

**Objectives** To study the conditions under which PrEP coverage can eliminate HIV among men who have sex with men (MSM) in the Paris region.

**Design** Mathematical modeling.

**Methods** We propose an innovative approach, combining a transmission model with a game-theoretic model, for decision-making about PrEP use. Individuals at high risk of HIV infection decide to use PrEP, depending on their perceived risk of infection and the relative cost of using PrEP versus antiretroviral treatment (ART), which includes monetary and/or non-monetary aspects, such as price and access model of PrEP, consequences of being infected and lifelong ART.

**Results** If individuals perceive fairly their infection risk, and the cost of using PrEP is sufficiently low, the PrEP coverage can lead to elimination. Specifically, assuming 86% PrEP effectiveness, as observed in two clinical trials, a minimum PrEP coverage of 55% (95% CI:43%–64%) among high-risk MSM would achieve elimination in the Paris region. A complete condom drop by PrEP users slightly increases the minimum PrEP coverage by  $\sim 1\%$ , while underestimation of their own HIV infection risk would demand PrEP programs to reduce the cost of using PrEP by a factor  $\sim 2$  to achieve elimination.

**Conclusions** Elimination conditions are not yet met in the Paris region, where at most 47% of high-risk MSM were using PrEP as of mid-2019. Further lowering the cost of PrEP and promoting a fair perception of HIV risk are required and should be maintained in the long run, to maintain elimination status.

## 1 Introduction

In many settings, men who have sex with men (MSM) are the most affected by HIV.[?] Pre-exposure prophylaxis (PrEP), the use of antiretroviral drugs by uninfected individuals, is a highly effective prevention method, currently recommended by the WHO for individuals at high risk of HIV infection.[?] Both IPERGAY and PROUD clinical trials showed that PrEP can reduce HIV incidence among MSM by 86%.[?] Modeling studies elaborating on these results suggested that PrEP has the potential to curtail, and even eliminate, HIV epidemics, notably among MSM.[?] For instance, it was found that, in the United States (US), a 40% PrEP coverage, among high-risk MSM, would lead to a 33% decrease in the number of new HIV infections, ten years after PrEP initiation.[?] In the Netherlands, HIV elimination would require 82% PrEP coverage in the highest-risk group.[?] Furthermore, in Sweden, a PrEP coverage of at least 10% for the sexually high active MSM could reduce HIV prevalence to nearly 0% in the long term.[?]

PrEP represents a promising prevention option, bringing new hope to end HIV epidemics. Yet, the question of how to achieve a certain PrEP coverage in a population has never been addressed; the coverage is only assumed to reach certain values, which may not be granted in practice. It is therefore unclear whether and

how target PrEP coverage levels, required to substantially impact or eliminate HIV  
 20 epidemics, can be reached and maintained in the long term. As of October 2019,  
 PrEP was approved by regulatory agencies in more than 40 countries,[?] ] but only  
 a few settings strongly promoted it.[?] ] In the US, 130 000–135 000 individuals were  
 on PrEP as of October 2019.[?] ] This represents  $\sim 34\%$  of the worldwide PrEP  
 users,[?] ] still falling short of the CDC estimate that 1.2 million persons in the  
 25 US have indications to consider PrEP use.[?] ] Furthermore, a recent US study  
 shows that only two in five individuals keep using PrEP for more than two years.[?] ]  
 Hence, PrEP remains underutilized in many settings.

Mathematical tools for qualitative and quantitative analyses of individual-level  
 decision-making are offered by game theory.[?] ? ] We propose an innovative ap-  
 30 proach, combining a compartmental model of HIV transmission at the population  
 level, and a game-theoretic model for decision-making about PrEP at the individual  
 level. We model PrEP adoption in a population at high risk of HIV infection to de-  
 termine whether and how certain PrEP coverage levels can be reached. Particularly,  
 we study the potential impact of PrEP among MSM in the Paris region of France,  
 35 where universal antiretroviral treatment (ART) is in place, and PrEP is available for  
 individuals meeting eligibility criteria. The HIV epidemiology among MSM in the  
 Paris region is similar to those of other urban settings in high-income countries.[?] ]

## 2 Methods

### 2.1 The mathematical model

40 We built an HIV transmission model to describe the epidemiological context where  
 individuals meeting eligibility criteria make their decision on PrEP adoption. We  
 assumed that individuals have a certain perception of the risk of infection and make  
 their decisions by judging pros and cons of PrEP and ART. According to game  
 theory, such a process can be modeled as a non-cooperative game, where individuals  
 45 act in their own interest to maximize the utility of adopting PrEP, or, in other  
 words, minimize the cost of using PrEP to later avoid using ART. However, an  
 individual’s decision is indirectly influenced by those of others. The sum of all  
 individuals’ decisions determines the proportion of the population that uses PrEP,  
 which, in turn, affects the epidemic progression and the probability of acquiring  
 50 infection. The game model is thus intertwined with the epidemic model. Below,  
 we describe the main features and assumptions of our two-component model; see  
 appendix section 1 for details.

#### 2.1.1 Modeling HIV transmission in an MSM population

The transmission model is compartmental, using ordinary differential equations.  
 55 The MSM population is stratified into two risk groups (low and high) to account for  
 heterogeneity in risk of HIV infection;[?] ] high-risk individuals have a higher number  
 of sexual partners and a higher risk of acquiring HIV than low-risk individuals.  
 The majority of partnerships occur within the same risk group (i.e., non-random  
 mixing)[?] ] and individuals at high risk of infection drive the epidemic.[?] ] The

60 model compartments represent susceptible individuals who are on or off PrEP, HIV-  
 infected individuals who are unaware of their HIV status, and those diagnosed and  
 undergoing ART. Once diagnosed, individuals immediately begin ART, no longer  
 transmitting HIV; that is, only infected individuals unaware of their status transmit  
 HIV. Only susceptible individuals at high risk of infection are eligible for PrEP  
 65 and, once on PrEP, they use condoms less frequently.[?] ] We varied the PrEP  
 effectiveness, denoted  $\varepsilon$ , from 0 to 100% to account for sub-optimal PrEP adherence.  
 The PrEP coverage, denoted  $p$ , was not fixed; rather, it was obtained by solving the  
 decision-making model; see next section.

We computed the effective reproduction number,  $R$ , defined as the expected  
 70 number of secondary HIV infections caused by a single infected individual, during his  
 entire infectious period, in an uninfected population subject to control interventions  
 (e.g., condom use before the introduction of PrEP).[? ? ] The introduction of PrEP  
 may change individual's preference for condom use, and adds PrEP parameters to  
 the HIV prevention profile. Hence,  $R$  becomes a function of PrEP coverage and  
 75 effectiveness, denoted  $R(p, \varepsilon)$ . The effective reproduction number measures how  
 close the epidemic is to elimination.  $R(p, \varepsilon) > 1$  indicates self-sustained transmission  
 and persistence of the epidemic, meaning that an endemic state will be reached.  
 Epidemic elimination requires  $R(p, \varepsilon) < 1$ , such that the disease-free state is reached.  
 Thus, HIV incidence is reduced to zero in some communities, but HIV can re-emerge  
 80 in absence of control interventions. We say that the epidemic is controlled through  
 the use of PrEP if  $R(p, \varepsilon)$  decreases due to the introduction of PrEP, although the  
 decrease is not below 1.

Our transmission model shows that HIV elimination is possible, provided that  
 prevention parameters exceed certain values. We identified two thresholds for PrEP  
 85 effectiveness:  $\varepsilon \geq \varepsilon_C$  is required for PrEP to contribute to epidemic control and  
 $\varepsilon \geq \varepsilon_E$  is required for PrEP to eliminate the epidemic. We call these thresholds  
 in  $\varepsilon$  the epidemic control threshold and the epidemic elimination threshold, respec-  
 tively; see appendix section 1.2.3 for details. It is important to note that reaching  
 these thresholds is necessary, but not sufficient, to achieve epidemic control and  
 90 elimination, respectively.

### 2.1.2 The individual-level decision-making on PrEP adoption

During an epidemic, individuals may adopt PrEP according to how they perceive  
 the risk of infection,[?] ] the consequences of being infected, the price and access  
 model of PrEP,[?] ] undesired secondary effects,[?] ] social stigma,[?] ] and other  
 95 pros and cons. These factors, summarizing monetary and/or non-monetary aspects,  
 are expressed in the decision-making model as costs perceived by the individual.

We assume that each individual makes his decision at the beginning of his sexual  
 mixing period, opting for one of two independent strategies. If an individual decides  
 not to use PrEP, he will start treatment upon positive HIV diagnosis, and pay the  
 100 cost of ART for the rest of his life; we use the notation  $C_{\text{No-PrEP}}$  for the lifetime cost  
 of this strategy. Otherwise, the individual decides to adopt PrEP prevention, he  
 takes and pays the cost of PrEP and, in the case of acquiring HIV despite PrEP  
 uptake, being diagnosed and starting ART, he pays the cost of treatment for the  
 rest of his life; we use the notation  $C_{\text{PrEP}}$  for the lifetime cost of the second strategy.

Hence, the total cost depends explicitly on the yearly cost of treatment and cost of PrEP, the PrEP parameters, and, implicitly, the yearly risk of acquiring HIV; see appendix section 1.3.2 for details. Introducing  $r$ , the relative cost of PrEP versus ART, the balance of cost, when the probability to adopt PrEP is  $p$ , is given by

$$C(p, \varepsilon, r) = p C_{\text{PrEP}}(p, \varepsilon, r) + (1 - p) C_{\text{No-PrEP}}(p, \varepsilon). \quad (1)$$

The particular value of  $p$  that minimizes the total expected cost  $C(p, \varepsilon, r)$ , denoted  $\hat{p}(\varepsilon, r)$ , provides an estimate of the probability that a typical high-risk individual decides to use PrEP, and also represents the voluntary PrEP coverage among high-risk MSM. The solution of the game represents a long-term equilibrium where individuals make decisions to adopt PrEP in stationary epidemiological context. Hence, we assume that individuals maintain their decisions about adopting PrEP.

### 2.1.3 Application to the HIV epidemic among MSM in the Paris region

We applied our model to the population the most at risk of HIV infection in mainland France: MSM in the Paris region, Île-de-France. Surveillance data collected before 2016, when PrEP was introduced, suggested that the HIV epidemic was close to an endemic state, where epidemiological indicators remain nearly constant.[? ? ]

We used latin hypercube sampling and bootstrap techniques to generate parameter sets and selected those which calibrated the HIV transmission model to the endemic state in 2016;[? ] see appendix section 2. In turn, these parameter sets revealed uncertainties in the model outputs and allowed estimation of confidence intervals.

In our baseline scenario, we assumed that MSM on PrEP get tested for HIV infection every three months, according to the recommendation in France,[? ] and most countries where PrEP is available. It is important to note that this testing frequency on PrEP is much higher than the testing frequency among MSM before the introduction of PrEP, when the median time from HIV infection to diagnosis for MSM was 3.1 years [? ]. Therefore, the introduction of PrEP has a dual effect on the HIV epidemiology: first, it offers the prevention benefits of the regimen, and, second, it acts as a test-and-treat strategy[? ? ] due to the dramatic change in HIV testing practice.

We further assumed that individuals have a fair sense of their risk of infection when making decisions about PrEP use. The risk of infection corresponds to the force of HIV infection and was computed using the transmission model. MSM dropped condom use from 30% to 20% when adopting PrEP,[? ] and condom effectiveness was set at 58%–80%.[? ] We performed sensitivity analyses, assuming that i) MSM misperceive their risk of HIV infection, ii) MSM adopting PrEP completely drop condom use, or iii) MSM do not change their HIV testing behavior when adopting PrEP; see appendix section 3.

## 3 Results

About 500 parameter sets passed the calibration filter constructed to reflect the HIV epidemiology among MSM, in the Paris region, before the introduction of PrEP: overall yearly mean incidence was 1.3%, mean prevalence was 17%, and 17% of

145 MSM living with HIV were unaware of their infection; see appendix section 2 and  
table S1. The mean number of MSM was  $\sim 111\,000$ , of which 13% (i.e.,  $\sim 14\,200$ )  
were at high risk of HIV infection and eligible for PrEP. Yearly mean HIV incidence  
for high-risk MSM was 7%.

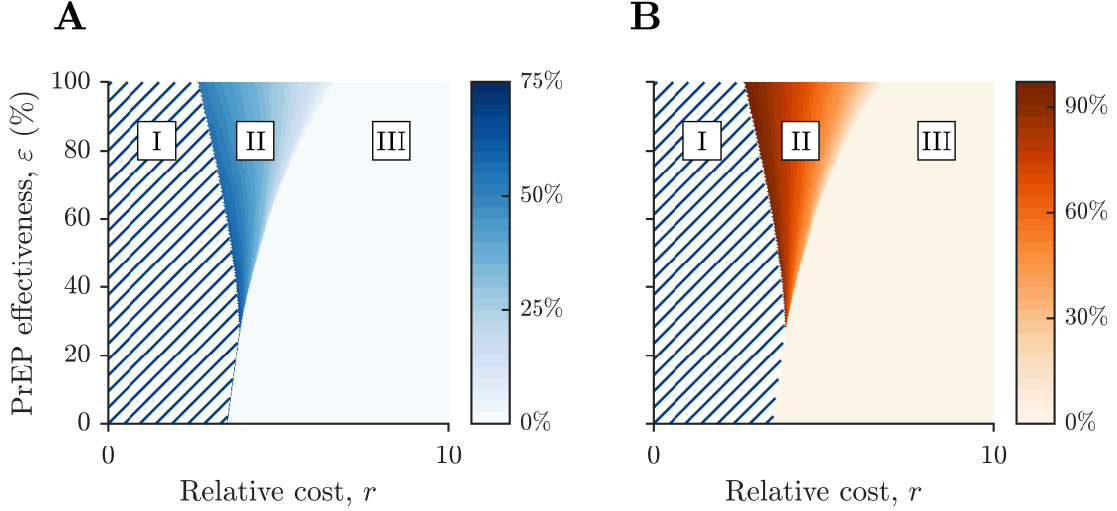
### 150 3.1 The voluntary PrEP coverage if individuals perceived correctly HIV risk

We first did computations for a typical parameter set calibrating our model. The  
PrEP coverage starts at zero, before introducing PrEP, and then reaches an optimal  
value where the expected cost of adopting PrEP is minimum. The final value reached  
depends on HIV parameters of the epidemic before the introduction of PrEP, the  
155 PrEP effectiveness,  $\varepsilon$ , and the perceived relative cost of PrEP versus ART,  $r$ . The  
color map in figure 1A shows the voluntary PrEP coverage reached among high-risk  
MSM,  $\hat{p}(\varepsilon, r)$ , as function of  $\varepsilon$  and  $r$ . Figure 1B shows the corresponding relative  
reduction in the overall HIV incidence in the MSM community. We identified three  
regions on each color map:

- 160 • Region III, where no high-risk MSM adopts PrEP for HIV prevention (i.e.,  
 $\hat{p} = 0\%$ ), because the relative cost of PrEP versus ART, perceived by the  
individuals, is too high. Therefore, HIV remains endemic, unaffected by the  
introduction of PrEP (i.e., no reduction in incidence).
- 165 • Region II, where some, but not enough, high-risk MSM adopt PrEP since the  
relative cost remains high. The epidemic is controlled and incidence decreases,  
but not enough for HIV elimination (i.e.,  $R(\hat{p}, \varepsilon) > 1$ ).
- 170 • Region I, where PrEP is offered at low relative cost. This allows reaching  
high levels of PrEP coverage ( $\sim 54\text{--}75\%$ ) and the epidemic can be eliminated;  
in region I,  $R(\hat{p}, \varepsilon) < 1$ . It is important to note that HIV elimination for  
low PrEP effectiveness (bottom part of figure 1A) occurs as a consequence  
of the test-and-treat effect of the PrEP rollout; consequently, the thresholds  
in PrEP effectiveness, to achieve epidemic control and elimination, are zero  
( $\varepsilon_C = \varepsilon_E = 0\%$ ). In this case, most MSM taking PrEP acquire HIV despite  
PrEP uptake. However, they are diagnosed and treated very early in the course  
175 of infection, because on-PrEP MSM get tested for HIV every three months.  
Early diagnosis and treatment prevent further HIV transmission. In contrast,  
when PrEP effectiveness is high (top part of figure 1A), most on-PrEP MSM  
do not acquire HIV, and thus do not transmit HIV, so the test-and-treat  
effect of the PrEP rollout is only marginal. It is PrEP, particularly its high  
180 effectiveness, that contributes decisively to epidemic elimination.

It is thus possible to reach the PrEP coverage levels required to eliminate HIV,  
provided that the perceived relative cost of PrEP versus treatment is low. In par-  
ticular, for a PrEP effectiveness of 86%, as observed in the IPERGAY and PROUD  
clinical trials, a minimum PrEP coverage of 56% among the high-risk MSM is re-  
185 quired to achieve epidemic elimination in the Paris region. However, it is important

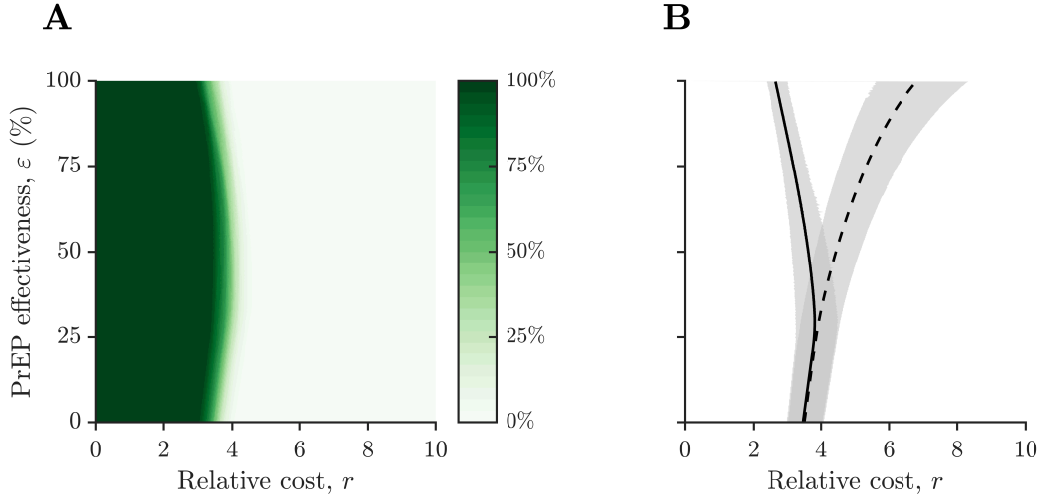
to note that elimination is temporary, as the disease-free state is unstable. Indeed, once the epidemic is eliminated, individuals' perception of HIV risk changes. The effectiveness of PrEP remains high, but the risk of HIV infection is perceived as being low. Individuals could then perceive less PrEP-induced advantages and more PrEP-induced disadvantages, that may severely increase the relative cost of PrEP versus ART. As fewer individuals will pay the cost of PrEP, the coverage decreases. Hence the epidemic dynamics in region I (i.e., the elimination region) can enter region II (i.e., the control region), where an endemic state can be reached, again.



**Figure 1: The voluntary PrEP coverage and its impact on HIV incidence, assuming fair risk perception**

Color maps of (A) the voluntary PrEP coverage among high-risk MSM,  $\hat{p}$ , and (B) the corresponding reduction in the overall endemic HIV incidence rate, as functions of  $\varepsilon$  and  $r$ , assuming that individuals have a fair sense of HIV risk. The model outputs were obtained for one typical parameter set calibrating our model. Three regions were identified, depending on  $\hat{p}$ : region III, where  $r$  is high and no MSM uses PrEP ( $\hat{p} = 0\%$ ), so HIV incidence is not reduced; region II, where some, but not enough MSM use PrEP, since  $r$  remains high, and thus the epidemic is controlled; and region I (marked by blue stripes), where epidemic elimination is possible.

We generated the outputs illustrated in figure 1 for each of the  $\sim 500$  calibrated parameter sets to reveal the role of parameter uncertainties and obtain uncertainty intervals for our results. Figure 2A shows the probability that HIV is eliminated, as a function of PrEP effectiveness and perceived relative cost of PrEP versus ART. The probability takes high values on the left, where region I is found, and declines severely toward region II. In figure 2B, we illustrate the boundaries between regions I and II (continuous line), and between regions II and III (dashed line). The three-region structure in figure 1 is thus robust to parameter uncertainties. In addition, we found that for 86% PrEP effectiveness, a minimum PrEP coverage of 55% (95% CI: 43%–64%) is required among high-risk MSM, for the HIV epidemic dynamics to reach region I.



**Figure 2: The probability of HIV elimination and boundary uncertainty for the three-regions structure**

(A) The probability of HIV epidemic elimination due to voluntary PrEP coverage, obtained from the  $\sim 500$  calibrated parameter sets. (B) The boundaries (the mean is represented as a line and the 95% confidence interval as grey area) between regions I and II (continuous line), and between regions II and III (dashed line).

## 205 3.2 Sensitivity analyses

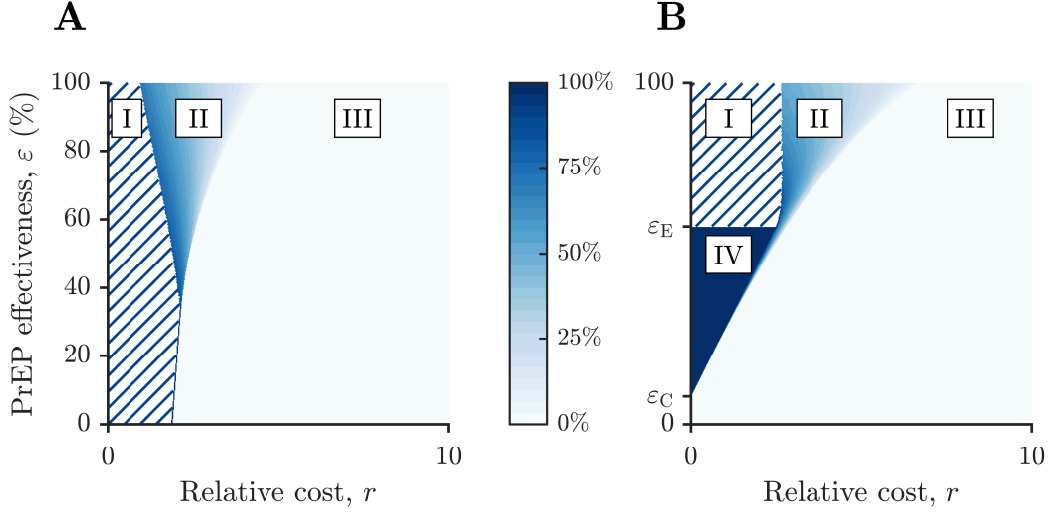
We assumed that individuals could misperceive their risk of infection and, particularly, underestimate this risk when deciding to adopt PrEP, and repeated our analyses. Specifically, we assumed that, rather than having a fair sense of the risk, based on the force of infection, high-risk MSM get a sense of HIV risk from, for instance, the proportion of their high-risk MSM peers being diagnosed with HIV each year; see appendix section 3.2.1 for further details. The voluntary PrEP coverage that can be achieved under this alternative scenario is shown in figure 3A. We obtained qualitatively similar results to those in figure 1; i.e., the three-regions structure. However, when high-risk MSM misinterpret and underestimate their HIV risk, the region of the parameter space corresponding to epidemic elimination (i.e., region I, blue stripes) is smaller, meaning that the relative cost of PrEP versus ART has to be significantly lower to reach epidemic elimination. In principle, individuals who underestimate HIV risk require a lower relative cost to adopt PrEP, than individuals who have a fair perception of risk. In particular, assuming 86% PrEP effectiveness, the relative cost needed to voluntarily reach the minimum PrEP coverage required to eliminate HIV (i.e., 56%) decreases by a factor of  $\sim 2$ . In turn, this can place significant constraints on the cost of PrEP, making region I harder to reach in practice.

We performed two other sensitivity analyses. First, we analyzed PrEP-driven risk compensation and condom drop. In the baseline scenario, we considered a drop from 30% to 20% in the probability of using condoms for PrEP users. Qualitatively similar results were obtained assuming that PrEP users stopped using condoms

completely;[? ] see figure S7 and appendix section 3.2.2. In this case, epidemic  
 230 elimination assuming PrEP effectiveness at 86% would require a coverage of at least  
 57%, rather than 56% in the baseline scenario. Hence, we found that condom drop  
 does not play an important role against HIV elimination when PrEP effectiveness  
 is high.

Second, we analyzed a scenario where PrEP uptake does not require higher rates  
 of HIV testing and MSM do not change their HIV testing behavior when adopting  
 235 PrEP; see figure 3B and appendix section 3.2.3. In this case, we found that HIV  
 elimination is entirely due to PrEP and can only be reached if PrEP effectiveness is  
 above the epidemic elimination threshold  $\varepsilon_E = 58\%$ . For high PrEP effectiveness,  
 the results are very close to those of the baseline scenario, as very few individuals fail  
 PrEP, and thus the testing frequency on PrEP does not affect the impact of the PrEP  
 240 rollout. For instance, for 86% PrEP effectiveness, a 58% PrEP coverage, rather than  
 56% in the baseline scenario, would be sufficient to achieve HIV elimination. For  
 low PrEP effectiveness, the color map of the voluntary PrEP coverage versus  $\varepsilon$  and  $r$   
 figure 3B shows a fourth region, where low relative cost encourages all high-risk MSM  
 to adopt PrEP ( $\hat{p} = 100\%$ ) and PrEP effectiveness is above the epidemic control  
 245 threshold ( $\varepsilon_C = 8\%$ ), but below the epidemic elimination threshold ( $\varepsilon_E = 58\%$ ).  
 Therefore, the epidemic is controlled, but not eliminated (i.e.,  $R(p, \varepsilon) > 1$ ), and a  
 new endemic state is reached.





**Figure 3: Sensitivity analyses for the baseline scenario**

Sensitivity analyses for the baseline scenario (A) Decision-making based on misperceived risk of acquiring HIV can significantly reduce the size of region I, where epidemic elimination is possible (blue stripes), despite high levels of PrEP effectiveness. (B) By assuming fair perception of HIV risk but no change in HIV testing behavior among PrEP users (i.e., the time to diagnosis remains at 3.1 years), the PrEP effectiveness thresholds required to reach epidemic control and epidemic elimination become  $\varepsilon_C = 8\%$  and  $\varepsilon_E = 58\%$ , respectively. In turn, this yields a fourth region, denoted region IV, where all individuals adopt PrEP but  $\varepsilon_C \leq \varepsilon < \varepsilon_E$ , so the epidemic is controlled but not eliminated. Regions II and III in both panels depict some and no PrEP adoption, respectively, similarly to figure 1A.

### 3.3 Perspectives on the PrEP rollout in the Paris region

In 2016, a PrEP rollout started in the Paris region, offering fully subsidized PrEP to qualifying individuals through specialized HIV centers. As aforementioned, for 86% PrEP effectiveness, we found that at least 55% (95% CI: 43%–64%) of the high-risk MSM would need to be on PrEP for the HIV epidemic be eliminated. Since, according to our calibration, the estimated number of PrEP eligible MSM in the Paris region is 14 200 (95% CI: 9 200–23 000), this implies that 7 700 (95% CI: 5 800–10 100) high-risk MSM should be on PrEP. This is a goal yet to be reached. As of June 2019,  $\sim 6\,700$  men were enrolled in the PrEP program of the Paris region,[?] with a marked growing trend; the 30-month drop out rate was  $\sim 32\%$ . [?] Therefore, the PrEP coverage among high-risk MSM was at most 47% (95% CI: 30%–73%), assuming that all men on PrEP were indeed MSM at high-risk of HIV infection. If all these MSM maintain their HIV prevention practices and the PrEP coverage remains stable in the long term, our model predicts epidemic control (i.e., region II), with a reduction of 90% (95% CI: 81%–100%) in HIV incidence at the new endemic state.

## 4 Discussion

We addressed, for the first time, the role of individual-level decision-making to evaluate the impact of PrEP on the HIV epidemic, and determined how a certain PrEP coverage level can be reached voluntarily. We modeled the voluntary PrEP coverage among MSM at high-risk of HIV infection, as a function of PrEP effectiveness, and the relative cost of PrEP versus ART, identifying the conditions for which epidemic control or elimination are possible. We obtained four major findings for PrEP roll-outs. First, HIV epidemics can be eliminated provided that the relative cost of using PrEP versus ART is sufficiently low. Second, frequent HIV testing while taking PrEP can compensate the lack of PrEP effectiveness, and act as a test-and-treat intervention. Third, HIV risk perception may play a major role for elimination, while drop in condom use among PrEP users may not. Fourth, epidemic elimination may be only temporary.

We applied our model to a typical urban area of a high-income country, the Paris region of France. Assuming a PrEP effectiveness of 86%, as reported by two major clinical trials, we found that at least 55% (95% CI: 43%–64%) of the high-risk MSM in the Paris region would need to be on PrEP to achieve HIV elimination. As of June 2019, at most 47% high-risk MSM were on PrEP in the Paris region, meaning that the current protocol of the PrEP rollout did not reduce enough the cost of PrEP for epidemic elimination, so far. Still, a recent update on new HIV diagnoses in the Paris region [?] by Santé publique France shows that the numbers among French-born MSM decreased by 28%, between 2015 and 2018, with no significant decrease for the other MSM. This decrease could be partly due to the PrEP rollout, which started in 2016, and, according to our modeling, should continue in the near future. In two other settings, a moderate-high PrEP coverage has been quickly reached. The region of New South Wales witnessed a rapid PrEP rollout (~ 9 000 MSM on PrEP within 2 years) during an implementation study providing PrEP for free at several sites, including public HIV and sexual health services, and private general practices with expertise in ART prescription.[?] About 41% of high-risk MSM were on PrEP in Australia in 2017.[?] Since April 2018, PrEP is subsidized by the Australian government and can be prescribed by any practitioner.[?] In San Francisco, a citywide coordinated PrEP rollout, within the Getting to Zero program, strongly promoted PrEP use and allowed many people to access PrEP for free or at low monetary cost, by using their insurance benefits or patient assistance programs. Close to 50% of the eligible MSM were estimated to be on PrEP in 2017, in San Francisco.[?] Although these levels of PrEP coverage contributed to decreasing HIV transmission,[? ? ?] HIV elimination has not been reported.

Moving toward epidemic elimination will require further decreasing the cost of PrEP, which may involve reducing monetary and non-monetary barriers to PrEP uptake, such as difficulties in accessing PrEP, pill burden, tolerability of the molecules, social stigma and discrimination, and the acquisition of other sexually transmitted infections in case of dropping condom use.[? ? ?] Online tools,[?] home-based programs[?] and long-lasting injectable versions of PrEP,[?] rather than daily or on demand pills, may also help reducing the perceived cost of PrEP and decrease the drop-out rate of PrEP. It is important to note that, in practice, estimating the

cost of PrEP relative to that of ART can be complex, but not strictly needed, as  
310 taking measures to reduce this cost may be intuitive and places the rollout in the  
right direction. Instead, the PrEP coverage and HIV incidence should be monitored  
for an indication on how far the rollout is from achieving elimination.

Moving toward epidemic elimination will also require reaching MSM who may  
not perceive themselves at high risk, and thus require a lower PrEP cost to join  
315 the prevention effort. Recent studies have found that some high-risk individuals  
underestimate their HIV risk[?] and there is a large number of missed opportunities  
for PrEP uptake.[?] Specifically, in France, more than 90% of the recently infected  
individuals were eligible for PrEP.[?] Therefore, assessing and communicating  
individual-level risk of acquiring HIV remains a key objective in the path toward  
320 HIV elimination. Promoting a fair perception of HIV risk can be achieved through,  
not only advertising and marketing PrEP,[?] but also actively identifying high-risk  
MSM through the use of electronic health records.[?]

If HIV elimination is achieved, active efforts will be needed for individuals to keep  
perceiving a low cost of PrEP and fair perception of HIV risk, in order to maintain  
325 a high PrEP coverage. Otherwise, HIV can re-emerge and reach again an endemic  
state. The situation is similar to that of vaccination prevention, which requires  
continuous vaccine coverage even though the disease is eliminated.[?] Elimination  
could be maintained, for instance, by constantly communicating risk information to  
the target population, as well as successes achieved owing to prevention.

Our study has some notable limitations. First, we assumed that MSM are homo-  
geneous regarding risk perception. In reality, the MSM population is certainly het-  
erogenous, fair perception co-existing with misperception. Nevertheless, our baseline  
and alternative scenarios can be regarded as optimistic and pessimistic scenarios,  
respectively. Second, we did not account for migration or travel,[?] nor for risk  
335 compensation among non-PrEP users,[?] which could influence the elimination fea-  
sibility. Third, our estimates of the number of high-risk individuals, who should be  
on PrEP for HIV elimination, depend on the size of the MSM community, which re-  
mains a metric difficult to estimate. On the practical side, the number of high-risk  
MSM on PrEP currently reported, and hence the PrEP coverage, could be over-  
340 estimated because establishing PrEP eligibility depends on self-reported behavior,  
which may not be a completely reliable metric.

In conclusion, perception of the cost of PrEP and HIV risk perception could  
be two important levers to increase voluntary use of PrEP, reach coverage levels  
necessary to eliminate HIV, and maintain epidemic elimination in a context of less  
345 epidemic adversity. Current PrEP rollouts should aim at lowering the perceived  
cost of using PrEP and promoting a fair perception of the risk of acquiring HIV, to  
realize the full potential of PrEP prevention.

## 5 References

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## 350 **Authors' contributions**

SJ, VS and RB conceived the model. SJ conducted the numerical simulations. All authors participated to the writing of the manuscript, analysis and interpretation of the results. All authors approved the final version of the manuscript.

## **Conflicts of interest**

355 SJ and RB declare no conflict of interest. J-MM has participated to advisory boards for Gilead, Merck, ViiV and Teva and his institution has received research grants from Gilead, outside the submitted work. DC declares grants from Janssen (2017–2018, 2019–2020) and MSD France (2015–2017), personal fees from Janssen (2018), MSD France (2017) and Gilead (2018, 2020) for lectures, and personal fees from  
360 Merck Switzerland (2017) for consultancy, outside the submitted work. VS has served on advisory boards for ViiV Healthcare (2016) and Gilead (2018) and reports lecture fees from Gilead (2017, 2019, 2020), Janssen (2018, 2020) and Viiv (2019), Abbvie (2018), outside the submitted work.

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