ORIGINAL ARTICLE

Targeted screening for human immunodeficiency virus infection in Spanish emergency departments: an analysis of epidemiologic and economic impact

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Objective. To evaluate the potential epidemiologic and economic impact of applying an HIV screening protocol in hospital emergency departments (ED) and compare it to current clinical practice in Spain.

Methods. We estimated the cumulative incidence of human immunodeficiency virus (HIV) infections and associated costs in Spain for a 20-year time horizon based on a model comprised of various health states with different risks for HIV transmission. The impact of current clinical practices in Spain, in which there is no established protocol for HIV screening, was compared to the potential impact of applying a targeted screening protocol in persons who come to the ED with certain conditions suggestive of HIV infection (diagnosis of a sexually transmitted infection, mononucleosis, herpes zoster infection, community-acquired pneumonia; practice of chemsex, and need for postexposure prophylaxis).

Results. Screening all persons with a condition suggestive of HIV infection in hospital EDs would require an investment of €20 million over 20 years, but it would prevent 13 615 new infections (reducing the incidence by 20.6%, down from 66 265 to 52 650 cases) in comparison with the current diagnostic approaches. Such a reduction in the incidence of HIV infection would potentially save €4411 million over 20 years, giving a return of €224 per euro invested.

Conclusion. A protocol for targeted screening of persons in circumstances suggestive of risk for HIV infection in Spain would increase diagnoses, avert new infections, and generate savings in comparison with screening practices currently in effect.

Keywords: Human immunodeficiency virus (HIV). Targeted screening. Hospital emergency departments. Transmission.

Cribado dirigido del virus de la inmunodeficiencia humana en los servicios de urgencias en España: análisis de las consecuencias epidemiológicas y económicas

Objetivo. El objetivo del análisis fue evaluar el impacto epidemiológico y económico de protocolizar el cribado dirigido del virus de la inmunodeficiencia humana (VIH) en los servicios de urgencias hospitalarios (SUH) comparado con la actual práctica clínica en España.

Método. Mediante un modelo formado por varios estados de salud con diferentes riesgos de transmisión se estimó la incidencia acumulada de infecciones por VIH y los costes asociados, en 20 años, en España. El análisis comparó la protocolización del cribado dirigido a personas que presentan alguna condición indicadora (CI) de infección por VIH (diagnóstico de enfermedad de transmisión sexual, síndrome mononucleósido, herpes zóster, neumonía adquirida en la comunidad, práctica del *chemsex* y profilaxis postexposición) que acuden a los SUH frente a la actual práctica clínica en España en la que el cribado del VIH no está protocolizado.

Resultados. El cribado dirigido a personas con alguna CI de VIH en los servicios de urgencias requeriría una inversión de 20 millones de euros en 20 años, pero evitaría 13.615 nuevas infecciones (de 66.265 a 52.650 casos; –20,6%) comparado con la actual estrategia de diagnóstico. La reducción de la incidencia de VIH supondría unos ahorros potenciales de 4.411 millones de euros en 2 décadas, con un retorno económico de 224 € por euro invertido.

Conclusiones. Protocolizar el cribado dirigido a personas con alguna CI de VIH en los SUH en España podría incrementar el diagnóstico, evitar nuevas infecciones de VIH y generar ahorros *versus* el cribado no protocolizado realizado en la práctica clínica actual.

Palabras clave: Virus de la inmunodeficiencia humana (VIH). Cribado dirigido. Servicios de urgencias hospitalarios. Transmisión.

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Introduction

Even though HIV infection is preventable, transmission of the virus has continued ever since its first detection in 1981[1,2].According to the latest report of the United Nations Assembly on HIV and AIDS (UNAIDS), an estimated 38 million people are living with HIV worldwide, and 1.7 million contracted the disease in 2020[3].

The increasing efficacy of antiretroviral therapy (ART) over the last 2 decades has contributed to the continuous decrease in AIDS-related morbidity and mortality, turning HIV infection into a chronic condition[4]. However, a certain proportion of people with HIV are unaware of their serological status and cannot access ART, a situation that contributes to a higher risk of developing AIDS and transmitting the virus; the risk of death is also higher in such patients than for individuals who are able to access early diagnosis and effective treatment[5,6].

Reducing the number of undiagnosed cases and increasing early diagnosis are key to reducing new infections and are priorities established by UNAIDS[7]. Among the new goals to be achieved by 2025 is the 95-95-95 target: diagnosing 95% of all HIV-positive individuals, providing ART for 95% of those diagnosed, and achieving viral suppression in 95% of those treated[7].

There is strong scientific evidence that people living with HIV who are effectively treated with ART and have achieved viral load suppression to undetectable levels will not transmit HIV through sexual contact[8]. Greater effort must be made to ensure that people living with HIV can access ART as soon as they are diagnosed (the test-and-treat strategy)[9]. A key first step is therefore the development of approaches that ensure the reduction of undiagnosed HIV.

In Spain, it is estimated that around 1 in 5 people living with HIV is undiagnosed[10] and that 50% of new diagnoses are late (indicated by a CD4 count of less than 350 cells/µL in the first measurement after diagnosis)[11]. With the aim of improving these figures, the Spanish Ministry of Health, in conjunction with the main scientific societies, developed a strategic plan for the prevention and control of HIV infection and other sexually transmitted diseases[12] in line with the targets set by UNAIDS.

Based on evidence that early diagnosis of HIV infection has individual and societal benefits, several diagnostic guidelines recommend screening strategies ranging from universal screening to targeted screening[13-16].

HIV testing has been routinely offered to pregnant women and those admitted to penitentiaries in Spain since the 1990s[13]; however, the diagnostic delay we see today shows that new approaches must be developed. Hospital emergency departments (EDs) are among the main points of access to the health care system for people living with HIV[17]. EDs see many patients in situations suggestive of HIV infection or with conditions that share the same route of transmission as HIV. Therefore, EDs are essential for developing ways to improve early diagnosis rates by promoting routine HIV serology in individuals with certain clinical profiles[18]. However, serology is rarely ordered in EDs at present unless the findings will change how the clinical process will be managed. An estimated 28.4% of diagnostic opportunities are missed in Spanish EDs[19], showing that screening programs at this level of care continue to be scarce[19].

HIV screening in the ED facilitates diagnosis in individuals with certain clinical profiles that may not be seen at other levels of care. Examples are sexually active young people, immigrants, or people of advanced age who are unaware of their HIV status but unable or unwilling to undergo HIV testing in their primary care center[18]. Certain indicator conditions (ICs), in which the prevalence of undiagnosed HIV exceeds 0.1%, may be associated with higher risk of HIV transmission. Examples of such conditions are community-acquired pneumonia, seborrheic dermatitis/exanthema, herpes zoster, sexually transmitted infection, hepatitis B or C, mononucleosis, malignant lymphoma, idiopathic lymphadenopathy, and idiopathic thrombocytopenia/leukocytopenia lasting more than 4 weeks[20]. Identifying ED patients with ICs can facilitate the implementation of targeted HIV screening protocols and promote diagnosis among people living with HIV who are unaware of their HIV status. Recently, the Spanish Society of Emergency Medicine (SEMES) published a consensus paper promoting emergency physicians' uptake of IC-guided HIV screening and the referral of patients to appropriate specialists[18].

The aim of this cost-benefit analysis was to evaluate the potential epidemiological and economic impact of implementing a targeted screening protocol for patients with ICs in all Spanish EDs in order to reduce the number of lost opportunities to diagnose HIV that occur under current clinical practices which do not include routine screening.

Methods

A previously developed transmission model in MS Excel was adapted to the Spanish National Health System (NHS) in order to analyze the costs and benefits of implementing an IC-guided screening program in EDs to detect HIV infection. To evaluate the health benefits, we estimated the incidence of new HIV cases over a 20-year time horizon. To quantify costs, we included the direct costs of screening and the costs that would be incurred for each HIV infection not detected.

The model simulated annual transmission in a cohort of people living with HIV who could transition between different health phases according to different risks for HIV transmission (undiagnosed, diagnosed and in follow-up, in follow-up but not on ART, and on ART and virologically suppressed). People living with HIV contributed to the incidence of new HIV infections each year based on their risk for transmission, which was estimated based on sexual contact between heterosexual men and women and among men who have sex with men (MSM), needle sharing among people who inject drugs (PID), HIV infection status, and ART or not. An annual mortality rate[21] was applied to each of the population subgroups (Figure 1). The model, parameters, and assumptions were approved by a panel of 3 experts in HIV and ED management.

The model was used to estimate and compare the cumulative incidences of new HIV infections over a 20-year time horizon under the 2 ED screening strategies. One strategy was the targeted screening protocol ap-

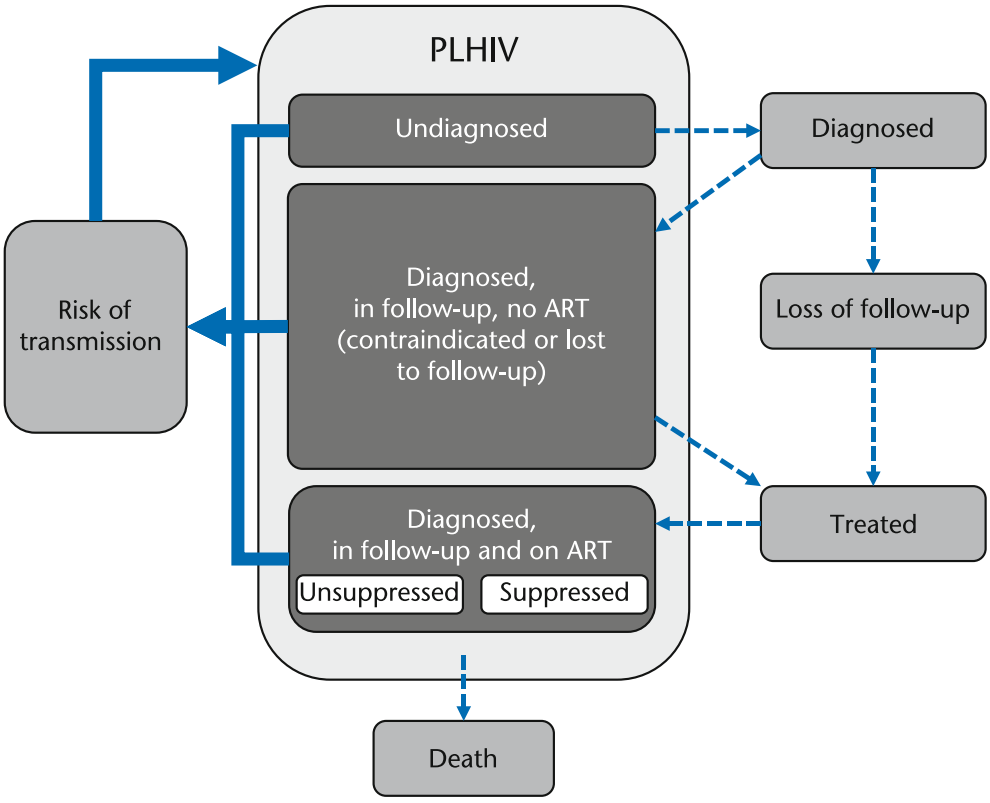

Figure 1. Flow diagram of the model's structure.
PLHIV refers to people living with HIV; ART, antiretroviral therapy.

plied in persons with certain ICs (diagnosis of a sexually transmitted infection, mononucleosis, or herpes zoster infection in patients aged 18 to 65 years; community-acquired pneumonia in patients aged 18 to 65 years; practice of chemsex; and need for postexposure prophylaxis)[18]. The other was current screening practice in Spain, in which no serology to detect HIV is ordered routinely according to protocol.

The population evaluated in the model included 3 of the subgroups the World Health Organization considers to be at the highest risk of HIV transmission: heterosexual men and women, MSM and PIDs. We assumed that the immigrant population would be included within those established subgroups. The population subgroups' characteristics are shown in Table 1.

The table's total figures for heterosexual men and women were obtained by subtracting the estimates for MSM and PID from population figures in the National Institute of Statistics[22]. We obtained the MSM estimate for Spain from the UNAIDS country report[23] and the PID estimate from the Spanish Observatory on Drugs and Addictions[24].

The total population living with HIV in Spain was 151 400 people according to the latest estimates made for 2017[25]. HIV incidence rates shown in Table 1 were distributed among the different population subgroups according to the incidences published by the Spanish Ministry of Health[26].

The HIV diagnosis rate associated with current clinical practice was considered to be 87.0% of all people living with HIV[25], and we estimated that the implementation of a protocol for IC-targeted screening in the ED would probably be associated with an increase in HIV diagnosis of 0.6%[17].

Recent Spanish publications report that 97.3% of diagnosed patients are on ART[25] and that the average time from diagnosis to initiation of ART is 44 days[27]. Taking into account the latest published hospital survey of patients with HIV infection[28] and the opinion of clinical experts, 49.8% of patients on ART are taking integrase strand transfer inhibitors, 25.4% are on nucleoside reverse transcriptase inhibitors, and 24.8% are on protease inhibitors. This distribution is in line with the recommendations of the Spanish national plan for AIDS[29].

Viral suppression was based on an estimate that it is achieved by 90.4% of patients on ART[25]. Viral load suppression per week and type of ART were extracted from data reported in various clinical trials[30-37]. Eleven percent of patients were estimated to have lost 1 year of follow-up, and new cases lost (incidence) was estimated at 19.8%[38].

The size of the population of candidates for HIV screening in the ED was estimated based on the latest data reported on emergency care in the Spanish NHS[39]. The proportion of patients seen in the ED with each of the ICs was estimated by the clinical experts and reported in SEMES recommendations on patients suspected of HIV infection[18]: 0.4% with sexually transmitted infections[40], 0.03% with mononucleosis, 0.08% with

Table 1. Population Parameters

Parameter	Subgroups			
	Heterosexual		MSM	PID
	Male	Female		
Total population	22 156 305[a22]	24 081 617[b22]	890 200[23]	13 136[24]
Prevalent cases of HIV	25 575[25,26]	21 204[25,26]	98 629[25,26]	5 665[25,26]
Incident HIV cases	548[26]	454[26]	2 113[26]	121[26]
Annual mortality rate	28.5/1000 inhabitants[21]	13.6/1000 inhabitants[21]	5.1/1000 habitantes[21]	38.2/1000 habitantes[21]
Probability of transmission per act in HIV-positive, ART-positive, unsuppressed[c] Wk 0	0.00159[41]	0.00318[d]	0.01767[41]	0.00963[d]
Probability of transmission per act in HIV-positive, ART-positive, unsuppressed[c] Wk 2-48	0.00010[41]	0.00021[d]	0.00134[41]	0.00072[d]

[a]After eliminating MSM and PID men from the total population.
[b]After eliminating PID women from the total population.
[c]> 50 copies/mL.
[d]Assumption.
ART: antiretroviral therapy; MSM: men who have sex with men; PID: people who inject drugs.

herpes zoster in the age range of 18 to 65 years, 0.3% with community-acquired pneumonia in the same age range, 0.01% of chemsex (sex with multiple partners under the influence of psychoactive drugs, mainly among MSM) and 0.3% needing postexposure prophylaxis.

The probability of HIV transmission was modelled for each of the population subgroups based on published risk estimates[41]. In the absence of published estimates for some groups, we formed the following assumptions: transmission in women with HIV infection > 50 copies/mL would be 2-fold that observed in heterosexual men, and transmission in women in the PID group would be the average reported for heterosexual men injecting drugs.

In the PID subgroup, 15.3%[42] were considered to engage in risky practices (sharing needles or syringes) 2.7 times per month on average[43]. Seroconversion in patients with risk behaviors was assumed to be 0.8[44].

The estimation of the cost of HIV screening took into account the costs of serology performed in the ED, the primary care visit to explain the results, Western blot testing to confirm the results, and referral for consultation with an infectious disease specialist in the case of HIV positivity. Resource use and unit costs (values in euros in 2020) were obtained from a national database of healthcare costs[45] (Table 2) and approved by the panel of experts. The cost per HIV infection avoided was estimated from the cost of HIV management over the patient's lifetime from diagnosis to death[46] (Table 2).

We assessed the robustness of the model and the results by running several deterministic sensitivity analyses (DSAs) in which the value of the following parameters were modified: 10-year time horizon, increase in the diagnosis rate with targeted screening (± 20% of the initial rate, with the value at the upper end of the range coinciding with the diagnosis rate estimated by SEMES [0.70%]), the cost of HIV management (reductions of 10% and 25% from the original value and an alternative estimate derived from several sources[47-49]), and the distribution and average time from diagnosis to initiation of ART (30 and 60 days).

Results

In the base case, the model estimated that the current HIV diagnostic strategy in clinical practice would result in 66 265 HIV infections over the next 20 years. The establishment of a targeted screening protocol in the ED would reduce HIV cases to 52 650, a reduction which would prevent 13 615 new HIV infections (20.6% reduction) over the period analyzed (Figure 2).

The implementation of the ED HIV screening protocol in the population with any of the 6 ICs could require a total investment of €20 million by the Spanish NHS over the next 20 years (€19 240 139 euros for HIV tests ordered in the ED and €418 867 for Western blot tests and consultation with an infectious disease specialist in HIV-positive cases).

The reduction in HIV incidence associated with targeted screening would lead to potential savings of €4411 million over the next 2 decades compared to current clinical practice for HIV diagnosis, resulting in an economic return of €224 for every euro invested.

The DSA confirmed the robustness of the results. The parameter with the greatest influence on the number of HIV cases averted was the increase in the diagnosis rate associated with targeted IC-based screening in the ED. Averted infections could reach a maximum of 15 290 if a 0.7% increase in the rate of diagnosis targeted screening were achieved. Conversely, infections averted would be reduced, to 11 665, if the increase in diagnosis were 0.5%. The potential savings are directly related to the cost of HIV management in the long term, noting that these savings could range between €7050 million and €3303 million when considering management costs of €519 280 or €244 056, respectively (Table 3).

Discussion

The HIV transmission model developed in this study suggests that implementing a targeted screening protocol in Spanish EDs could increase HIV diagnosis, prevent new

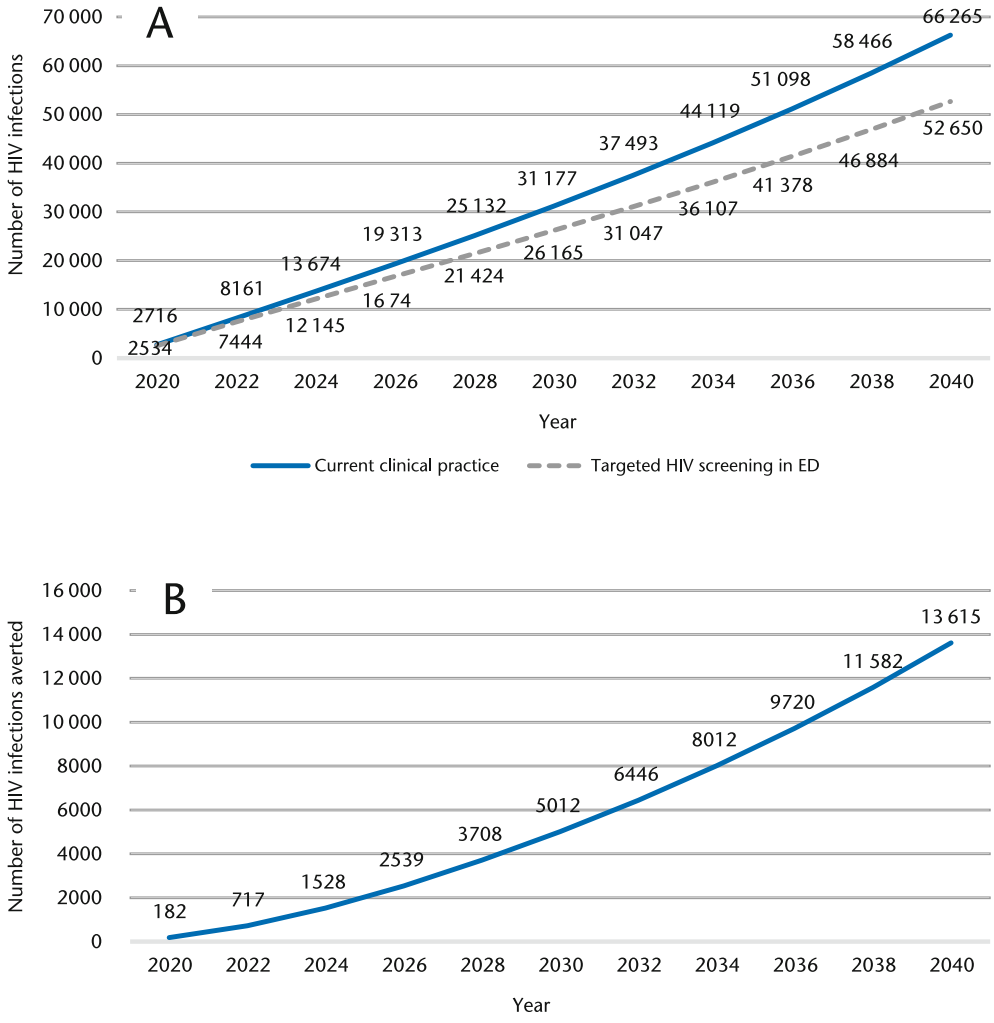

Figure 2. Cumulative number of HIV infections and cumulative number of HIV infections averted under the 2 testing protocols. A, Cumulative number of HIV infections with targeted screening in ED and current clinical practice. B, Cumulative number of HIV infections averted with targeted screening in ED vs current clinical practice.
ED: emergency department.

infections, and generate potential savings compared to the HIV diagnostic program currently used.

Various population-based studies have concluded that an increase in the proportion of HIV-infected patients being treated would reduce HIV transmission[50], but the achievement of this objective is closely related to the diagnosis of HIV cases, and 47.6% of diagnoses are made late in Spain[11].

Early diagnosis is a crucial step for achieving the UNAIDS objectives on pandemic control. To that end specific guidelines are published. One example can be found in the guidelines developed by SEMES on the management of patients with suspected HIV infection in the ED and the subsequent referral of confirmed cases[18].

Our literature review found international studies that conclude that targeted HIV screening is a cost-effective option that is widely accepted by candidate patients[51]. In Spain, although no cost-effectiveness analyses of possible HIV screening strategies have been published to date, several studies have attempted to demonstrate the importance of implementing targeted HIV screening in the ED or in primary care centers. HIV was diagnosed in 1.03% of the patients included in a cross-sectional study carried out in 6 primary care centers[52]. The patients targeted had an IC for HIV, a risk behavior for HIV infection, or came from countries with a high prevalence. A prospective study evaluating the impact of structured HIV screening in the ED and in primary care (the DRIVE program) that covered a significantly larger population found a rate of new diagnoses of 29.6 per 100 000 patients attended, significantly higher than the 3.1 per 100 000 diagnosed in routine practice[53].

Although our analysis was not designed to study a return on investment[54], our findings suggest that a targeted HIV screening program in the ED could return as much as €224 for each euro invested.

Certain limitations affect the interpretation of our results. Due to the absence of published evidence on the

Table 2. Unit costs

Item	Cost per item, €
ELISA test (per test)	€ 38.66[45]
Primary care consultation (per visit)	€ 38.77[45]
Infectious disease specialist consultation (in HIV-positive patients) (per visit)	€ 223.07[45]
Western blot (in HIV-positive patients) (per test)	€ 62.64[45]
Cost of HIV management[a]	€ 325 408[46]

[a]Amounts are in euro, in 2020 values.
[b]Includes specialist consultations, emergency department visits, primary care consultations, hospital admissions, antiretroviral therapy, laboratory tests, and societal costs due to loss of productivity due to HIV.
ELISA, enzyme-linked immunosorbent assay.

probability of HIV transmission in persons on each type of ART, we had to establish assumptions when setting up the transmission model. However, since the assumptions about the effect of ART apply to both strategies analyzed (IC-guided targeted screening and routine practice), the final impact on the results can be considered minor. Another limitation was that the HIV diagnosis rate associated with targeted screening (0.6%) was obtained from a study evaluating a program in which all ED patients were tested[17]. In the absence of other data and in view of the uncertainty of this value, we performed several DSAs. One of them revealed a variation of +20%, resulting in an HIV diagnosis rate of 0.7% with targeted screening, coinciding with the estimates made by SEMES. Finally, transmission specifically associated with migration is not included in this model because migration patterns are complex and there are no specific values for HIV prevalence, transmission and incidence for these populations. Therefore, it was assumed that the data for the subgroups we did analyze would also include migrants.

Beyond traditional settings for HIV diagnosis[55] there are others that could be explored in the future. However, the implementation of targeted HIV screening in the ED could be a first step in this direction and result in savings for Spain in general and the Spanish NHS in particular. In the absence of other studies that evaluate the efficiency of this type of strategy in Spain, evidence from the present cost-benefit analysis allow us to underline the importance of ordering serology tests in certain clinical scenarios in order to improve early diagnosis rates.

In conclusion, establishing a targeted screening protocol in the ED would facilitate the performance of serology in a high proportion of the population at risk for HIV infection, which could increase the rate of new HIV diagnoses in comparison with current practices and significantly decrease the number of new infections. This approach has the potential to generate savings.

Conflict of Interest Disclosure: J.M., J.G.C. and C.N. received fees from Gilead Sciences SL for consultancy work related to the validation of the parameters. None of them declare a conflict of interest. A.C. is an employee of Gilead Sciences Spain. M.P. and I.O. are employees of PORIB, a consulting firm specializing in the economic evaluation of health interventions. PORIB identified the parameters of the model, carried out the analysis, and drafted the manuscript. All the authors participated in the interpretation of the results and reviewed and approved the final version of the manuscript.

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Addendum

The preliminary results of this study were published at the International Health Economics Association (iHEA) Congress, held July 12-15, 2021.

Table 3. Deterministic sensitivity analysis results

Parameter	Base case value	DSA value	HIV infections in current clinical practice	HIV infections with selective ED screening	Infections prevented (N)	Potential savings
Base Case Results			**66 265**	**52 650**	**13 615**	**4411M €**
10 years time horizon	20 years	10 years	31 177	26 165	5012	1611M €
Increase in HIV diagnosis rate associated with selective screening in EDs	0.59%	0.71% (+20% over CB)	66 265	50 975	15 290	4956M €
		0.47% (–20% over CB)	66 265	54 600	11 665	3776M €
HIV management cost	€325 408	519 280 €[a]	66 265	52 650	13 615	7051M €
		292 867 € (–10% over CB)	66 265	52 650	13 615	3968M €
		244 506 € (–25% over CB)	66 265	52 650	13 615	3303M €
ART distribution	49.8%-INSTI, 25.4%-NNRT y 24.8%-PI	75.0%-INSTI 10%-NNRTI and 15.0%-PI	66 218	52 605	13 613	4410M €
Average time to initiation of ART since diagnosis	44 days	30 days	65 357	51 797	13 560	4393M €
		60 days	67 314	53 637	13 677	4431M €

[a]Cost derived from health care costs (13 116 €/year)[47], considering an average age at diagnosis of 36 years[48] and life expectancy of 76 years[49].
ART, antiretroviral treatment; DSA, deterministic sensitivity analysis; ED, emergency department; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitors.

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