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Comparing the cost-effectiveness of alternative policies for recommending and providing HIV pre-exposure prophylaxis to men who have sex with men in the EU

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In the European Union (EU), HIV disproportionately affects men who have sex with men (MSM), with prevalence rates ranging from 2.4% to 29%. Pre-exposure prophylaxis (PrEP) is highly effective in preventing HIV, yet access and uptake remain uneven. We used a stochastic agent-based model of HIV transmission among MSM to evaluate the effectiveness and cost-effectiveness of five PrEP eligibility policies across 20 EU countries, incorporating data on sexual behavior, adherence, and healthcare costs. US, CDC and Belgian guidelines, which recommend broad eligibility, achieved the highest reductions in HIV infections and deaths, whereas WHO guidelines consistently emerged as the most cost-effective option, particularly in countries with constrained budgets. Our analyses further show that lowering drug costs would expand the range of cost-effective options in settings without PrEP reimbursement. Finally, we estimated willingness-to-pay thresholds for injectable, long-acting PrEP. Long-acting injectable formulations are emerging as new PrEP options. Current prices largely exceed these thresholds, but cabotegravir could approach cost-effectiveness under WHO guidelines in some countries. Overall, broad eligibility criteria maximize effectiveness, while WHO guidelines balance affordability and impact. Expanding oral PrEP access and reducing drug costs remain essential for HIV prevention in Europe, while injectable PrEP is likely to require substantial price reductions or targeted use in selected populations to become economically attractive. Our findings highlight the need for policy adjustments to improve PrEP accessibility, inform national health strategies, and achieve sustainable HIV prevention across diverse settings.

Keywords HIV pre-exposure prophylaxis (PrEP), Cost-effectiveness analysis, Men who have sex with men (MSM), Agent-based modeling, European Union

Countries in the European Union (EU) have achieved substantial progress in the fight against the HIV/AIDS epidemic in the last decades. However, men who have sex with men (MSM) are still disproportionally affected, and intersecting vulnerabilities exacerbate this: it is the case of migrant MSM who exhibit high rate of acquisition following migration to Europe[1]. Improving primary prevention among MSM has been identified as a crucial step to avert infections in this population[2]. Primary prevention for MSM is based on combination prevention, including condom use, regular HIV testing, treatment as prevention, and post-exposure prophylaxis[3]. This involves pre-exposure prophylaxis (PrEP), the use of antiretroviral medication to prevent HIV acquisition even during unprotected sex. Oral PrEP, the most common formulation and currently available in generic form, has been shown to be safe and effective in preventing HIV acquisition[4–8] but its availability and uptake is highly heterogeneous across European countries. Injectable, long-acting PrEP formulations are now also authorized in the EU formulations including lenacapavir (Yeytuo, Gilead Sciences, Foster City, California; EMA approved in 2025) and cabotegravir[9], and have shown to be highly effective with the potential to reduce the adherence burden typical of oral PrEP, which is taken daily for sustained periods of time. However, unlike oral PrEP, injectable formulations are not generally reimbursed across EU healthcare systems, with limited exceptions such as France

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where it is accessible under specific medical conditions[10]. Barriers to the scale-up of PrEP include concerns over its possible negative effects on the circulation of bacterial sexually transmitted infections[10] and their rates of antibiotic resistance[11]. At the same time, evidence in support of these concerns is mixed[12], and these barriers might themselves reinforce stigma[13] and hamper comprehensive prevention strategies[14]. As a result of these opposing arguments, countries in the EU have made considerable different choices on how much to invest on, make available, and encourage PrEP among MSM. Some countries, like France, fully reimburse PrEP (at least in its oral formulation) and recommend it to all those who identify as gay men or report having sex with men. Others, like Belgium, reimburse it, but prescribe it only to those with an estimated high risk of being exposed to HIV, and only through specialized visits in national healthcare centers or hospitals. In others, like Hungary, PrEP is not reimbursed but it is available upon prescription. Finally, in others like Romania, PrEP is not available[15].

A crucial determinant of the different PrEP policies is their definition of eligibility. Eligibility criteria vary across guidelines and generally rely on estimating the risk of HIV exposure based on socio-demographic factors and sex-related behaviors. These behaviors include reported condom use, being in a serodiscordant partnership, the use of postexposure prophylaxis, a history of sexually transmitted infections, or the use of psychoactive substances during sex. This results in substantially different pools of eligible individuals across different guidelines, with substantially different risks of acquiring HIV[16,16,17,17].

This heterogeneity of approaches across EU countries highlights the need for an assessment of PrEP effectiveness and cost-effectiveness across healthcare systems and policy guidelines. A unified modeling framework enables valid cross-border comparisons, often impossible with single-country studies, allowing policymakers to benchmark strategies against local budget constraints. Beyond methodological harmonization, EU-level cost-effectiveness analyses may also have strategic value for access and price negotiation. Comparable estimates across countries can provide a common reference for coordinated procurement strategies, joint pricing discussions, and future health technology assessment of novel PrEP formulations, particularly long-acting ones. Such analyses may additionally help identify inequalities in access and affordability across healthcare systems, thereby informing both EU-level coordination and country-level decisions[18]. Currently, most studies assessing the cost-effectiveness of PrEP policies in high-income countries focus on the United States[19]. Assessments of the cost and cost-effectiveness of PrEP in the EU are scarce, and focus on single countries[20],van [21–24]. Results are varied across countries and settings, indicating that PrEP may be cost-effective only under certain conditions, like reduced drug price [25]. Some studies recommended providing PrEP only to high-risk MSM, while others found that risk-based eligibility may reinforce stigma and decrease the overall effectiveness of the prevention campaign[26,27]. Crucially, two elements are still missing: to systematically evaluate the cost-effectiveness of the PrEP policies that each country is adopting, and to determine the potential benefits of switching to an alternative policy. To address these knowledge gaps, in this study, we focused on eleven countries in the EU which currently provide free PrEP to MSM. We estimated the impact and cost-effectiveness of their current PrEP policies on HIV infections and related deaths over the next decades. We also tested the hypothetical implementation of alternative policies among those recommended by a set of EU and non-EU authorities. Additionally, we studied eleven other EU countries which currently have no free PrEP policy, and tested the impact and cost-effectiveness of the different policies. Finally, we performed a threshold analysis to estimate the maximum acquisition cost at which long-acting injectable PrEP could remain cost-effective under each eligibility policy. This analysis was intended to assess economic price limits rather than to predict real-world uptake or allocation between oral and injectable PrEP. We employed a previously developed stochastic, agent-based model[28] of HIV infection among MSM, and used Incremental Cost-Effectiveness Ratio (ICER) to determine cost-effectiveness[29]. In the following, PrEP should be intended as oral PrEP (specifically TDF/FTC, available as generic or branded as Truvada, Gilead Sciences, Foster City, California) unless otherwise specified. F/TAF (Descovy, Gilead Sciences, Foster City, California) is not included, as it is not generically available and priced differently.

Methods

Countries and PrEP guidelines under study

We considered the following countries of the EU which currently provide PrEP free of charge: Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Portugal, Slovenia, Spain. We also considered these countries which do not currently reimburse PrEP: Bulgaria, Greece, Hungary, Latvia, Lithuania, Poland, Cyprus, Malta, Romania. We tested five PrEP eligibility guidelines, labeled by the recommending organization or country. The most restrictive, labelled POR, corresponds to the Portuguese Ministry of Health recommendations[16,17]. It recommends prescribing PrEP to those reporting unprotected anal sex and whose partner has not tested for HIV in the past six months. It was used to represent countries applying similar eligibility criteria, namely Finland, Ireland, the Netherlands and Slovenia. The second most restrictive is the World Health Organization's Implementation Tool for Pre-exposure Prophylaxis of HIV Infection (WHO)[30], which recommends PrEP to those declaring unprotected anal sex and have more than one sex partner. It is currently in use in Denmark. The third one is the European AIDS Clinical Society's Guidelines Version 12.0 (EACS)[31] which recommends PrEP to those reporting unprotected anal sex in non-main partnerships. A policy very similar to EACS is currently in force in Italy. The least restrictive are the United States Centers for Disease Control and Preventions (CDC) Public Health Service[32], which recommends PrEP to all those identifying as MSM and is currently in use in France and Germany, and that of the Belgian Federal Office of Health (BEL). BEL recommends PrEP to all those reporting unprotected anal sex[33] and is currently in use in Belgium and Spain. See Fig. 1 for a map of the countries under study, the situation of their HIV epidemic among MSM, and the PrEP policy now in effect.

Transmission model and PrEP dynamics

We used a stochastic agent-based model of HIV transmission implemented in the EpiModel framework[28] in R version 4.5.2, which has already been used to model the impact of PrEP on the HIV epidemics[34,35]. In our study,

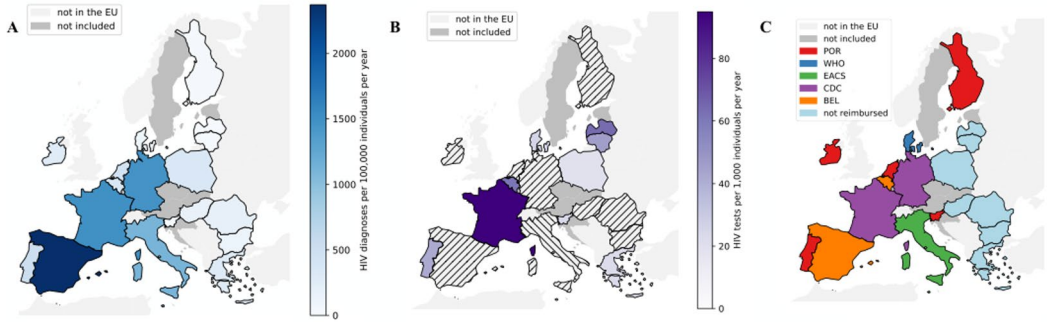


Fig. 1. Countries considered in the study. (**A**) Rate of HIV diagnoses among men, with acquisition occurring through sex with men, per year, per 100,000 individuals. Data from 2019 (ECDC). (**B**) Number of HIV tests performed, except anonymous tests, per year, per 1000 individuals. Data from 2022 (ECDC). Hashing indicates that data were not available. (**C**) Currently adopted PrEP policies in each country. Abbreviations POR, Portugal (most restrictive); WHO, World Health Organization; EACS, European AIDS Clinical Society; CDC, United States; BEL, Belgium (least restrictive).

we adopted a weekly time scale and a synthetic population of 10,000 men. The model uses exponential random graphs to encode primary, casual, and one-time partnerships[36], and accommodates individual characteristics such as ethnicity, circumcision status, sexual preference (receptive/insertive), and propensity for unprotected anal sex. The model was parametrized using the EMIS cross-sectional study[37], the Lisbon Cohort study[38] and [39] to inform partnership network dynamics (Figure S1). Individuals enter at 18 years of age and exit at death or at 65. HIV rates were initialized using Ref [37] (Fig. 1). After discarding an initial transient, we simulated the HIV epidemic 20 years into the future. For each model setup, 1,000 runs were performed and observables of interest measured as median and 95% confidence intervals across runs. Additional details on the agent-based model are available in the Supplementary Appendix. We assumed a 20% weekly probability of PrEP initiation, based on previous studies from high-income countries[38]. We estimated injectable PrEP to be 1.01 times more effective than daily oral PrEP in preventing HIV acquisition, following [40].

Health economics analysis

In the countries where PrEP is reimbursed, we adopted a modified healthcare payer perspective (drug acquisition only). While clinical monitoring and laboratory costs were excluded from the base-case to facilitate cross-country comparison of drug policies, these were evaluated in sensitivity analyses to ensure the robustness of the results. We estimated annual PrEP cost using the minimum reimbursable price in each country[15]. To focus on drug acquisition, we adopted a modified payer perspective excluding routine clinical monitoring costs in the base-case, though these were examined in sensitivity analyses to assess their impact. We used the ECDC progress report[41] for the cost of antiretroviral therapy (ART) in each country. For the cost-effectiveness analysis, we used Quality-Adjusted Life Year (QALY). QALY measures the quality and quantity of life lived and is commonly used in health economics and cost-effectiveness analyses. We assumed a utility of 1.0 for HIV-negative individuals and for HIV-positive individuals prior to AIDS progression (conservative assumption), a utility value of 0.7 was only upon progression to the AIDS stage [42]. We then computed the Incremental Cost-Effectiveness Ratio (ICER) which is the additional cost per QALY gained. To assess stochastic uncertainty, 95% uncertainty intervals (UI) for the ICERs were estimated using non-parametric bootstrap resampling with 1,000 iterations. ICERs and threshold prices were calculated relative to a 'No PrEP' scenario. As customary, we set the threshold of cost-effectiveness to twice the gross domestic product (GDP) per capita, based on World Bank data[43]. In the countries that reimburse PrEP, a policy was considered cost-effective if its ICER was below that threshold. We also compared different policies according to their ICER, to determine their relative cost-effectiveness. In the countries that do not reimburse PrEP, we used the cost-effectiveness threshold to determine the willingness-to-pay threshold. The willingness-to-pay threshold is the highest cost of PrEP at which the policy would still be cost-effective. For injectable PrEP, we conducted a willingness-to-pay threshold analysis. We calculated the maximum weekly injectable PrEP acquisition cost at which the ICER would equal the cost-effectiveness threshold, set at twice the GDP per capita. In this threshold analysis, injectable PrEP was assumed to replace oral PrEP among eligible individuals under each policy; this simplified scenario was intended to estimate an economic price limit. Because data on user preferences, injection acceptability, provider allocation, and switching from oral to injectable PrEP are not available in a harmonized and directly generalizable form across EU countries, we did not model a behavioural mixed-use implementation scenario in the base case. We instead added an exploratory post-hoc mixed-use sensitivity analysis in the Supplementary Appendix. Both costs and QALYs were discounted at an annual rate of 3% in the base-case analysis, in line with standard practice in economic evaluation, with sensitivity range 0–4%. All costs were converted to constant 2020 euros, the model start year, by inflating values from source years using country-specific consumer price indices[44]. We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines[45].

Results

Policy effectiveness on infections, deaths and PrEP coverage

We first analyzed countries that reimburse PrEP. Expectedly, stringent policies led to a long-term PrEP coverage that was substantially lower than that of less stringent policies. Coverage values are in Tables S5 and S6. After 20 years, POR achieved about 48% PrEP coverage, nearly half of CDC's 90%. Moreover, we observed that PrEP coverage stabilized across countries and policies within the first 10 years of implementation (compare PrEP coverage after 10 (Table S5) and 20 years (Table S6)). As expected, all policies substantially reduced HIV infections and deaths over 20 years compared to no PrEP (Figure S2). Their effectiveness, however, was heterogeneous. Tables 2, S5, and S6 report the rates of estimated averted infections and deaths across countries and guidelines, while Fig. 2 ranks them by their effectiveness. We can observe that CDC was the most effective in preventing infections; EACS ranked second in 9 of 10 countries. These policies were able to avert, respectively, 76–142 and 68–134 infections per 1000 individuals. In terms of estimated averted deaths, the BEL and CDC policies were the most effective: 15–24 and 13–27 per 1000 individuals, respectively. BEL also showed substantial impact on averted infections, ranging from 63 to 129 per 1000 individuals. The impact of EACS on averting deaths was negligible. WHO and POR, the two most restrictive policies, had a comparable impact on averting infections, albeit strongly country-dependent: 52–100 and 33–71, respectively. Their impact on averting deaths was substantially stronger than EACS: 7–17 and 8–20, respectively (Table 2).

Over the period of 20 years, CDC and BEL remained the most effective, with infection and death rates doubling from 10 to 20 years, thus reaching maximum effectiveness by year 10. Instead, EACS showed a limited increase in averted infections with respect to the 10-year horizon, bringing down its effectiveness ranking in 5 of the countries in which used to rank second. But its effectiveness in averting deaths substantially improved:30–45 for 1000 individuals. WHO kept the same performance as after 10 years, ranked fourth in terms of averted infections and third or fourth in terms of averted deaths. Overall, rates broadly doubled with respect to the 10-year window, again indicating that the policies had achieved its maximum effectiveness after 10 years. Even though POR also roughly doubled the rate of averted infections and deaths from the 10-year window, it still was the policy leading to the smallest number of averted infections and ranked third in terms of averted deaths.

In countries without PrEP reimbursement, coverage stabilized between 35% (WHO) and 88% (CDC) by year 10, with little change by year 20 (Table S6), and PrEP significantly reduced HIV infections and deaths versus no PrEP. After 20 years, infection reduction rates varied substantially across countries. While the CDC policy, for example, had 56–148 averted infections per 1,000, POR had 44–100. The ranking of intermediate policies (WHO, EACS, and BEL) also varied by country: in Cyprus and Latvia, for instance, BEL outperformed WHO which in turn outperformed EACS, whereas in Italy EACS outperformed BEL, which in turn outperformed WHO (Table S5).

Health economics analysis in countries reimbursing PrEP

The assumed cost-effectiveness threshold, set at twice the GDP per person, was heterogeneous across the countries which currently reimburse PrEP, ranging from 212,118 euros per QALY in Ireland to 57,938 euros per QALY in Portugal (Table 1 reports all the assumed cost-effectiveness thresholds). The cost of PrEP was also heterogeneous[15] (Table 1). We evaluated the cost-effectiveness of currently implemented policies in the countries that reimburse PrEP again at the time horizons of 10 and 20 years (Table S8 and S9). Additionally, we estimated the cost-effectiveness of all possible alternatives, under the assumption that countries could switch from the one they are currently implementing to any other. Figure 3A reports Incremental Cost-Effectiveness Ratio (ICER) at the time horizon of 10 years and shows that the currently implemented policies were cost-effective only in Denmark (policy WHO), the Netherlands (POR) , Spain (BEL) and Italy (EACS). It is possible to also observe that

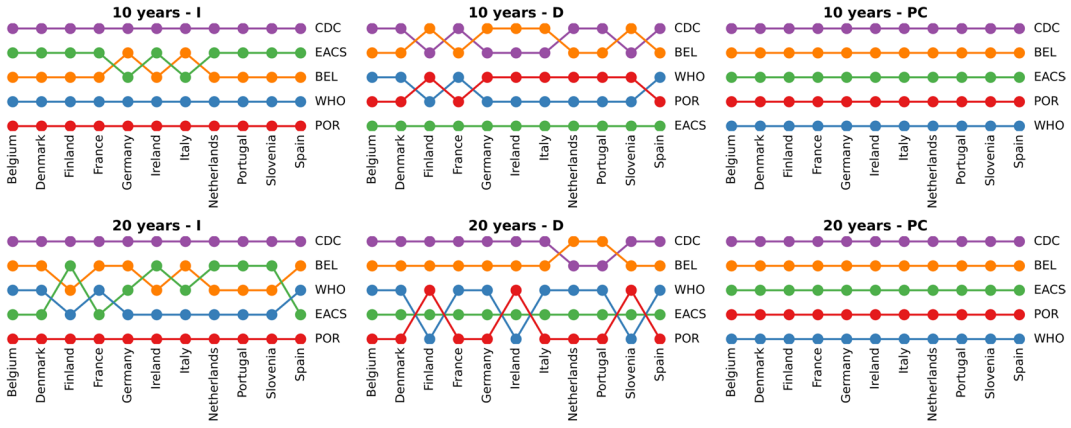


Fig. 2. Ranking of PrEP policies in each country according to their effectiveness in averting HIV infections (I), in averting HIV-related deaths (D) and in achieving high PrEP coverage (PC). Rankings evaluated over 10 and 20 years. See table S6 and table S7 for the estimated effectiveness values. Abbreviations: POR, Portugal (most restrictive); WHO, World Health Organization; EACS, European AIDS Clinical Society; CDC, United States; BEL, Belgium (least restrictive).

Country	Monthly PrEP price (€/30-day supply)*	Assumed cost-effectiveness threshold (€/QALY)**
Ireland	139.29	212,118
Denmark	447.86	155,282
Belgium	334.29	136,158
Netherlands	64.29	127,500
Finland	417.86	110,254
Germany	128.57	108,582
France	332.14	94,718
Italy	64.29	67,480
Malta	–	61,292
Portugal	18.21	57,938
Cyprus	–	57,010
Lithuania	–	41,896
Greece	–	38,054
Latvia	–	36,320
Hungary	–	32,952
Poland	–	31,388
Bulgaria	–	19,656

Table 1. Monthly PrEP medication costs and assumed cost-effectiveness thresholds by country.

		EACS	CDC	WHO	POR	BEL
Belgium	10-year	114(93–120)	127(123–135)	93(90–95)	61(55–65)	98(97–118)
Denmark	10-year	114(93–120)	127(123–135)	93(90–95)	61(55–65)	98(97–118)
Finland	10-year	68(45–93)	76(70–90)	52(49–74)	33(30–51)	63(54–92)
France	10-year	114(93–120)	127(123–135)	93(90–95)	61(55–65)	98(97–118)
Germany	10-year	104(87–105)	127(98–127)	96(79–105)	71(68–73)	105(100–110)
Ireland	10-year	68(45–93)	76(70–90)	52(49–74)	33(30–51)	63(54–92)
Italy	10-year	104(87–105)	127(98–127)	96(79–105)	71(68–73)	105(100–110)
Netherlands	10-year	134(100–136)	142(128–152)	100(88–107)	55(43–66)	129(89–136)
Portugal	10-year	134(100–136)	142(128–152)	100(88–107)	55(43–66)	129(89–136)
Slovenia	10-year	68(45–93)	76(70–90)	52(49–74)	33(30–51)	63(54–92)
Spain	10-year	114(93–120)	127(123–135)	93(90–95)	61(55–65)	98(97–118)
Belgium	20-year	107 (151–161)	183 (175–194)	148 (144–153)	100 (99–101)	161 (153–172)
Denmark	20-year	107 (151–161)	183 (175–194)	148 (144–153)	100 (99–101)	161 (153–172)
Finland	20-year	97 (82–104)	112 (89–121)	84 (81–89)	65 (63–68)	91 (91–111)
France	20-year	107 (151–161)	183 (175–194)	148 (144–153)	100 (99–101)	161 (153–172)
Germany	20-year	139 (128–139)	162 (143–159)	129 (114–136)	94 (94–95)	147 (135–152)
Ireland	20-year	97 (82–104)	112 (89–121)	84 (81–89)	65 (63–68)	91 (91–111)
Italy	20-year	139 (128–139)	162 (143–159)	129 (114–136)	94 (94–95)	147 (135–152)
Netherlands	20-year	176 (156–171)	197 (174–198)	138 (132–147)	96 (84–108)	166 (157–179)
Portugal	20-year	176 (156–171)	197 (174–198)	138 (132–147)	96 (84–108)	166 (157–179)
Slovenia	20-year	97 (82–104)	112 (89–121)	84 (81–89)	65 (63–68)	91 (91–111)
Spain	20-year	107 (151–161)	183 (175–194)	148 (144–153)	100 (99–101)	161 (153–172)

Table 2. Number of averted HIV infections per 1000 individuals, in the countries that currently reimburse PrEP, under the different PrEP policies, at the 10-year time horizon and 20-year horizon. The reported values are median and 95% confidence interval from the stochastic iterations of the model. POR, Portugal (most restrictive); WHO, World Health Organization; EACS, European AIDS Clinical Society; CDC, United States; BEL, Belgium (least restrictive).

the WHO policy would be cost-effective if implemented in Belgium, Germany, Italy, the Netherlands, Portugal and Spain. The EACS policy would be cost-effective, if implemented, in Germany, Ireland, the Netherlands, Italy, Portugal and Spain. The CDC policy would be cost-effective in Ireland, Italy, the Netherlands, Portugal and Spain. Finally, the BEL policy would be cost-effective in the Netherlands, Italy and Portugal. Notably, all policies would be cost-effectiveness in the Netherlands, while none would be cost-effective in Finland and Slovenia. The currently implemented policy was the most cost-effective only in Denmark (WHO). In all the other countries,

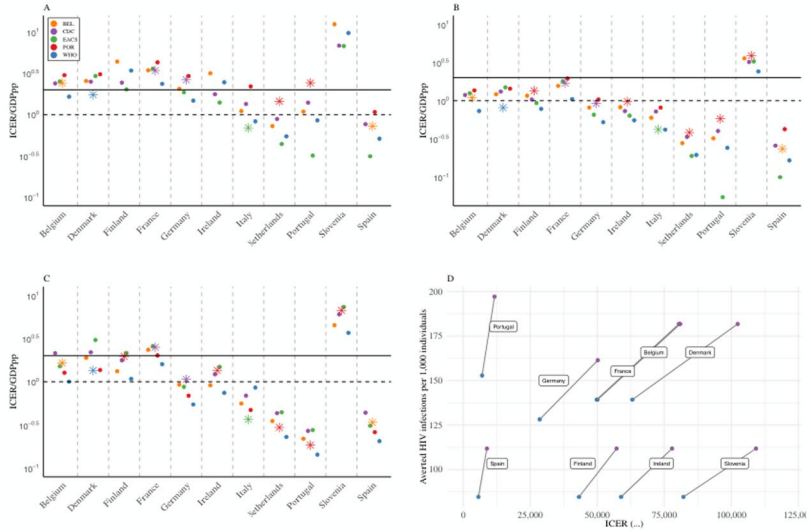


Fig. 3. Cost-effectiveness of the different PrEP policies in the 10 countries currently reimbursing PrEP. (**A**) ICER over GDP per person at the 10-year time horizon; (**B**) ICER over GDP per person at the 20-year time horizon; (**C**) ICER over GDP per person at the 20-year time horizon, assuming that each country keeps the current policy for 5 years and then switches to the selected policy. In (**A**), (**B**) and (**C**) the solid horizontal line corresponds to an ICER of twice the GDP per person. (**D**) Comparison between the most effective policy (CDC) and the most cost-effective policy (WHO) in terms of ICER and averted infection rates. The slope of the gray lines indicates measure the change in averted infections per unit increase in ICER. Abbreviations: POR, Portugal (most restrictive); WHO, World Health Organization; EACS, European AIDS Clinical Society; CDC, United States; BEL, Belgium (least restrictive).

which reimbursed PrEP, the most cost-effective policy was either WHO (Belgium, France and Germany) or EACS (Finland, Italy, Ireland, the Netherlands, Portugal, Slovenia—tied with CDC—and Spain).

Figure 3B reports ICER at the time horizon of 20 years, and we observed that all the examined policies were cost-effective in all the countries which currently reimburse PrEP, except in Slovenia, where still none of the policies were cost-effective. Again, the currently implemented policy was the most cost-effective only in Denmark (WHO) and Italy (EACS). WHO was the most cost-effective policy in all the countries where it was already so at the 10-year horizon. EACS was still the most cost-effective in the Netherlands (albeit tied with WHO), Portugal and Spain, but it was no longer so in Finland and Slovenia, replaced by WHO. However, it is worth noting that in both countries WHO had been among the least cost-effective at the 10-year horizon.

In Fig. 3A and B, we assumed that each country immediately switched to each examined policy, if not already adopted. Instead, in Fig. 3C we examine the scenario in which a country kept the current policy for five years and then transitioned to another policy. Describing the results, we refer to the policy adopted after the five-year period. In Slovenia, no policy was cost-effective; elsewhere, all were except EACS in Denmark, Finland and France, CDC in Belgium and Denmark, France, and BEL in France. WHO was the most cost-effective policy everywhere, tied with POR in Denmark.

In Fig. 3D we compare the CDC policy, the most effective policy in averting infections, with the WHO policy, the most cost-effective policy emerging from Fig. 3C, at the 20-year horizon. We show ICER vs averted infections and the slope of the line connecting the two policies indicates the additional number of HIV infections averted per unit increase in the ICER. The Netherlands, Portugal and Spain feature steep slopes, meaning that the rate of averted infections beyond the most cost-effectiveness policy would entail a limited increase in costs. In opposition, flatter slopes in Ireland and Slovenia show that increasing averted infections beyond the most cost-effective policy would incur higher costs. Finally, in Figure S3, we show the effect of different economic assumptions through a sensitivity analysis. Yearly discounting rate, ART cost and PrEP implementation costs (including physician visits, lab testing, and counseling) appear as the two factors most impacting cost-effectiveness estimates. However, they did not alter our main conclusion that all policies remained cost-effective (below twice the GDP per capita threshold).

Health economics analysis in countries not reimbursing PrEP

We estimated the willingness-to-pay (WTP) threshold for each policy, in the countries which currently do not reimburse PrEP, at the 20-year horizon. The WTP threshold is the maximum cost of PrEP for which a policy is cost-effective. Any cost at or below the WTP threshold causes the policy to be cost-effective. We estimated

the WTP threshold in the countries under study and compared it to the reported cost of generic PrEP, and of Truvada (the branded tenofovir disoproxil fumarate/emtricitabine product) in the case of Hungary, where it is available. In Fig. 4, we present our estimations and we can observe that the cost of Truvada exceeded the WTP threshold of any policy by more than 500 Euros per month, making it extremely not cost-efficient. All the tested policies were instead cost-effective at the current cost of generic PrEP in Cyprus and Greece, while none was cost-effective in Bulgaria and Hungary. BEL and WHO policies were cost-effective in all the remaining countries.

Health economics analysis for injectable PrEP

We estimated the willingness-to-pay (WTP) threshold of injectable PrEP for of the eligibility policies under study in the countries which currently reimburse oral PrEP. The WTP varied across policies and countries. Under the assumption of a cost-effectiveness threshold of twice the GDP per capita, Countries such as Finland, Portugal and Slovenia yielded comparatively lower willingness-to-pay thresholds across policies.This went below 49 euros/month in Slovenia. Denmark instead had the overall the highest WTP threshold, with the policy WHO reaching 781 euros/month. WHO was, across countries, the policy leading to the highest WTP threshold, while POR the lowest. No WTP threshold, however, went above 800 euros/month across countries and policies. For comparison, in France, according to one source, the cost of injectable is estimated to be around 1600 euros/month, while the cost of injectable cabotegravir is estimated to be around 100 euros/week[46]. In the United States estimates put Yeytuo at 2160 USD/month and Apretude 1680 USD/month[47]. Figures S11 and S12 in the Supplementary Appendix also present a mixed-use (oral and injectable) analysis, in which only the fraction of PrEP user-time costed as injectable PrEP was varied, produced the same qualitative conclusion: injectable PrEP would require low prices or limited targeted use to remain cost-effective.

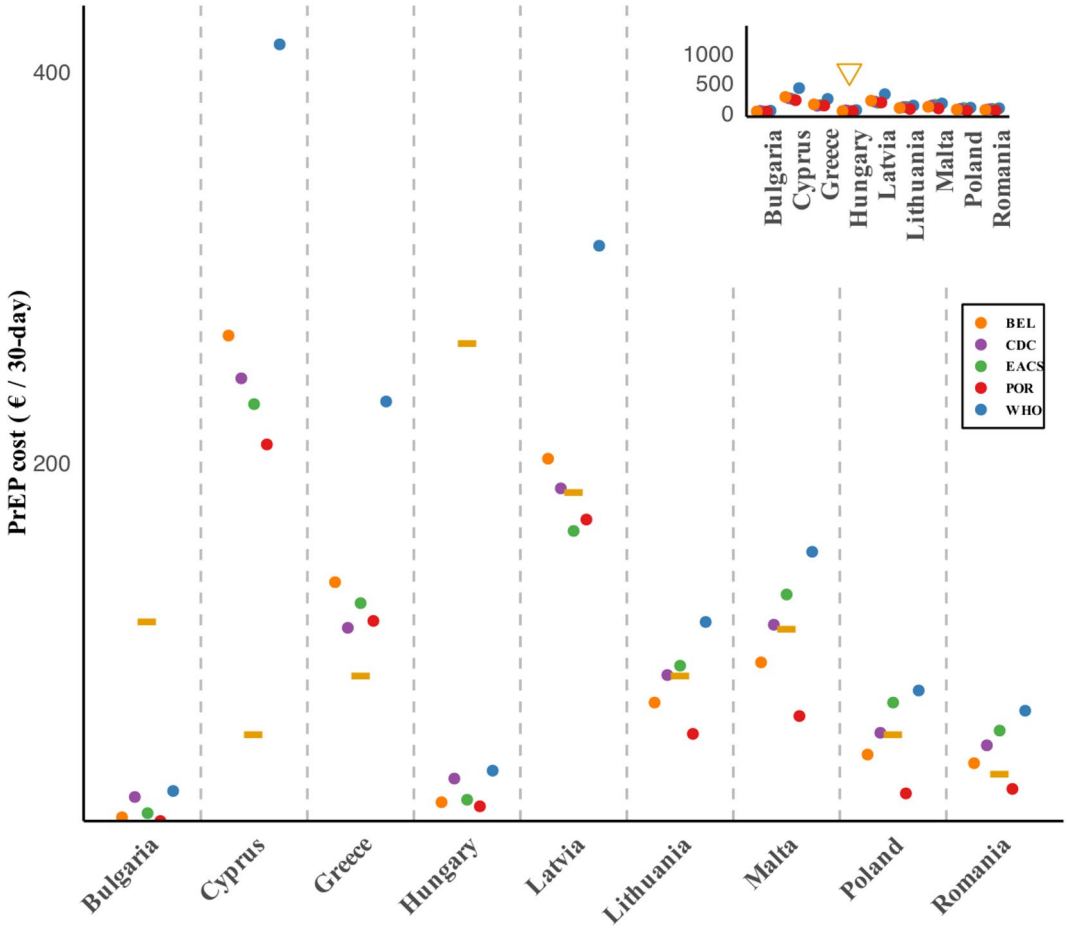


Fig. 4. Willingness-to-pay threshold of each examined PrEP policy in the countries not reimbursing PrEP, vs the currently estimated cost of generic oral PrEP/TDF/FTC (yellow bar) and branded emtricitabine/tenofovir disoproxil fumarate (Truvada, Gilead Sciences, Foster City, California) (yellow triangle). The main plot excludes Truvada, the inset includes Truvada. Abbreviations: POR, Portugal (most restrictive); WHO, World Health Organization; EACS, European AIDS Clinical Society; CDC, United States; BEL, Belgium (least restrictive).

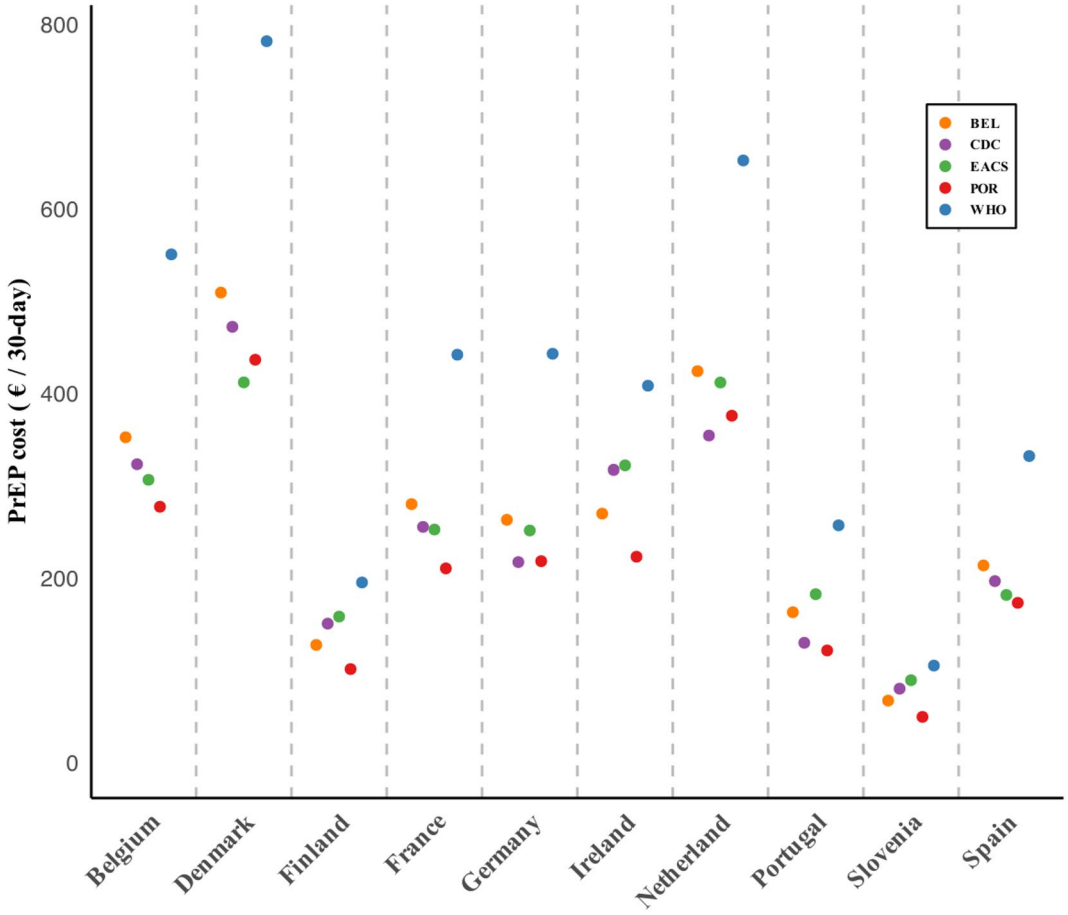


Fig. 5. Willingness-to-pay threshold for long-acting, injectable PrEP of each examined PrEP policy in the countries which currently reimburse at least oral PrEP. Abbreviations: POR, Portugal (most restrictive); WHO, World Health Organization; EACS, European AIDS Clinical Society; CDC, United States; BEL, Belgium (least restrictive).

Discussion

In this study, we assessed how alternative PrEP eligibility policies influence both the epidemiological impact of HIV prevention and the economic sustainability of PrEP programmes across EU countries using a unified modelling framework. Our main finding was that broader PrEP eligibility maximises epidemiological impact among MSM, whereas the WHO-based policy consistently provided the best affordability-impact balance across EU settings. Drug price was the dominant driver of whether broader strategies remain cost-effective, and price reductions would expand the set of feasible policies, especially in countries without reimbursement. For long-acting injectable PrEP, current prices are generally above the willingness-to-pay thresholds we estimate, but injectable PrEP is likely to require substantial price reductions or targeted use among individuals for whom oral PrEP is not feasible, acceptable, or easy to adhere to. Over a 20-year horizon, all policies remained cost-effective below a threshold of twice the GDP. This is consistent with previous findings in the Netherlands as well as other high-income regions like the US, UK, and Australia[48–51]. Only Denmark, however, currently adopts the most cost-effective strategy. This hints at a current knowledge gap in quantitatively assessing policy effectiveness and cost-effectiveness, which this study aimed at addressing. We also noted that the WHO policy was consistently the most cost-effective, both in the shorter and longer term. This is compatible with the fact that targeted PrEP strategies may be preferable in high-income settings[27]. In practice, our analyses show that the WHO policy can be an option in those countries, like Slovenia, where the cost of PrEP is high, and thus deviating from optimal cost-effectiveness is expensive. This is true both as an initial choice and as a policy to switch to. Countries which currently do not provide PrEP free-of-charge could start providing it following the WHO guidelines, and countries which already provide PrEP and are following other policies might benefit from transitioning to WHO's policy.

Instead, in countries where PrEP is cheaper, such as Spain, Portugal and the Netherlands, policies that achieve high PrEP coverage (CDC and BEL) appeared to be appropriate, as they maximize the number of averted infections and deaths at a limited additional cost. We highlight that these policies are also appropriate where maximizing the number of averted infections may outweigh economic considerations, as it is likely to be currently the case in France and Germany. In this context, our results also suggest that those countries should not switch to WHO unless cost saving becomes pressing, as this would reduce effectiveness.

As expected, national PrEP cost strongly impacts policy cost-effectiveness. Given the widespread availability of generic TDF/FTC, the discussion on cost should arguably shift from drug pricing to delivery and implementation. However, for countries still facing budget constraints or looking to adopt newer, expensive injectable formulations, reducing procurement costs remains crucial. Harmonizing PrEP policies across the EU toward broader eligibility could reduce cross-border health disparities. To achieve this "ideal" scenario of high access and sustainability, EU member states could leverage mechanisms such as grouped procurement (joint purchasing) to negotiate lower prices for both oral generics and novel long-acting injectables. This would allow countries currently restricting access (e.g., to WHO guidelines) to transition to more effective, broad-coverage strategies (e.g., CDC/BEL) without compromising budgetary sustainability. However, harmonized benchmarks should not be interpreted as one-size-fits-all targets. Countries differ in financing capacity, delivery infrastructure, clinical workforce, and reimbursement mechanisms, so benchmarks derived from a unified framework may be difficult to achieve in weaker systems. Their value is therefore to support price negotiation, resource planning, and progressive expansion of access, rather than to prescribe identical implementation across countries. Our estimates imply that current procurement costs are generally an obstacle to having cost-effective policies involving long-acting PrEP in the European countries under study, and in line with what found in other parts of the world[52–55]. Injectable cabotegravir may, however, be close to the willingness-to-pay threshold in some countries under the WHO policy, provided that costs are similar to what reported for France, which is indeed already providing it free-of-charge[9], albeit only in the case the option of oral PrEP is not viable.

Our study has limitations. First, cost estimates focused on PrEP and ART, and may underestimate the total cost of PrEP policies. Notwithstanding, our conservative estimates consistently demonstrated the cost-effectiveness of PrEP interventions. Additionally, our model assigns a utility of 1.0 to HIV-positive individuals in the pre-AIDS stage and 0.7 for AIDS. This assumption simplifies quality-of-life variation associated with treatment status, viral suppression, or treatment burden. Because the base-case assumes no quality-of-life decrement for most of the HIV-positive lifespan, it likely underestimates the QALY gains from infections averted and therefore provides conservative cost-effectiveness estimates. Second, to inform HIV prevalence among MSM, we used reported rates of HIV diagnosis, which may be biased where testing rates are low or unknown [37]. Third, we deliberately excluded other sexually transmitted infections (STIs) from the analysis. The purpose of PrEP is to protect from HIV and we believe that it is useful to assess its effectiveness and cost-effectiveness on the basis of its impact on HIV infections and related negative health outcomes. In addition, both the evidence of the effect of PrEP on the spread of other STIs is mixed[13,50] and the circulation of STIs in Europe among MSM is poorly known[56]. Including STIs in the analysis would thus inevitably increase the uncertainty of our predictions, without informing on what factors really determine the effectiveness and cost-effectiveness of policies. Fourth, our model simplifies the PrEP care continuum and does not explicitly simulate the full country-specific PrEP cascade (screening, linkage to care, and retention). Integrating these granular cascade data would be essential for health authorities to refine budget planning and manage the operational challenges of expected increases in PrEP initiations. Our model also simplifies PrEP dosing behavior. In particular, it does not explicitly distinguish between event-driven PrEP and daily PrEP. Instead, it contains adherence classes as broad protection categories rather than as direct proxies for specific dosing regimens. While country-specific cohort data, including from France and the Netherlands[57], contain information on daily and event-driven PrEP use, patterns vary substantially across European settings and cannot be directly generalized to all countries in our analysis. Finally, our injectable PrEP analysis should be interpreted as a threshold and sensitivity analysis rather than as a realistic implementation model. A full mixed-use implementation model for injectable PrEP was beyond the scope of this study because it would require empirical data on preferences, acceptability, provider selection, and switching behaviour between oral and injectable PrEP, which are not currently available in harmonized form across EU countries.

Conclusions

Our analysis showed that PrEP guidelines that maximize coverage in the MSM population, like CDC and BEL, which apply broad eligibility criteria, are the most effective, but are costly unless PrEP procurement is cheap. WHO guidelines, which restrict eligibility to individuals reporting condomless sex with multiple partners, instead offer a cost-effective option. Most countries under study could consider switching to more cost-effective strategies without compromising PrEP effectiveness. Finally, lowering oral PrEP costs is essential for expanding coverage in countries that currently do not provide it free of charge. For injectable PrEP, our analyses suggest that cost-effectiveness would require substantial price reductions or targeted use in selected groups for whom oral PrEP is not feasible, acceptable, or easy to adhere to. These findings suggest that EU member states should prioritize generic oral PrEP access and consider joint procurement mechanisms to reduce costs, enabling a transition toward broader eligibility strategies. Harmonizing PrEP policies across the EU, guided by cost-effectiveness evidence, represents a concrete step toward more equitable and sustainable HIV prevention.

Data availability

All data supporting the findings of this study are provided in the Supplementary Information and publicly available at [https://github.com/peasantxuan/PrEP_Cost_effectivness_EU_MSM] (https://github.com/username/projectname)]. The analysis codes are available at the same GitHub repository.

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Author contributions

B.W. and E.V. conceptualized the study, designed the research, developed the methodology, wrote the original draft, and interpreted the data. J.B. curated the data, performed the formal analysis, and reviewed the manuscript. A.S.T. and E.V. discussed the results, acquired funding, supervised the project, and reviewed the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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