mortality at a population level was not observed until 1996, with the combination of three or more drugs. The objective was to estimate the clinical and economic benefit of ART in Spain in the 32-year period between 1987 and 2018.

Methods: A cost-benefit analysis was performed, using a second-order Monte Carlo simulation, from the societal (base case) and the National Health System (NHS) perspectives. New cases of HIV, AIDS and related deaths were obtained from the SINIVH and UNAIDS registries, with population projections without ART using triple exponential smoothing. Expenditure on ART was obtained from the National AIDS Plan reports and market studies.

Results: The NHS invested 6185 million euros in 32 years. In that period, 323,651 AIDS-related deaths, 500,129 AIDS cases and 161,417 HIV cases were averted, with total savings of 41,997 million euros. The net benefit (net savings) is estimated at 35,812 million euros (societal) and 1032 million euros (NHS). For every euro invested in ART, a return on investment of € 6.79 and € 1.16 was obtained, respectively.

Conclusions: The use of ART over 32 years prevented a large number of deaths and cases of AIDS and HIV, providing significant economic savings for the NHS. ART is an efficient intervention for the NHS.

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Beneficio clínico y económico de 32 años de tratamiento antirretroviral de personas que viven con VIH en España: ¿ha sido una intervención eficiente?

RESUMEN

Introducción: Aunque el tratamiento antirretroviral (TAR) del VIH/sida se introdujo en 1987, la mejora en la progresión de la enfermedad y reducción de la mortalidad poblacional no se observó sino hasta 1996, con la combinación de tres o más fármacos. El objetivo fue estimar el beneficio clínico y económico del TAR en España en el periodo de 32 años, comprendido entre 1987 y 2018.

Palabras clave:

Sida

Análisis coste-beneficio

Tratamiento antirretroviral

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Métodos: Se realizó un análisis de coste-beneficio mediante la simulación de Monte Carlo de segundo orden, desde las perspectivas de la sociedad (caso base) y el Sistema Nacional de Salud (SNS). Los nuevos casos de VIH, sida y muertes relacionadas se obtuvieron de los registros SINIVIH y ONUSIDA, con proyecciones poblacionales sin TAR mediante suavizamiento exponencial triple. El gasto en TAR se obtuvo de informes del Plan Nacional del SIDA y estudios de mercado.

Resultados: El SNS invirtió 6.185 millones de euros en 32 años. Durante este periodo se evitaron 323.651 muertes por sida, 500.129 casos de sida y 161.417 casos de VIH, con un ahorro total de 41.997 millones de euros. El beneficio neto (ahorros netos) se estima en 35.812 millones de euros (sociedad) y 1.032 millones de euros (SNS). Por cada euro invertido en TAR, se obtuvo un retorno de la inversión de 6,79 € y 1,16 €, respectivamente.

Conclusiones: La utilización de TAR durante 32 años ha evitado gran número de muertes y casos de sida y VIH, generando significativos ahorros económicos para el SNS. El TAR es una intervención eficiente para el SNS.

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Introduction

The introduction of zidovudine (AZT) in 1987, the first antiretroviral treatment (ART), provided modest control of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS)¹. HIV, however, developed rapid resistance to this drug². In fact, in Spain a significant impact of ART on disease progression and mortality reduction was not observed until 1996 with the combination of three or more drugs^{3,4}. Since then, ART has led to a steady reduction in AIDS cases⁴ and related mortality in Spain³. It is estimated that 151,400 people with HIV are currently living in Spain, 87% of whom (131,775) are aware of their infection; that 97.3% of them are on treatment (128,216); and finally that 90.4% of these (115,900) achieved HIV viral suppression^{5,6}, with a consequent reduction in the transmission of the disease.

According to a recent cost-benefit study⁷, globally ART averted 9.5 million deaths in the 1995–2015 period. The global net cost of ART in that period is estimated at US\$ 301 billion, while the benefits of ART (as a result of HIV and AIDS cases and AIDS deaths averted) amounts to US\$ 1053 billion. As a result, the net benefit of the health impact of ART amounts to US\$ 752 billion⁷. In Spain, however, the cost-benefit of ART has not been assessed, according to a systematic review carried out by us. This study aims to estimate ART's clinical and economic impact in Spain over a 32-year period (1987–2018).

Methods

Cost-benefit model

A cost-benefit analysis was conducted. Costs and health outcomes (benefits) are measured in monetary units in this type of analysis. In this study, the costs (2020 euros [€]) are the costs of purchasing ART and the benefits are the averted costs (i.e. savings) from the clinical outcomes of ART compared to a hypothetical scenario in which ART would not have been available: (i) new HIV infections averted; (ii) new AIDS cases averted; and (iii) AIDS deaths averted (Fig. 1). These clinical outcomes were assumed based on the following assumptions: (i) viral suppression by ART eliminates the transmissibility of HIV and, therefore, the appearance of new HIV cases^{8,9}; (ii) avoiding the progression of HIV patients to AIDS would reduce new AIDS cases^{10,11}; and (iii) reducing new AIDS cases would reduce AIDS-associated deaths⁷.

The cost-benefit analysis was modelled by a probabilistic analysis, using second-order Monte Carlo simulations, with 1000 simulations. This methodology made it possible to analyse the uncertainty of the model variables^{12–14}, mainly the following: (i) the annual cost of ART in Spain; (ii) life expectancy in HIV patients, according to the period analysed; (iii) AIDS deaths averted; (iv) AIDS cases averted; and (v) new HIV cases averted. Continuous variables (costs, number of cases) were adjusted to gamma distributions^{12,13}, based on the minimum and maximum values available or, alternatively,

natively, a variability of $\pm 20\%$ of the variable's mean or available value.

General characteristics of the model

The analysis was conducted according to a defined base case, agreed upon and validated by a panel of 4 experts in HIV management, including the average or most plausible (clinically or epidemiologically speaking) values of the variables. The base case defined established the following assumptions: annual discounted costs and benefits of 3%, societal perspective (including both direct health costs of HIV and AIDS cases and indirect costs – mainly employment – associated with the premature death of AIDS patients), the economic value of deaths averted based on the gross domestic product (GDP) per capita^{7,15–17} and considering additional life expectancy from the study by Gueller et al.¹⁸ Several sensitivity analyses were also performed, modifying some of the variables in the model to assess the robustness of the base case. In particular, the following variables were analysed: (i) annual discounting of costs and benefits: 0% and 6%; (ii) economic value of deaths averted: using the monetary value of statistical life (the monetary value of a statistical life is called the value, measured in monetary units, that society as a whole attributes to preventing any one of its members from dying; it can be calculated using the declared preferences method)¹⁹; and (iii) sensitivity analysis from the National Health System (NHS) perspective, considering only direct healthcare costs and without annual discounting, because health decision-makers are interested in the real budgetary impact without applying discounts²⁰ of both ART costs and benefits, on the understanding that the NHS decision-maker (budget holder) is particularly interested in the actual costs to the healthcare system at any given time, not discounted²¹. Finally, two sub-analyses were carried out: (i) the estimation of the cost-benefit for the NHS attributable to the ART drugs marketed by Gilead Sciences in the period between 2002 and 2018, estimating the percentage of the total population based on patients treated annually according to sales data; and (ii) the analysis of three periods (years 1987–1996; 1997–2007 and 2008–2018) to analyse the evolution of the cost-benefit of ART over the 32-year time period.

Assumptions and sources of the economic model

The main assumptions and sources of the economic model are summarised in Table S1 (Supplementary appendix). It was assumed that in a hypothetical scenario in which ART would not have been available, there would have been more cases of HIV infection, more AIDS cases and more AIDS deaths. The projection of new HIV cases, new AIDS cases and AIDS deaths in Spain in a scenario without ART was estimated from the cases described between 1981 and 1995, published by the United Nations Programme on HIV and AIDS (UNAIDS) and the Spectrum programme^{22,23} (Table 1). The

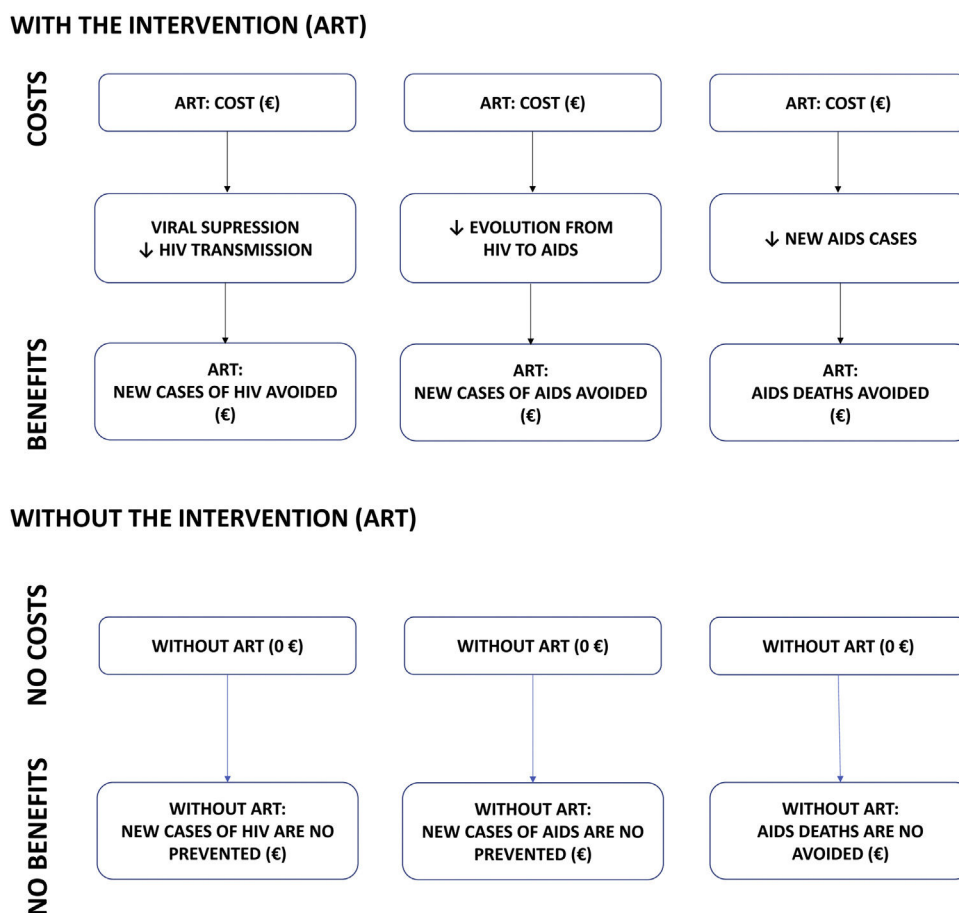


Fig. 1. Economic model scheme. AIDS: Acquired Immune Deficiency Syndrome; ART: antiretroviral therapy; HIV: Human Immunodeficiency Virus.

projections were estimated using the triple exponential smoothing method²⁴. New HIV diagnoses registered in Spain in the period 1987–2012 were also obtained from UNAIDS/Spectrum^{22,23} and those registered in the period 2013–2018 from the Information System on New HIV Diagnoses (SINIVIH) in Spain²⁵ (Table 1).

The estimate of HIV viral suppression in Spain (90.4% [87.5%–92.8%]) was obtained from reports by the HIV and Risk Behavior Surveillance Unit of the National Epidemiology Centre^{3,5}. Annual transmission rates (men who have sex with men [16.6%; 12.2%–22.3%], injection drug use [7.6%; 4.9%–11.0%], heterosexual [1.0%; 0.7%–1.3%], mother-to-child [22.6%; 17.0%–29.0%], blood products or transfusions [92.5%; 80.9%–96.1%]) were estimated from data in the systematic review by Patel et al.²⁶

The annual cost of ART in Spain in the period 1987–1996 were calculated using the number of patients with HIV/AIDS collected by UNAIDS/Spectrum²³ and the annual cost per patient of ART marketed each year²⁷. The annual cost of ART in Spain (also considering the cost of generic drugs) in the periods 1997–2012 and 2013–2016 were obtained from reports of the National AIDS Plan^{4,28}. The annual cost per ART in 2017–2018 were obtained from annual sales data in Spain²⁹.

The annual cost per HIV-positive patient (1987–2018), assuming they had not been treated with ART, was estimated from the cost in 1995, according to the study by Antónanzas et al.³⁰ adjusted for the year-on-year CPI and considering a population of 29,062 HIV-prevalent patients in 1995, according to UNAIDS/Spectrum²³ data. The annual cost of an AIDS patient without ART in the same period (1987–2018) was estimated using the same study, adjusted for the CPI²³.

In the base case of the analysis, the monetary value of a life was estimated as the annual GDP per capita over the period 1987–2018, as in a previously published study^{7,16,17}.

A conservative assumption was made to estimate the benefit of the ART marketed by Gilead Sciences, as 100% of the benefit was captured in the case of full treatment and 50% of the benefit in the case of treatment in combination with other non-Gilead drugs.

Results

Base case

Clinical benefit

It is estimated that, over the 32-year period analysed (1987–2018), ART averted 323,651 AIDS deaths (Fig. S1-Supplementary appendix; Fig. 2), 500,129 AIDS cases (Fig. S2-Supplementary appendix; Fig. 2) and 161,417 HIV cases (Fig. S3-Supplementary appendix; Fig. 2).

Economic impact

The economic impact of ART intervention is shown in Fig. 3 and Table 2. The cost of ART over the 32-year period amounts to 6185 (95%CI 5545; 6821) million euros. The benefit (savings) from averted deaths amounts to 34,780 (95%CI 23,346; 49,034) million euros; from averted AIDS cases to 6161 (95%CI 5511; 6844) million euros; and from averted HIV cases to 1057 (95%CI 1041; 1073) million euros. The total benefits (savings) associated with ART, for the given period, amounts to 35,812 (95%CI 24,353; 50,131) million euros (Table 2).

Table 1

AIDS deaths, AIDS cases and HIV cases projected (expected) without ART (mean values) and observed with ART.

Years	AIDS deaths		AIDS cases		HIV cases	
	Expected*	Observed	Expected*	Observed	Expected*	Observed
1987	433	433	1095	1095	5726	3615
1988	800	800	2279	2279	6717	4184
1989	1378	1378	3173	3173	7716	4720
1990	2033	2033	3937	3937	8560	5149
1991	2657	2657	4579	4579	9269	5408
1992	3477	3477	5103	5103	9630	5460
1993	4227	4227	5527	5527	9745	5324
1994	5058	5058	7511	7511	9642	5056
1995	5857	5857	8760	7205	9465	4722
1996	6656	5749	10,013	6773	9257	4374
1997	7455	3019	11,265	4983	9087	4037
1998	8254	1878	12,517	3758	9007	3714
1999	9053	1844	13,769	3173	9017	3399
2000	9852	1717	15,022	2941	7667	2595
2001	10,651	1635	16,274	2536	7336	2171
2002	11,450	1614	17,526	2387	7569	1925
2003	12,249	1635	18,778	2334	7954	2018
2004	13,048	1554	20,031	2107	8427	2140
2005	13,847	1450	21,283	1889	8870	2257
2006	14,646	1315	22,535	1771	9283	2363
2007	15,445	1313	23,788	1660	9836	2456
2008	16,244	1215	25,040	1577	10,141	2528
2009	17,043	1079	26,292	1437	7655	74
2010	17,842	1020	27,544	1458	6334	539
2011	18,641	953	28,797	1293	6712	499
2012	19,440	880	30,049	1175	6375	273
2013	20,239	750	31,301	858	4914	139
2014	21,038	700	32,553	688	4970	81
2015	21,837	633	33,806	611	4704	0
2016	22,636	498	35,058	549	4702	887
2017	23,435	445	36,310	514	4414	807
2018	24,234	397	37,562	415	4408	780
Total	381,444	59,502	589,078	87,296	245,111	83,694

AIDS: Acquired Immune Deficiency Syndrome; ART: antiretroviral therapy; HIV: Human Immunodeficiency Virus.

*Triple Exponential Smoothing formulas: General equation:

$$S_t = \alpha \frac{y_t}{I_{t-L}} + (1 - \alpha)(S_{t-1} + b_{t-1})$$

Trend smoothing:

$$b_t = y(S_t - S_{t-1}) + (1 - \gamma)b_{t-1}$$

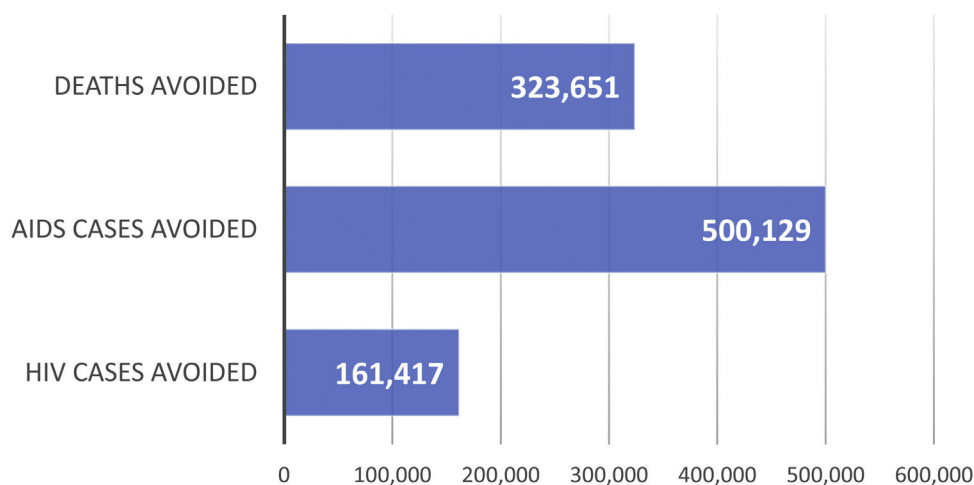
Seasonal smoothing:

$$I_t = \beta \frac{y_t}{S_t} + (1 - \beta)I_{t-L}$$

Forecast:

$$F_{t+m} = (S_t + mb_t)I_{t-L+m}$$

where, α , β , γ are constants that takes the value from the range [0;1]; y is the observation value; S is the smoothed observation value; b is the trend rate; I is the seasonality index; F is the forecast for m periods ahead; t is an index denoting a time period.

**Fig. 2.** Clinical impact of ART (1987–2018) in Spain. Societal perspective.

AIDS: Acquired Immune Deficiency Syndrome; ART: antiretroviral therapy; HIV: Human Immunodeficiency Virus.

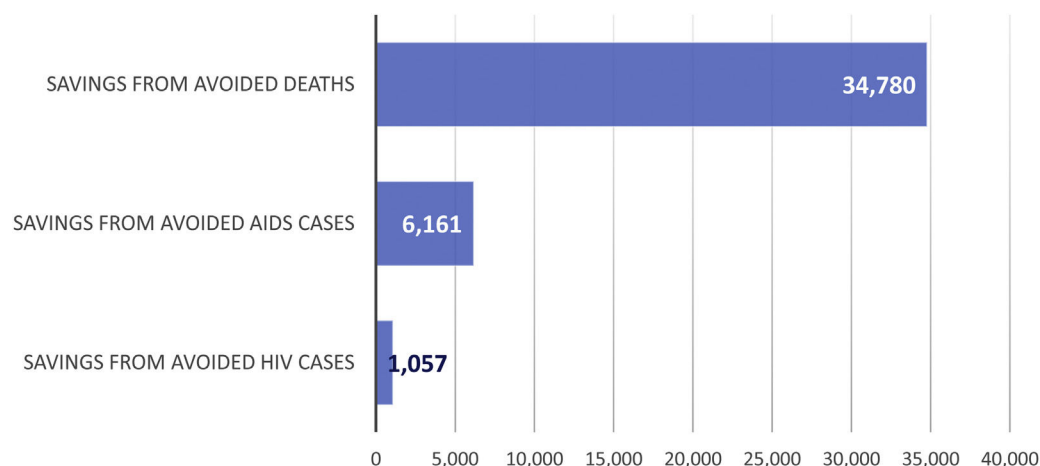


Fig. 3. Economic impact of ART (1987–2018) in Spain (million euros [€]). Societal perspective.

AIDS: Acquired Immune Deficiency Syndrome; ART: antiretroviral therapy; HIV: Human Immunodeficiency Virus.

Table 2

Results of the benefit/cost analysis of ART in Spain over a 32-year period (1987–2018) (million euros [€]). Base case. Societal perspective (3% annual discount).

	Mean	95% CI
ART costs	6185	5545; 6821
ART benefits		
For deaths avoided	34,780	23,346; 49,034
For AIDS cases avoided	6161	5511; 6844
For HIV cases avoided	1057	1041; 1073
Total benefits	41,997 ^b	29,898; 56,952
ART net benefit	35,812	24,353; 50,131
Benefit/cost index ^a	6.79	5.39; 8.35

^a A benefit/cost ratio greater than 1 indicates that ART has been profitable in Spain in the period analyzed. AIDS: Acquired Immune Deficiency Syndrome; ART: antiretroviral therapy; CI: confidence interval; HIV: Human Immunodeficiency Virus.

^b The sum is not 41,998 due to rounding.

Table 3

Results of the benefit/cost analysis of ART in Spain over a 32-year period (1987–2018) (million euros [€]). NHS perspective (0% annual discount).

	Mean	95% CI
ART costs	11,809	10,749; 13,067
ART benefits		
For deaths avoided	12,243	10,922; 13,603
For AIDS cases avoided	1772	1746; 1796
For HIV cases avoided	14,015	12,668; 15,399
ART Net benefit	2206	1919; 2332
Benefit/Cost index ^a	1.19	1.18; 1.18

^a A benefit/cost ratio greater than 1 indicates that ART has been profitable in Spain in the period analyzed. AIDS: Acquired Immune Deficiency Syndrome; ART: antiretroviral therapy; CI: confidence interval; HIV: Human Immunodeficiency Virus.

Benefit/cost ratio. ART over the 32-year period had a benefit/cost ratio of 6.79 (95%CI 5.39, 8.35). Thus, ART was benefit/cost (with a ratio of greater than 1) in Spain over the analysis period (Table 2).

Sensitivity analysis

As shown in Table 3 and Table S2-Supplementary appendix, ART was equally profitable when the analysis was conducted from NHS's perspective without annual discounting of costs and benefits or with discounts of 6%. Specifically, from the NHS's perspective and without considering discounts, the cost of ART amounted to 11,809 million euros over the 32 years, and the benefits would amount to 14,015 million euros, resulting in a net benefit of 2206 million

euros (Table 3). When the statistical lifetime's monetary value was considered, the net benefit of the ART was €1,961,943 million over the 32 years (Table S2-Supplementary appendix).

Sub-analysis

The results of the two sub-analyses are in Sub-analysis-Supplementary appendix.

Discussion

According to the present study, ART to HIV-positive patients in Spain were highly profitable, both in deaths and AIDS and HIV cases averted, and in economic terms. According to the results obtained in our study, ART produced a benefit/cost ratio of 6.79, which is equivalent to that for every euro invested in ART, a societal return on investment of €6.79 was obtained. This societal return on investment is more favourable than that observed with other interventions analysed in our healthcare setting, namely €1.83 for multiple sclerosis³¹, €3.25 for heart failure³² and €5.04 for psoriasis³³.

Among the strengths of the present study, the following should be highlighted: (i) actual epidemiological data with ART (deaths, new cases) were obtained from official sources and registries (UNAIDS, Spectrum, SINIVIH)^{22,23,25}; (ii) all model assumptions were validated by Spanish experts in epidemiology and management of HIV/AIDS patients; and (iii) all study variables were analysed using a probabilistic model with a proven methodology, which allowed us to analyse the uncertainty of the model variables and to obtain the mean results of the net benefit and the benefit/cost ratio with their 95% confidence intervals^{14,34}. This present benefit/cost analysis was performed following the guidelines and recommendations published in Spain^{35,36}.

As in the global study by Forsythe et al.⁷, our nationwide study confirms that in the historical series ART has been a profitable health intervention, with the benefits (both health and economic) far outweighing the costs of acquiring ART. This cost-effectiveness has been greater since the use of highly active ART (HAART).

Although amply offset, according to this analysis, ART spending in Spain must be put into context. Our study estimate amounts to 6185 million euros applying the discount recommended by the economic evaluation guidelines and 11,809 million euros undiscounted over 32 years. By way of example, in 2019, it was 677 million euros. Spain's NHS expenditure on pharmaceuticals and medical devices in 2019 was 23,638 million euros³⁷. Therefore,

annual expenditure attributable to ART constituted 2.86% of total NHS expenditure on pharmaceuticals and medical devices.

However, the most crucial aspect of ART is its impact on health outcomes in reducing HIV/AIDS incidence/mortality and maximizing patient health³⁸. According to this study, in the period between 1987 and 2018, ART averted 323,651 AIDS deaths, 500,129 new AIDS cases and 161,417 new HIV cases.

Regarding the possible limitations of the study, first it should be borne in mind that a theoretical model has been used, which is, by definition, a simplified simulation of reality. Second, it was necessary (as is usual in this type of analysis) to make some assumptions in the model due to lack of data. The primary assumption was the projection of mortality and new HIV or AIDS cases under the hypothetical assumption that ART would not have been available in the period 1987–2018. These projections of expected deaths and cases were made using a proven method such as triple exponential smoothing^{24,39}. This projection method is conservative compared to the linear least squares regression method, which would have yielded more cost-effective results for ART. The projection of deaths from AIDS and AIDS cases expected since 1996, was calculated from the trend observed between the years 1987–1995. Therefore, to carry out the projection, all the factors and prevention measures that determined the cases observed in the period 1987–1995 were taken into account. However, a limitation of the model could be the fact that the projections without ART did not explicitly consider the possible effect of the reinforcement of preventive measures that would have occurred in the event that ART had not been established in the period analyzed. However, an attempt has been made to compensate for this possible limitation by using a conservative calculation approach, based on triple exponential smoothing. On the other hand, the predictions made were contrasted with the behavior of HIV in countries with limited access to ART, as well as using the UNAIDS Spectrum predictive model.

ART has radically changed the impact of HIV infection from a lethal disease to a manageable chronic disease⁴⁰. The UNAIDS target for 2030 is to have 95% of people living with HIV knowing their HIV status, 95% of people diagnosed with HIV receiving ongoing ART and 95% of these achieving viral suppression^{6,41}. UNAIDS set this target because HIV treatment is critical to ending the AIDS epidemic and making HIV transmission a rare event, and that treatment prevents AIDS-related deaths, prevents new infections and saves money⁴¹. These assumptions have been analysed and confirmed in this study.

Conclusions

For more than 32 years in Spain, investment in ART has limited the number of AIDS deaths and new cases of HIV and AIDS while providing (through maximised return on investment) significant economic savings for the NHS. ART's cost-effectiveness has progressively increased over the 32-year period analysed, mainly due to ART's increased efficiency and effectiveness.

Authors' contributions

All authors contributed to the design of the study, the interpretation of the data, the critical review of the publication and approved the final version of the manuscript for publication. Carlos Rubio Terrés and Darío Rubio Rodríguez made the economic model.

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Conflicts of interest

MJPE has done consulting work, received research grants, received session funding, and developed educational materials, now or in the last three years, for AbbVie, Gilead Sciences, Janssen, Merck, and Viiv Healthcare. DPP has received research funding and/or consulting and/or conference fees from Viiv, Gilead, Janssen, and MSD. PV has received consulting and/or conference fees from AbbVie, Viiv Healthcare, Gilead Sciences, Janssen, and MSD. IJ has received training fees from Viiv Healthcare and consulting fees from Gilead. AC is an employee of Gilead Sciences, SL. DRR and CRT are consultants for Health Value, a company that received payments in connection with the study.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: <https://doi.org/10.1016/j.eimce.2021.05.011>.

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