Can HIV epidemics among men who have sex with men be eliminated through participation to PrEP rollouts?

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Abstract

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 ~1%, while underestimation of their own HIV infection risk would demand PrEP programs to reduce the cost of using PrEP by a factor ~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.

Keywords: Pre-exposure prophylaxis; HIV; men who have sex with men; behavioral epidemiology; game theory; prevention coverage.

Introduction

In many settings, men who have sex with men (MSM) are most affected by HIV [1]. Pre-exposure prophylaxis (PrEP) is a highly effective prevention method recommended by the WHO for individuals at high risk of infection with HIV [2]. Both IPERGAY and PROUD clinical trials showed that PrEP can reduce HIV incidence among MSM by 86% [3,4]. Modeling studies, elaborating on these results, suggested that PrEP has the potential to curtail, and even eliminate HIV epidemics, notably among MSM [5–8]. For instance, in the Netherlands, elimination would require 82% PrEP coverage in the highest-risk group [6].

The question of whether it is possible to achieve a certain PrEP coverage in a population has not been addressed; modeling studies only assume that the coverage reaches certain values, which may not be granted in public health practice. It is therefore unclear whether, and under what conditions, target PrEP coverage levels, required to eliminate HIV epidemics, can be reached voluntarily and maintained in the long run. Currently, PrEP remains underutilized in many settings [12]. For instance, in the United States, 220,000–225,000 individuals were on PrEP as of April 2020 [9], still short of the CDC estimate that 1.2 million persons have indications for considering PrEP use [10]. Furthermore, a recent study shows that only two in five individuals keep using PrEP for >2 years [11].

Mathematical tools for modeling individual-level decision-making are offered by game theory [13–15]. We propose an innovative approach, combining an epidemic model 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

54 to determine whether and under what conditions certain PrEP coverage levels can be
55 reached voluntarily. Particularly, we study the potential impact of PrEP among MSM in
56 the Paris region of France, where universal antiretroviral treatment (ART) is in place, and
57 PrEP is available for eligible individuals.

Methods

We built an HIV epidemic model (Figures S1 and S2) to describe the epidemiological context of an MSM community where eligible individuals make informed decisions about adopting PrEP. The decision making is modeled as a non-cooperative game, where individuals act to maximize the utility of adopting PrEP, or, in other words, minimize the cost of using PrEP to avoid acquiring HIV and lifelong ART. Individual's decision is, however, indirectly influenced by that of others. The sum of all individuals' decisions determines the PrEP coverage, which, consequently, affects epidemic progression and the risk of acquiring HIV. The decision-making game model is thus intertwined with the epidemic model. Below, we describe the main features of our two-component model; see the Supplementary Material (SM) for further details.

The epidemic model

The epidemic model stratifies the MSM population into two risk groups (low and high), to account for heterogeneity in the infection risk. The majority of partnerships occur within the same risk group and individuals at high risk of infection drive the epidemic. The model also stratifies over HIV status, disease progression, diagnosis and the use of PrEP or ART. Once diagnosed, individuals immediately begin ART, no longer transmitting HIV. We varied PrEP effectiveness, denoted ε, from 0 to 100% to study sub-optimal PrEP adherence. The PrEP coverage, p, was not fixed; rather, it was obtained through the decision-making game model (see below).

We computed the effective reproduction number for the epidemic model, R, defined as the expected number of secondary cases caused by one infected individual, during his

entire infectious period, in an uninfected population subject to control interventions [20,21]. PrEP use may change individuals' preference for other prevention tools, turning R into a function of PrEP parameters. $R(p,\varepsilon) > 1$ indicates epidemic persistence, meaning that an endemic state will be reached. Elimination requires $R(p,\varepsilon) < 1$, such that the disease-free state will be reached. Elimination implies that incidence is reduced to zero in the studied population, but HIV can re-emerge in absence of control interventions, as it does not imply eradication. We say the epidemic is controlled using PrEP if $R(p,\varepsilon)$ decreases with the PrEP parameters, although the decrease is not below 1. Our model shows that epidemic control and elimination can occur through PrEP, provided that two thresholds in PrEP effectiveness are exceeded; $\varepsilon \geq \varepsilon_C$ is required for epidemic control and $\varepsilon \geq \varepsilon_E$ for epidemic elimination (see SM section 1.2.3). These thresholds are called the epidemic control and the epidemic elimination thresholds, respectively.

The decision-making game model

During an epidemic, individuals may adopt PrEP according to their perceived HIV risk [18], price [19] and access model of PrEP [20], adverse effects [21], social stigma [22], consequences of being infected, lifelong ART, and other pros and cons. These factors, summarizing monetary and/or non-monetary aspects, are expressed in our decision-making model as costs perceived by the individual.

We assume that individuals choose between two mutually-exclusive strategies. If an individual decides not to use PrEP, then in the case of acquiring HIV he will start ART upon positive HIV diagnosis, and pay the 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. Thus, he takes and pays the cost of PrEP and, in the case of acquiring HIV despite PrEP uptake, being diagnosed and starting ART, pays the cost of ART for the rest of his life. We use the notation C_{PrEP} for the lifetime cost of the second strategy. The total cost explicitly depends on the yearly costs of ART and PrEP, the PrEP parameters, and, implicitly, the yearly risk of acquiring HIV. Introducing r, the relative cost of PrEP versus ART, the balance of cost, when the probability to adopt PrEP is p, becomes

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

where all functions and parameters, other than p, are given in our mathematical modeling. The value of p that minimizes $C(p, \varepsilon, r)$, denoted $\hat{p}(\varepsilon, r)$, estimates the probability that a typical high-risk individual adopts PrEP, and also represents the voluntary PrEP coverage among high-risk MSM. The solution of the game represents a endemic state where individuals make decisions to adopt PrEP in stationary epidemiological context. We thus assumed that, for the long run, individuals stand by their decisions about adopting PrEP.

Application to the HIV epidemic among MSM in the Paris region

We calibrated the epidemic model to represent the epidemiological context before the introduction of PrEP [23,24], and obtained many HIV parameter sets, to reveal uncertainty in the model output (SM section 2 and Tables S1-S4). In our baseline scenario, we assumed that MSM on PrEP get tested for HIV quarterly, according to the French recommendations [25]. The testing frequency on PrEP was thus much higher than that observed off PrEP, as data shows 3.1 years for the median time from HIV infection

130 to diagnosis among MSM before the introduction of PrEP (personal communication with
131 VS). We further assumed that individuals have a fair perception of their infection risk
132 when making decisions about PrEP use; the infection risk was determined by the force of
133 HIV infection of the epidemic model. Furthermore, MSM were assumed to drop condom
134 use from 30% to 20% when adopting PrEP [3], and the condom effectiveness was 58%–
135 80% [26]. Sensitivity scenarios were explored assuming that i) MSM misperceived their
136 risk of acquiring HIV, ii) MSM adopting PrEP completely dropped condom use [27], or
137 iii) MSM did not change their HIV testing behavior upon adopting PrEP (SM Section 3).

Results

About 500 parameter sets calibrated our epidemic model to the HIV epidemiology among MSM in the Paris region, before the introduction of PrEP: total yearly mean incidence was 1.3%, prevalence was 17%, and 17% of MSM living with HIV were undiagnosed (Table S3). The mean number of MSM was ~111,000, of which 13% (i.e., ~14,200) were at high risk of infection and eligible for PrEP. Yearly incidence for high-risk MSM was 7%. The model parameters implied that the PrEP rollout had two effects: first, it offered the prevention benefits of the regimen, and, second, it behaved as a test-and-treat strategy [28,29], imposing a major change in HIV testing practice (SM Section 3.1 and Figure S3).

The voluntary PrEP coverage if individuals perceived correctly HIV infection risk

We first investigated a typical parameter set calibrating our model; Table S2. The PrEP coverage starts at zero, before introducing PrEP, and then reaches an equilibrium 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 PrEP effectiveness, ε, and the perceived relative cost of PrEP versus ART, r. Figure 1A shows the voluntary PrEP coverage reached among high-risk MSM, $\hat{p}(\varepsilon, r)$. Figure 1B shows the corresponding relative reduction in HIV incidence in the MSM community. Each of these two figures shows three regions:

- Region III, where no high-risk MSM adopts PrEP, because the perceived relative cost of PrEP versus ART is too high. Therefore, HIV remains endemic, unaffected by the introduction of PrEP (i.e., no reduction in incidence);

- 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 elimination (i.e., $R(\hat{p}, \varepsilon) > 1$);
- Region I, where PrEP is offered at low relative cost. This allows reaching high levels of PrEP coverage (~54–75%) and the epidemic can be eliminated; for Region I, $R(\hat{p}, \varepsilon) < 1$. 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, $\varepsilon_C = \varepsilon_E = 0\%$. In this case, MSM taking PrEP are poorly protected against HIV. However, they are diagnosed and treated very early in the course of infection, because they 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, so the test-and-treat benefit of the PrEP rollout is marginal. It is PrEP, particularly its high effectiveness, that contributes decisively to epidemic elimination. If $\varepsilon = 86\%$, as observed in the IPERGAY and PROUD trials, a minimum PrEP coverage of 56% should be reached among high-risk MSM, to eliminate HIV; Figure S4.

It is important to note that elimination is temporary, as the disease-free state is unstable. Indeed, once the epidemic is eliminated, individuals perceive HIV risk as being low and may reevaluate PrEP-induced advantages and disadvantages; this may severely increase the relative cost of PrEP versus ART, since the epidemic is considered to be eliminated. As fewer individuals consider PrEP use, the PrEP coverage decreases and the HIV

184 epidemic dynamics in Region I can enter Region II, where the epidemic reemerges and
185 becomes again of public health concern.
186
187 We generated the outputs in Figure 1 using each of the ~500 parameter sets obtained
188 through calibration, to estimate uncertainty intervals for our results (SM Section 2).
189 Figure 2A shows the probability that HIV is eliminated, as a function of ε and r. The
190 probability is high on the left, where Region I is found, and declines severely toward
191 Region II. In Figure 2B, we illustrate the boundaries between Regions I and II (continuous
192 line), and between Regions II and III (dashed line); the three-region structure appears
193 robust to parameter uncertainties. Additionally, when $\varepsilon = 86\%$, we found that the 95%
194 confidence interval (CI) of the minimum PrEP coverage needed for elimination (i.e.,
195 55%) is 43%–64%.
196
197 **Sensitivity scenarios**
198 We assumed that individuals could misperceive their HIV risk when deciding to adopt
199 PrEP, and repeated our analyses. Specifically, rather than having a fair sense of HIV risk,
200 based on the force of infection, high-risk MSM could get a sense of HIV risk from, for
201 instance, the proportion of their high-risk MSM peers being diagnosed each year with
202 HIV (SM Section 3.3.1). The voluntary PrEP coverage computed for this scenario is
203 illustrated in Figure 3A and reveals a qualitatively similar structure to that in Figure 1.
204 However, when high-risk MSM misinterpret and underestimate their HIV risk, Region I
205 is smaller, implying that the relative cost of PrEP versus ART must be lower to achieve
206 epidemic elimination. In particular, when $\varepsilon = 86\%$, the relative cost needed for epidemic

elimination decreases by a factor of ~2, making Region I harder to reach in practice of public health.

We performed two other sensitivity analyses. First, we analyzed PrEP-driven condom drop. In our baseline scenario, MSM dropped condom use from 30% to 20% when adopting PrEP. Similar results were obtained assuming that PrEP users stopped using condoms completely (SM Section 3.3.2 and Figure S5). We thus concluded that condom drop is not a major factor against HIV elimination when PrEP effectiveness is high. Specifically, epidemic elimination where $\varepsilon = 86\%$ requires a coverage of >57%, rather than >56% in the baseline scenario.

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 PrEP; Figure 3B and SM Section 3.3.3. In this case, HIV elimination is entirely due to PrEP and can only be reached if $\varepsilon \geq \varepsilon_{\mathrm{E}} = 58\%$. For high PrEP effectiveness, the results are very close to those of the baseline scenario, as very few MSM fail PrEP and the testing frequency on PrEP does not impact many MSM. For instance, epidemic elimination when $\varepsilon = 86\%$ requires a coverage of >58%, rather than >56% in the baseline scenario. For low PrEP effectiveness, 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 threshold ($\varepsilon_{\mathrm{C}} = 8\%$), but below the epidemic elimination threshold ($\varepsilon_{\mathrm{E}} = 58\%$). Therefore, the epidemic is controlled, but not eliminated, and a new HIV endemic state is reached; $R(\hat{p}, \varepsilon) > 1$.

Perspectives on the PrEP rollout in the Paris region

In 2016, a PrEP rollout started in the Paris region, offering fully subsidized PrEP to eligible individuals. As aforementioned, under the baseline scenario, for 86% PrEP effectiveness, we found that at least 55% (95%CI: 43%–64%) of the high-risk MSM would need to take 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 means that 7,700 (95%CI: 5,800–10,100) high-risk MSM should be on PrEP. This is an objective to be reached. As of mid-2019, ~6,700 men were on PrEP in the Paris region [30], with a marked growing trend; the 30-month dropout rate was ~32% [31]. The PrEP coverage among high-risk MSM was then estimated to be at most 47% (95%CI: 30%–73%), assuming that all men on PrEP were indeed high-risk MSM. If all these MSM maintained using PrEP in the long term, our model predicted epidemic control (i.e., Region II), with a reduction of 90% (95%CI: 81%–100%) in HIV incidence at the new endemic state.

Discussion

We addressed the role of individual-level decision-making in the potential impact of PrEP on the HIV epidemic, identified the conditions for epidemic control or elimination, and estimated PrEP coverage levels which can be reached voluntarily. We obtained four major findings for PrEP rollouts. 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 for poor PrEP adherence 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 the Paris region. Assuming a PrEP effectiveness of 86%, as reported in two major clinical trials, we found that at least 55% (95%CI: 43%–64%) of the high-risk MSM would need to be on PrEP to achieve HIV elimination. As of mid-2019, at most 47% high-risk MSM were on PrEP in the Paris region, meaning that the PrEP-rollout protocol did not reduce enough the cost of PrEP for epidemic elimination, so far. Still, a recent update on new HIV diagnoses in Paris [32] shows that the numbers among French-born MSM decreased by 28%, between 2015 and 2018, with no significant decrease for other MSM. This decrease could be partly due to the PrEP rollout starting 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

271 prescription [33]. About 41% of the high-risk MSM in Australia were on PrEP in 2017
272 [34]. Since April 2018, PrEP is subsidized by the Australian government and can be
273 prescribed by any practitioner [35]. In San Francisco, a citywide-coordinated PrEP
274 rollout, within the Getting to Zero program, strongly promoted PrEP use and allowed
275 many people to access PrEP for free or at low monetary cost, through insurance benefits
276 or patient assistance programs. Close to 50% of the eligible MSM were on PrEP in 2017
277 in San Francisco [36]. Although these levels of PrEP coverage contributed to decreasing
278 HIV transmission [33,36,37], HIV elimination has not been reported.
279
280 Moving toward epidemic elimination will require further decreasing the cost of PrEP,
281 which may involve reducing monetary and non-monetary barriers to PrEP uptake, such
282 as difficulties in accessing PrEP, pill burden, tolerability of the molecules, social stigma
283 and discrimination, and the acquisition of other sexually transmitted infections in case of
284 dropping condom use [20–22]. Online tools [38], home-based programs [39], long-lasting
285 injectable versions of PrEP [40], rather than daily or on-demand pills, allowing trained
286 general practitioners to prescribe PrEP and interventions that increase awareness,
287 motivations and behavioral skills about risk reduction [41] may also help reduce the
288 perceived cost of PrEP and decrease the drop-out rate. It is important to note that, in
289 practice, estimating the cost of PrEP relative to that of ART can be complex, but not
290 strictly needed, as reducing this cost may be intuitive and places the PrEP rollout in the
291 right direction. Instead, the PrEP coverage and HIV incidence can serve as indicators for
292 how far the PrEP rollout is from achieving elimination.
293

294 Moving toward epidemic elimination will also require reaching MSM who may not
295 perceive themselves at high risk, and thus require a lower cost for adopting PrEP, in order
296 to join the prevention effort. Recent studies found that high-risk individuals can
297 underestimate their HIV risk [42] and there are many missed opportunities for PrEP
298 uptake [43]. Specifically, in France, >90% of the recently infected individuals were
299 eligible for PrEP [43]. Therefore, assessing and communicating individual-level risk for
300 acquiring HIV remains a key objective for achieving elimination. Promoting a fair
301 perception of HIV risk can be achieved through, not only advertising and marketing PrEP
302 [44], but also through using electronic health records for identifying high-risk MSM [45].
303
304 Importantly, if HIV is eliminated, interventions will be needed so individuals keep
305 perceiving a low cost for PrEP and fair perception of HIV risk, to maintain a high PrEP
306 coverage. Otherwise, HIV can reemerge and reach again an endemic state of concern for
307 public health. The situation is similar to that of vaccination prevention, which requires
308 continuous vaccine coverage even though the disease is nearly eliminated [46].
309
310 Our study has some limitations. First, we assumed that individuals act out of self-interest
311 and do not cooperate to avoid getting infected by HIV. Modeling PrEP adoption through
312 other theories of health behavior, considering for instance interactions between
313 individuals [15], remains a subject to be studied in further work. Second, we assumed that
314 MSM are homogeneous regarding risk perception. In reality, the MSM population is
315 certainly heterogenous, fair perception co-existing with misperception. Nevertheless, our
316 baseline and alternative scenarios can be regarded as optimistic and pessimistic scenarios,
317 respectively. Third, we did not account for migration or travel [47], nor for condom drop

318 among non-PrEP users [48], which could influence elimination efforts. Fourth, our
319 estimates of the number of high-risk individuals, who should be on PrEP for HIV
320 elimination, depend on the size of the MSM community, which is a metric difficult to
321 estimate. Also, the number of high-risk MSM on PrEP currently reported, and hence the
322 PrEP coverage, may represent an overestimate because establishing PrEP eligibility relies
323 on self-reported behavior, which is difficult to appraise by practitioners.
324

325 **Conclusion**

326 Perception of the cost of PrEP and of HIV risk are two important levers to increase
327 voluntary use of PrEP, reach coverage levels necessary to eliminate HIV, and maintain
328 elimination in the context of less epidemic adversity. Current PrEP rollouts should aim at
329 lowering the perceived cost of using PrEP and promoting a fair perception of the risk of
330 acquiring HIV, to realize the full potential of PrEP prevention.

Authors' contributions

SJ, VS an 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 read and approved the final manuscript.

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List of abbreviations

ART: Antiretroviral treatment; MSM: Men who have sex with men; PrEP: Pre-exposure prophylaxis; CI: confidence interval.

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Figure legends

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 men who have sex with men (MSM), $\hat{p}$, and **(B)** the corresponding reduction in the overall endemic HIV incidence rate, as functions of ε and r, assuming that individuals have a fair perception 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.

Figure 2. The probability of HIV elimination and boundary uncertainty for the three-region structure

(A) The probability of HIV epidemic elimination due to voluntary PrEP coverage, obtained from the ~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).

525 **Figure 3. Sensitivity analyses for the baseline scenario**

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

536

Figures

Figure 1

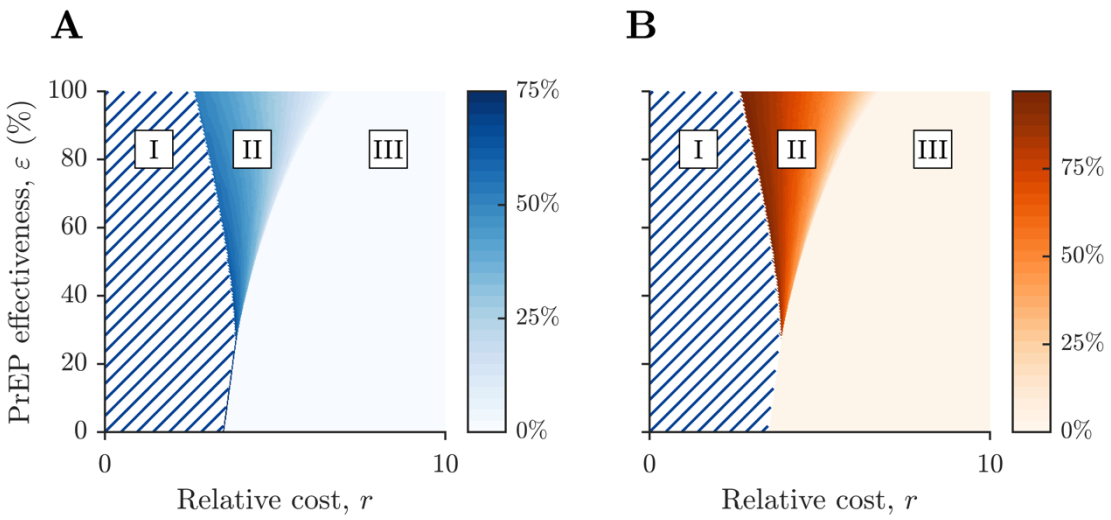
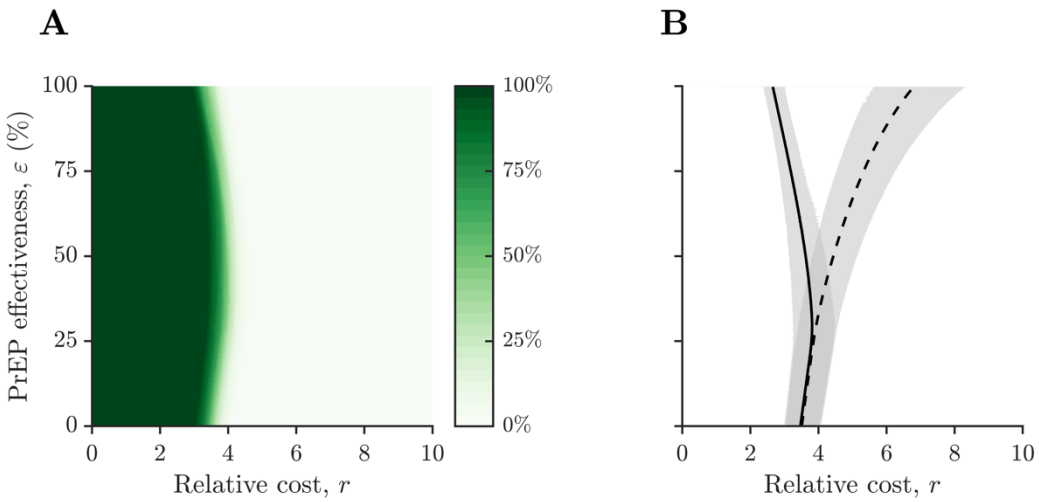
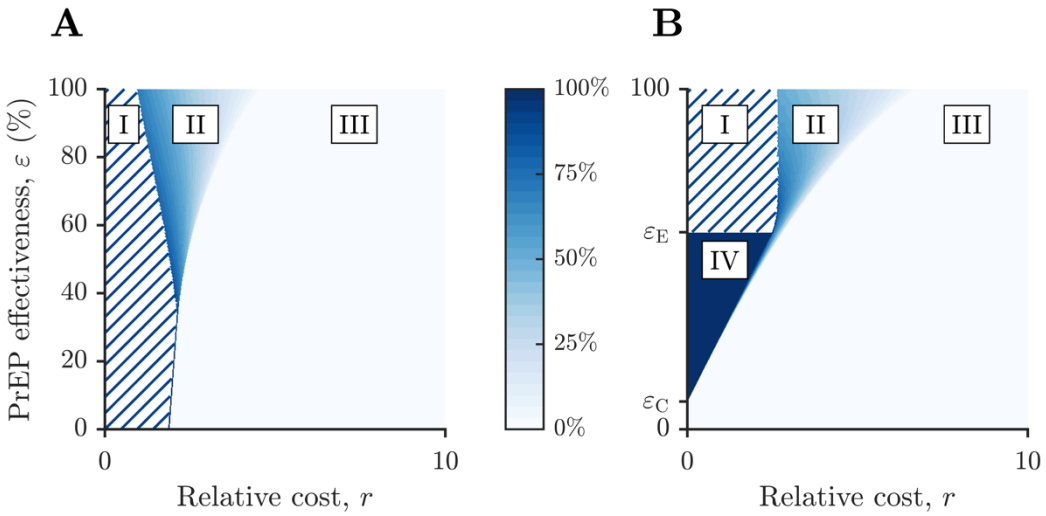


Figure 2


A
B
PrEP effectiveness, ε (%)
100
75
50
25
0
0
2
4
6
8
10
Relative cost, r
100%
75%
50%
25%
0%
Relative cost, r

545 **Figure 3**



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548 **Supplemental Digital Content**

549 Supplementary Material (pdf document containing the model description, model
550 calibration and supplementary results).

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