ORIGINAL RESEARCH ARTICLE

Epidemiologic and Economic Analysis of Rapid Antiretroviral Therapy Initiation with Bictegravir/Emtricitabine/Tenofovir Alafenamide in Spain

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Abstract

Objective This study aimed to assess the potential epidemiological and economic impact of rapid initiation of human immunodeficiency virus (HIV) treatment with bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) on HIV transmission compared with the current initiation observed in clinical practice in Spain.

Methods A transmission model was adapted to estimate the cumulative HIV infection incidence and potential cost savings based on the number of HIV infections prevented among men who have sex with men, heterosexual males and females, and people who inject drugs (PWID) over a 20-year time horizon. The analysis compared rapid antiretroviral therapy (ART) initiation with B/F/TAF (9 days from diagnosis until treatment initiation) versus current ART initiation practice (with an average of 35 days from diagnosis to treatment). People living with HIV were distributed according to their treatment status. Risk for transmission was assigned to undiagnosed, diagnosed in care and not receiving ART, and receiving ART but virally unsuppressed, which was estimated by sexual contact, needles and syringes shared among PWID, state of HIV infection, and ART use.

Results In the base-case analysis, rapid ART initiation with B/F/TAF is expected to prevent 992 new HIV infections over the next 20 years compared with current ART initiation practices. Considering the lifetime costs of treating HIV infection, the reduction in HIV incidence could result in potential cost savings of €323 million.

Conclusions These results suggest that rapid ART initiation with B/F/TAF in newly diagnosed patients with HIV is a high-value strategy for the Spanish National Health System and society, reducing HIV incidence and thereby reducing future related direct and indirect costs of care.

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Key Points for Decision Makers

Rapid antiretroviral therapy (ART) initiation with bictegravir/emtricitabine/tenofovir alafenamide on day 9 after human immunodeficiency virus (HIV) diagnosis could prevent 992 potential HIV infections over the next 2 decades compared with the current ART initiation practices on day 35.

The reduction in HIV incidence with rapid ART initiation versus current ART initiation could result in €323 million potential savings for the Spanish National Health System and society over the next 2 decades.

Clinical benefits and savings could be achieved if the period between HIV diagnosis and ART initiation is reduced.

1 Introduction

Recent research efforts have led to important advances in the treatment and prevention of human immunodeficiency virus (HIV) and hence acquired immunodeficiency syndrome (AIDS), thereby decreasing the worldwide incidence of infection. An estimated 1.7 million individuals worldwide acquired HIV in 2019, marking a 23% decline in new HIV infections since 2010 [1].

AIDS-related mortality has reduced from the peak observed in 2006, with a decrease from 1.95 million deaths around the world to 0.95 million deaths observed in 2017 [2]. The availability of increasingly effective antiretroviral therapies (ARTs) developed during the last 2 decades has been one of the key interventions that have contributed to this continued decline in global AIDS mortality.

Access to effective ART has been due in part to the evolution of international strategies, most of which are integrated at the United Nations Joint Programme on HIV/AIDS (UNAIDS). The latest data published by UNAIDS reported that in 2019, almost 38.0 million people were living with HIV (PLWH) worldwide, and approximately 26.0 million were able to access ART as of the end of June 2020 [1]. Increasing the proportion of PLWH under treatment is one of the priorities established by UNAIDS [3], which defined the three following main targets in the fight against HIV/AIDS for 2030 [4]: 95% of all PLWH are aware of their HIV status; 95% of all people with diagnosed HIV infection are treated with sustained ART; and 95% of all people receiving ART reach viral suppression.

The aim of ART is to achieve an undetectable plasma viral load, leading to a state of viral suppression that enables immune recovery and controls disease progression by reducing the risk of developing AIDS. There is strong evidence that PLWH who are taking effective ART and whose level of HIV is suppressed to maintain an undetectable viral load (< 50 copies/mL) will not transmit HIV infection by sexual contact [5]; therefore, stronger efforts should be made to ensure that PLWH can access ART as soon as they are diagnosed. Late diagnosis means individuals have delayed access to effective ART, and both factors are linked to the further expansion of the epidemic as well as to a greater risk for developing AIDS and an increased risk of mortality compared with those who are diagnosed soon after infection and who have access to effective treatment early on [6, 7].

The criteria for ART initiation have varied depending on the availability of ART. It was initially recommended for PLWH based on levels of CD4 cells [8, 9], and subsequently, by 2015 [10], it was recommended for all PLWH irrespective of their CD4 count, which was supported by the effectiveness of early ART studies reported on in clinical trials [11]. Two large, randomized trials (TEMPRANO and START) reported evidence supporting that early ART initiation in the course of HIV infection resulted in both public health benefits attributable to reduced transmission and individual-level benefits of improved health. In short, it was stated that ART should be initiated as soon as possible after the diagnosis of HIV [12]. In line with these conclusions, the World Health Organization (WHO) [13] recommended that adapted protocols for care, such as HIV screening, prophylaxis, rapid ART initiation and intensive adherence interventions, should be offered to PLWH. Within the context of the strategy of extended treatment, the WHO strongly recommended that rapid ART initiation, i.e. within 7 days of HIV diagnosis, should be offered to PLWH following a confirmed diagnosis and clinical assessment [13].

In recent decades, many antiretroviral drugs have been developed and approved as therapies for PLWH [14, 15]. ART with combinations of two or three drugs constitutes the treatment of choice for chronic HIV infection [9]. Among the recommended first-line regimens for ART-naïve PLWH, the European AIDS Clinical Society (EACS) recommends options consisting of two nucleoside reverse transcriptase inhibitors [NRTIs] in combination with an unboosted integrase strand transfer inhibitor [INSTI] [16]. Until recently, this drug class comprised first-generation agents, such as raltegravir and elvitegravir, or the second-generation agent dolutegravir.

The latest incorporation to the second-generation group of INSTIs was bictegravir, which was approved as a once-daily, single-treatment regimen, in combination with emtricitabine and tenofovir alafenamide (B/F/TAF) [17]. Among the preferred regimens, the EACS favours those containing

Fig. 1 Model structure. *ART* antiretroviral therapy, *LTFU* lost to follow-up, *PLWH* people living with HIV
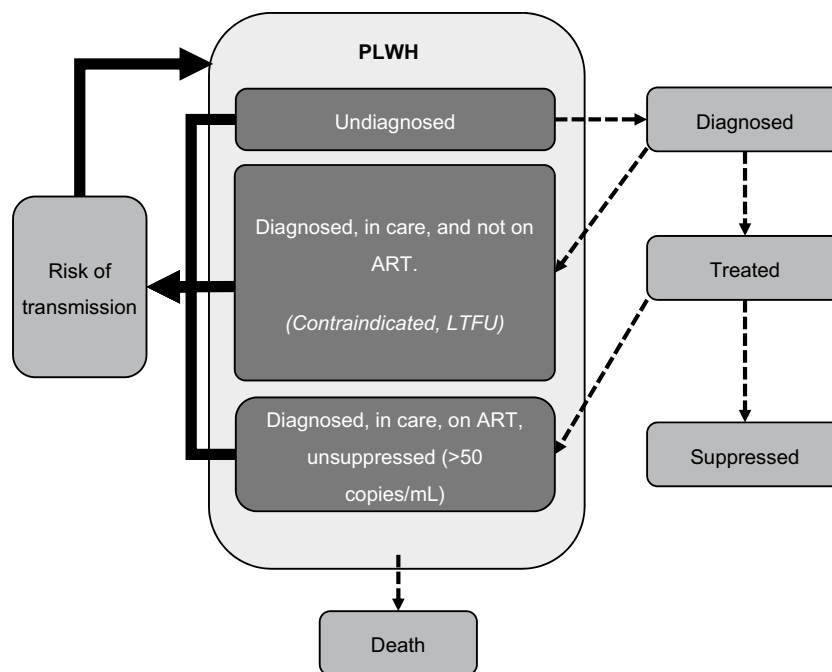
dolutegravir or bictegravir as a third agent, and the 2020 GeSIDA/Spanish National AIDS Plan recommends bictegravir as a preferent treatment [18].

B/F/TAF is a treatment option for individuals co-infected with HIV and hepatitis B virus (HBV); this treatment avoids the need to wait for the results of HBV testing before initiating treatment, does not require baseline HLA-B*5701 testing before initiating treatment and does not trigger hypersensitivity reactions. Therefore, B/F/TAF has been shown to meet all the criteria for rapid ART initiation.

In Spain, in recent years, despite access to effective ART, the incidence of HIV, far from being reduced, has remained stable. According to the Spanish System of Information on New Diagnoses of HIV Infection, 3244 and 2698 new diagnoses were recorded in 2018 and 2019, respectively [19, 20]. Because people with unsuppressed viral loads contribute to the incidence of new HIV infections every year due to their risk for transmission (by sexual contact or by sharing needles and syringes for injected drugs), additional strategies are required to reduce the number of new infections in Spain.

The present study aimed to evaluate, through a transmission model, the potential epidemiologic and economic impact of rapid treatment initiation with B/F/TAF on HIV transmission among heterosexuals, men who have sex with men (MSM) and people who inject drugs (PWID) in Spain compared with the current ART initiation observed in clinical practice.

2 Material and Methods

The effect of early therapy on disease dissemination by reducing new HIV cases was derived by comparing two different scenarios: the current clinical practice for ART initiation following an HIV infection diagnosis, and a new strategy based on early therapy initiation with B/F/TAF.

2.1 Modelling Approach

A dynamic transmission model for HIV was customized to the Spanish setting to assess the impact of the new treatment strategy on the number of cumulative HIV infections over a 20-year time horizon. The model was design as a Markov tree with a 1-year cycle with associated transition probabilities (specific for each subgroup of population) between each state. These probabilities included a dynamically varying transition probability, estimated by an exponential distribution, to obtain the rate of new infections based on the number of patients who were at risk of transmitting. Tunnel states were used to account for average durations greater than one cycle. The probability of new infections was based on the number of patients among three groups: undiagnosed patients, untreated patients, and patients with detectable viral load (> 50 copies/mL) (Fig. 1).

The population assessed in the model included the three key subgroups considered by the WHO as those with the highest risk of exposure to HIV: heterosexual males and females, MSM and PWID, all of which were modelled separately. Because human migration patterns are complex, there is a significant barrier to the collection of accurate data

relating to these populations over time. Therefore, migrant HIV transmission was not specifically captured in the model and it was assumed that data pertaining to the included population subgroups would be inclusive of migrants. Sexual behaviours in heterosexuals and MSM subgroups were captured by propagation parameters, estimating the new infections followed a Poisson's process [new infections = $X *$ $(1 - (1 - $ average transmission risk per act$)^{\text{Propagation factor}}$]. For PWID, the risk of transmission was based on the risk of being exposed to infected equipment and the number of non-infected PWID (new infections = non infected * prevalence * percentage of equipment sharing * $(1 - (1 - $ average transmission risk per act$)^{\text{Number of shared injections per month*12}}$).

Propagation factor that reproduced the incidence observed by the European Centre for Disease Prevention and Control (ECDC) in 2016 [21] was estimated by applying the model on the historic data. New HIV infections estimated by the model at the beginning of the simulation (3215 cases) were compared with national HIV figures in the year 2019 (3264 cases) [22] to check reproducibility.

2.2 Model Parameters

The model, inputs and assumptions considered in the present analysis were validated by an advisory board composed of four physicians who were experts in the management of HIV. In the consensus process, experts made decisions by agreement, working together to find a mutually acceptable value.

In the current clinical practice scenario, the average time from diagnosis to ART initiation was fixed at 35 days, derived from a market study (data on file) developed in Spain that assessed the period from HIV infection diagnosis to ART initiation in the second quarter of 2019. This parameter was validated by an expert panel and represents a conservative approach, taking into account that the average time from diagnosis to ART initiation in a Spanish cohort of naïve HIV-infected patients included in the Research Network on HIV/AIDS (CoRIS) was 44 days [23]. The average time to B/F/TAF initiation in the early therapy scenario was established at 9 days in consideration of the expert panel's opinion.

The distribution of the third component of the ART regimen, provided and validated by the expert panel as representative of the Spanish setting, was 77.0% of INSTIs, 3.0% of non-nucleoside reverse transcriptase inhibitors (NNRTIs), and 20.0% of protease inhibitors (PIs). These proportions are in line with current clinical practice and with the GeSIDA/Spanish National AIDS Plan, which recommends initiating combination therapy with an INSTI due to its high efficacy, low risk of toxicity and rapid virologic suppression [18]. The dynamics of viral load suppression per week and the type of ART prescribed, as detailed in Table 1, were derived from data reported in clinical trials [24–31].

The HIV lifetime cost, including HIV-direct and -indirect costs, in Spain (€325,408) was identified in the literature [32] and was updated from 2015 to 2020 values.

The total numbers of heterosexual males and females were obtained from the Spanish Statistics National Institute [33], adjusting the male population with the MSM and PWID population. MSM figures were derived from UNAIDS country factsheets [34], and PWID figures were derived from the Spanish Observatory of Drugs and Additions [35]. Total numbers and other inputs related to these population subgroups are detailed in Table 2.

HIV prevalence in Spain was established at 151,400, according to the most recent data [36]. The distribution of prevalence among the population subgroups was performed according to HIV incidence data published by the Spanish Ministry of Health, after the deletion of maternal and transfusion HIV transmission (314 cases) (Table 2) [19].

The HIV diagnosis for the current practice was fixed at 87.0% of the total PLWH [36]. In the absence of data on specialist derivation in the national and European reports, figures related to HIV cases already under treatment (97.3% of those diagnosed with HIV), as reported by the most recent data actualization for Spain [36], were also assumed for the proportion of cases in care. Viral suppression was observed in 90.4% of PLWH [36].

Loss to follow-up, definitive (7.34%) [37] or for 1 year (6.01%) [37], was applied to the incidence data, reducing the number of patients in care and also the number of treated patients. An annual death rate for each subgroup of

Table 1 Dynamics of viral suppression per ART type and weeks of therapy

ART	Weeks of Therapy						
	0	2	4	12	24	36	48
INSTIs	0.1	30.4	62.7	86.3	91.3	90.9	91.2
NNRTIs	0.0	7.2	16.8	63.8	86.7	84.9	85.0
PIs	0.0	1.4	9.0	58.0	86.8	86.1	88.2
B/F/TAF [26, 27]	0.0	38.6	77.2	96.0	95.8	93.9	91.9

Data are expressed as percentages

ART antiretroviral therapy, *B/F/TAF* bictegravir/emtricitabine/tenofovir alafenamide, *INSTIs* integrase strand transfer inhibitors, *NNRTIs* non-nucleoside reverse transcriptase inhibitors, *PIs* protease inhibitors

Table 2 Population inputs

Parameter	Subgroups			
	Heterosexuals		MSM	PWID
	Males	Females		
Total population size [33–35]	22,156,305[a]	24,081,617[b]	890,200	13,136
Prevalence of HIV cases [19, 36]	24,619	20,412	94,945	5454
Incidence of HIV cases [19]	548	454	2113	121
Annual death rate [38]	28.5/1000 inhabitants	13.6/1000 inhabitants	5.1/1000 inhabitants	38.2/1000 inhabitants
Per-act transmission probability HIV-positive under ART unsupressed[c]—week 0 [39]	0.00159	0.00318[d]	0.01767	0.00963[d]
Per-act transmission probability HIV-positive under ART unsupressed[c]—weeks 2–48 [39]	0.00010	0.00021[d]	0.00134	0.00072[d]

ART antiretroviral therapy, *HIV* human immunodeficiency virus, *MSM* men who have sex with men, *PWID* people who inject drugs

[a]Data resulting after deleting the number of MSM and male PWID from the total figure

[b]Data resulting after deleting the number of female PWID from the total figure

[c]> 50 copies/mL

[d]Assumption

the population was applied to the yearly number of patients in medical follow-up [38].

The HIV transmission probability was modelled for each of the subgroups according to scientific published evidence [39]. Given the lack of some data in the literature, it was assumed that the transmission in HIV-infected females with > 50 copies/mL was double that observed in heterosexual males, and the transmission in PWID females was the average between transmission observed in PWID and heterosexual males. Specifically, for the PWID subgroup, it was considered that 15.3% [40] of people in that group show risk behaviours (needle or syringe sharing during the injection process) an average of 2.7 times per month [41] and that seroconversion due to these risk behaviours is 0.8% [42].

2.3 Sensitivity Analyses

One-way sensitivity analyses (OWSAs) were carried out to test the model's robustness. The values of the following parameters varied in each analysis: time horizon (10 years), average time to ART initiation in current practice (44 days from HIV diagnosis, according to CoRIS, and 25 days as an alternative scenario), average time to B/F/TAF initiation in the early therapy strategy (7 days from HIV diagnosis), HIV lifetime cost (± 25% and estimation from various sources [43–45]), viral suppression for INSTIs per week of treatment (assuming efficacy of B/F/TAF) and distribution of the third component of the ART regimen (49.8%, INSTIs; 25.4%, NNRTIs; and 24.8%, PIs), according to the Spanish

surveillance system referred to as the 'Hospital survey of patients infected with HIV' [46].

3 Results

The model estimated that 47,399 HIV infections would occur in a 20-year time horizon with continuation of the current clinical practice, where ART is initiated following an average of 35 days after an HIV-infection diagnosis. In the scenario representing an early initiation with B/F/TAF at day 9 after diagnosis, the number of HIV cases over the same period would be 46,407. The strategy of rapid ART initiation with B/F/TAF would protect 992 (− 2.09%) patients over the same 20-year period (Fig. 2).

By subgroup analysis, 71.41% of the prevented cases corresponded to MSM, 26.88% to heterosexuals, and the remaining 1.71% to PWID. The detailed number of infections per HIV testing strategy is shown in Table 3.

Cumulative costs were estimated at €15,424 million for the current clinical practice strategy and €15,101 million for early treatment initiation with the B/F/TAF strategy. Compared with the current treatment strategy observed in clinical practice, the reduction in HIV incidence associated with the implementation of early treatment initiation with B/F/TAF would result in potential savings for the Spanish National Health System and society of almost €323 million over the next 2 decades.

Fig. 2 Cumulative HIV cases avoided with rapid B/T/TAF therapy initiation versus current clinical practice along the time horizon. *HIV* human immunodeficiency virus
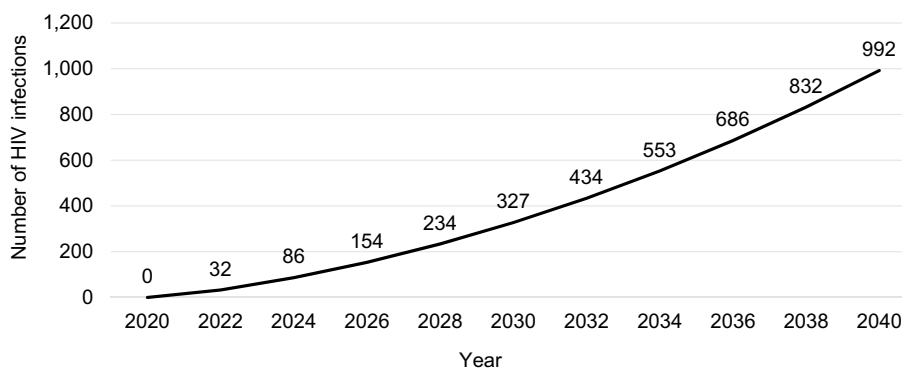

Table 3 HIV cases by subgroup and strategy in the 20-year time horizon

Subgroup	Number of HIV infections		HIV infections prevented with early therapy strategy vs. current practice [*n* (%)]
	Current practice	Early B/T/TAF therapy initiation	
Heterosexuals	13,038	12,771	267 (− 2.09%)
MSM	33,175	32,466	709 (− 2.18%)
PWID	1187	1170	17 (− 1.45%)

B/T/TAF bictegravir/emtricitabine/tenofovir alafenamide, *HIV* human immunodeficiency virus, *MSM* men who have sex with men, *PWID* people who inject drugs

The OWSA showed that the results are generally robust (Table 4). The parameters with the highest influence on the number of prevented HIV cases were, first, the time horizon (cases avoided in 10 years would be 327) and second, the reduction to 25 days of the average time to ART initiation in current practice, which would imply the prevention of 632 new HIV cases if B/F/TAF was initiated at day 9 from diagnosis.

Alternative costs of management of PLWH led to variations in the potential accumulated cost savings from €242 million to €515 million along the 20-year time horizon.

4 Discussion

Several population-based studies have concluded that an increase in the proportion of PLWH receiving ART reduces HIV transmission [47]. Rapid ART initiation has been demonstrated to decrease the reservoir of HIV, providing clear health benefits, but the question 'How early is early enough' is still unanswered [48].

Spain, with an estimated population of 151,400 PLWH [36], adopted policies for early ART initiation in 2016 [49, 50]. Although the GeSIDA/Spanish National AIDS Plan recommends starting ART as soon as possible after diagnosis [18], in the cohort of the Spanish HIV research network (CoRIS cohort), the period observed between HIV diagnosis and ART initiation was 44 days [23], highlighting the

need to reinforce the relevance of the conditions that indicate early ART initiation. In Spain, a cross-sectional survey carried out in 19 hospitals with the objective of analysing the barriers to ART initiation revealed that the most frequent barriers among HIV-infected patients who did not receive ART were physician-related, followed by patient-related [51].

With respect to rapid ART initiation with B/F/TAF, with high-quality evidence for adults and adolescents, the WHO recommends rapid ART initiation for all PLWH following an HIV diagnosis, defining rapid initiation as the start of ART within 7 days from the day of HIV diagnosis [13]. In our study, taking into account a conservative approach, we considered a period of 9 days from diagnosis to ART initiation, bearing in mind that 7 days would represent an ideal scenario that in most cases would be difficult to achieve. Nevertheless, the average time to B/F/TAF initiation in the early therapy strategy varied in the OWSA, demonstrating that initiating B/F/TAF at day 7 from diagnosis could avert 1063 new HIV cases.

Previous evaluations focused on our setting supported that the recommendations for ART initiation irrespective of CD4 count were expected to prevent 20,100 new HIV cases over 2 decades, compared with the strategy of ART initiation based on CD4 level, which had been followed up until then; this was considered a cost-effective policy [52].

The results of the present analysis support the contention that greater clinical benefits could be achieved if the period

Table 4 One-way sensitivity analyses results

Parameter	Base-case value	OWSA value	Number of avoided infections	Potential savings
Base-case result			992	€322,856,609
Time horizon	20 years	10 years	327	€106,475,905
Average time to therapy initiation in current practice	35 days	44 days	1319	€429,272,290
		25 days	662	€205,762,819
Average time to therapy initiation with B/T/TAF in early ART initiation strategy	9 days	7 days	1063	€345,833,471
HIV lifetime cost	€325,408	€244,506 (− 25% over BC)	992	€242,142,457
		€406,760 (+ 25% over BC)	992	€403,570,761
		€519,280[a]	992	€515,209,487
Viral suppression for INSTIs per week	See Table 1	B/F/TAF viral suppression	959	€312,164,507
ART distribution	77.0%—INSTIs, 3.0%—NNRTIs, and 20.0%—PIs	49.8%—INSTIs, 25.4%—NNRTIs, and 24.8%—PIs	1021	€332,079,609

ART antiretroviral therapy, *BC* base case, *B/T/TAF* bictegravir/emtricitabine/tenofovir alafenamide, *HIV* human immunodeficiency virus, *INSTIs* integrase strand transfer inhibitor, *NNRTIs* non-nucleoside reverse transcriptase inhibitor, *OWSA* one-way sensitivity analysis, *PIs* protease inhibitor

[a]Cost derived from health cost (€13,116/year) [43], considering an average age at diagnosis of 36 years [44] and 76 years of life expectancy [45]

between HIV diagnosis and ART initiation is reduced. Early therapy with B/F/TAF on day 9 from diagnosis instead of the current practice of ART initiation at day 35 could prevent up to 992 cases in the 20 years assessed in this simulation.

Based on the current published evidence, the B/F/TAF combination is considered an effective therapy with an acceptable tolerability profile, which makes it a convenient initial and ongoing treatment alternative for PLWH (including those co-infected with HBV). It is also the first non-pharmacologically boosted INSTI-based, triple-combination, single-treatment regimen suitable for use in patients with impaired renal function [17]. The results from our simulation suggest that rapid initiation with B/F/TAF is linked to epidemiologic and economic benefits in comparison with the delayed treatment initiation in current clinical practice.

There are some limitations to be considered in the interpretation of the results. One limitation of our study is that in the absence of other data, the per-act risk of HIV transmission was extracted from a study with a small sample size but with a rigorous and detailed collection of virological data [39]. The per-act transmission probability among HIV-positive patients depends largely on the viral suppression achieved with the combination of ART, and this parameter was varied in the OWSA, showing that it did not have a great impact on the results. The number of new HIV infections ranged between 992 HIV infections prevented in the base case and 959 HIV infections prevented assuming B/F/TAF viral suppression for INSTIs. Another factor that could influence HIV transmission probability is the behaviour of individuals who become aware of their serological status. It is possible that these people modify their risky acts (i.e., using condoms, reducing sexual acts or not sharing needles); however, there is no quantitative evidence about the influence of these acts on the probability of HIV transmission for virologically unsuppressed individuals. Finally, our current study does not consider the potential drug resistance developed by HIV-positive individuals over the projected time horizon. The model methodology and the lack of robust evidence in the literature required simplifying assumptions about certain parameters that could impact the number and costs of new HIV infections. Regarding the HIV lifetime cost, in the absence of robust data for Spain, an HIV cost derived from a cost-effectiveness analysis was used. This cost included all health care inputs consumed and occupational losses generated during HIV disease, from the median age at diagnosis until death [32]. To analyse its impact on the results, an alternative HIV cost was tested in the OWSA, estimating the lifetime cost based on the annual healthcare cost by HIV patients in Spain obtained from a systematic review [43], and the life expectancy [44, 45].

5 Conclusion

Early ART initiation with B/F/TAF within 9 days of diagnosis with HIV infection is associated with a reduction in the number of new cases that could generate savings for the Spanish National Health System and society.

Declarations

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