Preexposure prophylaxis for men who have sex with men in the Netherlands: impact on HIV and Neisseria gonorrhoeae transmission and cost-effectiveness

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Preexposure prophylaxis for men who have sex with men in the Netherlands: impact on HIV and *Neisseria gonorrhoeae* transmission and cost-effectiveness

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Objectives: To assess the impact of a preexposure prophylaxis (PrEP) programme for high-risk men who have sex with men (MSM), which includes gonorrhoea testing and treatment, on the transmission of HIV and *Neisseria* among MSM in the Netherlands and the cost-effectiveness of such programme with and without risk compensation (in the form of reduced condom use).

Methods: We developed a stochastic agent-based transmission model of HIV and gonorrhoea. We simulated a capped (max 2.5% of MSM) and uncapped (5.5% of MSM in 2018 declining to 3% in 2027) daily PrEP programme for high-risk MSM, with 3-monthly HIV and gonorrhoea testing, with and without risk compensation. Epidemiological outcomes were calculated from the transmission model and used in an economic model to calculate costs, quality-adjusted life-years (QALY), and incremental cost-effectiveness ratios (ICER), over 2018–2027, taking a healthcare payer perspective.

Results: Without risk compensation, PrEP can lead to a reduction of 61 or 49% in the total number of new HIV infections in 2018–2027, if the programme is uncapped or capped to 2.5% of MSM, respectively. With risk compensation, this reduction can be 63 or 46% in the uncapped and capped programmes, respectively. In all scenarios, gonorrhoea prevalence decreased after introducing PrEP. Without risk compensation, 92% of simulations were cost-effective (of which 52% cost-saving). With risk compensation, 73% of simulations were cost-effective (of which 23% was cost-saving).

Conclusion: A nationwide PrEP programme for high-risk MSM can result in substantial reductions in HIV and gonorrhoea transmission and be cost-effective, even with risk compensation.

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Introduction

Preexposure prophylaxis (PrEP) with emtricitabine/tenofovir is highly effective in preventing HIV acquisition among MSM with high adherence [1,2]. According to Dutch guidelines, PrEP users should be tested 3-monthly for bacterial sexually transmitted infections (STIs) [3]; that could lead to lower STI prevalence [4]. On the other

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hand, reduced fear of HIV acquisition can lead to risk compensation in the form of lower condom use or more sexual partners, which could result in increased STI prevalence [5,6]. Concerns also exist about the cost-effectiveness of PrEP.

Earlier modelling studies have found contradicting results about the cost-effectiveness of PrEP, because of differences in how PrEP was implemented and assumptions about the costs, efficacy, and adherence to PrEP [4,7]. A study for PrEP implementation among MSM in the Netherlands found that PrEP can be cost-effective [8]. In this study, we assessed the cost-effectiveness of PrEP and its impact on the transmission of HIV and of *N. gonorrhoeae* among MSM in the Netherlands, using an agent-based model and an economic model. PrEP eligibility criteria were based on Dutch guidelines on PrEP use [3]. In contrast with earlier modelling studies, we examined the impact of PrEP assuming either a PrEP programme where all eligible MSM can initiate PrEP or a PrEP programme with a capped size (allowing PrEP provision to a maximum of 2.5% of MSM). Additionally, we examined the effect of risk compensation and the effect of PrEP on gonorrhoea.

Methods

The transmission model

We extended a stochastic agent-based transmission model of HIV and *N. gonorrhoeae* transmission in MSM [9]. The progression of HIV infection was modelled using data from the national database of HIV-positive individuals in the Netherlands [10]. Parameters relating to sexual behaviour were obtained from data from Amsterdam [11,12]. The model was calibrated to data on annual HIV diagnoses in the years 2008–2014 and gonorrhoea positivity in the years 2009–2014. The 100 best-fitting parameter combinations were selected and model calculations were repeated 20 times with each of the 100 parameter combinations (see, also [9] and supplement, http://links.lww.com/QAD/B630).

Eligibility criteria for preexposure prophylaxis use

Following the recent Dutch guidelines on PrEP use [3], an MSM was eligible for PrEP in our model, if he was HIV-negative and met one or more of the following criteria:

(1) He had a steady partner who was HIV-positive with a detectable viral load.
(2) He was diagnosed with anogenital gonorrhoea in the preceding 6 months.
(3) He had condomless anal intercourse (CAI) with at least one casual partner in the preceding 6 months.

Eligibility was evaluated when MSM presented at healthcare facilities for HIV/STI testing. Additionally, we assumed that the PrEP programme did not result in any change in testing behaviour.

Implementation of the preexposure prophylaxis programme

MSM meeting one or more of the PrEP eligibility criteria when tested for HIV/STI in the last 6 months of 2017, were eligible to start daily PrEP on 1 January 2018. Among those who were eligible, we assumed a probability of 75% to start PrEP to account for the fact that some MSM may decline to start PrEP. The 75% was an assumption and was varied in the sensitivity analysis. We assumed men initiating PrEP would remain on PrEP for at least 12 months, unless HIV diagnosis or death occurred. MSM on PrEP were monitored every 3 months, being tested for HIV/STIs and for renal function. At the 12-month check-up, PrEP use could continue with another 12 months with a probability of 75% if the PrEP user still met at least one of the eligibility criteria. If no criterion was met at this point, PrEP was discontinued. After the start of the programme, MSM not on PrEP could continuously enter the programme with a 75% probability if one of the criteria was met.

Preexposure prophylaxis scenarios

We simulated four different PrEP scenarios:

(1) Standard PrEP scenario: The number of PrEP users was uncapped and no risk compensation was assumed.
(2) Risk compensation scenario: The number of PrEP users was uncapped. If at least one of the sexual partners engaging in CAI was on PrEP, the probability of CAI was increased by 75%.
(3) Capped scenario: The PrEP programme size was capped at 2.5% of MSM. Men can go on PrEP on a first-come, first-serve basis. No risk compensation was assumed.
(4) Capped scenario with risk compensation : The PrEP programme size was capped at 2.5% of MSM. Men can go on PrEP on a first-come, first-serve basis. If at least one of the sexual partners engaging in CAI was on PrEP, the probability of CAI was increased by 75%.

The probability of condom use during a sex act depends on characteristics of the men and the number of sex acts they have had together (Table A6, http://links.lww.com/QAD/B630). In all scenarios we assumed PrEP reduces the probability of acquiring HIV in the PrEP user by 86% [2].

Costs of preexposure prophylaxis

The cost of PrEP medication ranged from €90 to €150 per 3 months [13]. We assumed daily PrEP use. The PrEP programme included 3-monthly monitoring, which

consisted of tests for HIV, chlamydia, gonorrhoea, and HCV infections, and a kidney function test. We assumed PrEP monitoring to be provided by STI clinics (or Public Health Services in areas without STI clinics). PrEP was provided for the next 3 months if there were no clinical contraindications. The cost of routine consultations (after the first 3 months) for PrEP monitoring was €150 to €163 per 3 months, calculated by itemizing individual tests and applying the reference costs as listed by the Dutch Healthcare Authority [14] (Table B11, http://links.lww.com/QAD/B630)

Costs outside the preexposure prophylaxis programme

Costs outside the PrEP programme, such as monitoring and cART for HIV-positive MSM in care, were obtained from our earlier cost-effectiveness study [15]. We used an activity-based costing approach, identifying all individual activities and costed the time, tests, and medication used. The costs of HIV/STI testing outside of PrEP monitoring depend on the healthcare provider. In the model, we accounted for three major testing providers in the Netherlands: STI clinics (or Public Health Services), general practitioners, and hospitals (Tables B5, B6, B8, http://links.lww.com/QAD/B630). Undiagnosed HIV-positive MSM were assumed to only generate extramedical costs because of opportunistic infections when they reach late-stage HIV, 9 years after infection. Monitoring costs for HIV-positive MSM in care were estimated for the first 6 months after entry to care, and subsequently for each year after the initial 6 months including 2.35 visits each year on average (Table B7, http://links.lww.com/QAD/B630). Costs for cART were calculated based on the most frequently used cART regimens in the Netherlands [10] and their listed prices [16] (Table B5, http://links.lww.com/QAD/B630), resulting in an average cost of €10 566.70 per year per patient (see also [15] and Supplement, http://links.lww.com/QAD/B630). Average costs of HIV and gonorrhoea testing, monitoring and cART for those in care are as reported in [15] and are repeated in Tables B5, B10, http://links.lww.com/QAD/B630 in the Supplement, http://links.lww.com/QAD/B630. Costs of gonorrhoea testing and treatment were also included (section B2 and Tables B5, B8 in Supplement, http://links.lww.com/QAD/B630).

Effects

Health effects were expressed in quality-adjusted life-years (QALY). Utilities and durations of nonfatal health states were derived from the literature (Tables B2–B4, http://links.lww.com/QAD/B630). The conditions affecting the quality of life were symptomatic acute or chronic HIV infection, late stage HIV, AIDS, symptomatic gonorrhoea, and epididymitis (Table B3, http://links.lww.com/QAD/B630).

Time horizon and discounting

The impact of the PrEP programme was evaluated over the 10-year time horizon, 2018–2027. Costs were discounted with 4% and QALYs with 1.5%, in line with Dutch guidelines for cost effectiveness analyses [17].

Cost-effectiveness analysis

The total impact of the PrEP programme on the costs and quality of life was assessed from a healthcare payer's perspective. The Incremental Cost Effectiveness Ratio (ICER) was calculated as the ratio of incremental costs divided by QALYs gained because of PrEP, compared with without PrEP. For the cost-effectiveness of a scenario, we used the threshold of €20 000 per QALY gained, as frequently used in the context of public health interventions [18]. Results shown are mean and 95% uncertainty intervals, which is the range between the 2.5th and 97.5th percentile.

Sensitivity analyses

In sensitivity analyses, the calculations for the standard scenario were repeated with different effectiveness of PrEP (64 and 96%), with zero effectiveness of PrEP (to assess the impact of HIV/*Neisseria gonorrhoeae* testing provided by the PrEP programme), lower probability to start PrEP among eligible MSM (50%), and higher increase in the probability to have CAI when one of the partners was using PrEP (200%). Also, we calculated the costs and QALYs for the standard scenario using reduced costs for antiviral agents used for HIV treatment (80% reduction of costs shown in Table B10, http://links.lww.com/QAD/B630) and with 3.5% discounting rates for costs and QALYs; see Table B12 in Supplement, http://links.lww.com/QAD/B630.

Results

Standard preexposure prophylaxis scenario

After introducing PrEP, HIV incidence rates declined from 0.292 infections per 100 person-years (100PY) in 2017 to 0.093 infections per 100PY in 2027. Cumulatively, 3486 HIV infections were averted over 2018–2027, that is 61% of infections over these years (Fig. 1 and Table 1). HIV incidence rate was also reduced in MSM not on PrEP (Fig. 2). Gonorrhoea prevalence also decreased from 0.782% at the end of 2017, to 0.023% at the end of 2027. The number of MSM eligible for PrEP declined from 10 573 in 2017 to 7417 in 2027 (Fig. 2). The cumulative total costs of the scenario with uncapped PrEP were €3.7 million lower than the cumulative total costs without PrEP and 1482 QALYs were gained because of PrEP (Table 1). PrEP was cost-effective in 92% of simulations (52% cost-saving). Over 2018–2027, the cumulative costs for PrEP medication and monitoring were €22.0 million and €39.2 million, respectively (Table 1).

Risk compensation scenario

In 2018, PrEP users had a median of 13 (IQR: 5–26) CAI acts per 3 months with risk compensation, but 11 (IQR: 3–26) acts per 3 months without risk compensation.

Table 1. Effects and costs of preexposure prophylaxis programmes, the Netherlands, 2018–2027 (mean and 95% uncertainty interval).

	Standard[e]	RC[f]	Capped[g]	Capped+ RC[h]
Epidemiological results				
HIV incidence 2017 (infections per 100PY)	0.292 (0.130–0.498)	0.292 (0.130–0.498)	0.292 (0.130–0.498)	0.292 (0.130–0.498)
HIV incidence 2027 (infections per 100PY)	0.093 (0.034–0.164)	0.084 (0.033–0.142)	0.130 (0.034–0.275)	0.141 (0.037–0.292)
Cumulative averted HIV infections[a] 2018–2027 (*n*)	486 (1273–6102)	3550 (1309–6131)	2691 (1200–4424)	2530 (1044–4198)
Percent of cumulative HIV infections 2018–2027 averted	61% (54–69%)	63% (54–70%)	49% (38–59%)	46% (36–54%)
Gonorrhoea prevalence 31-12-2017 (%)	0.782 (0.334–1.242)	0.782 (0.334–1.242)	0.782 (0.334–1.242)	0.782 (0.334–1.242)
Gonorrhoea prevalence 31-12-2027 (%)	0.023 (0.000–0.099)	0.212 (0.015–0.543)	0.192 (0.002–0.626)	0.560 (0.143–1.132)
MSM on PrEP 31-12-2018 (*n*)	11 038 (7629–13 651)	11 621 (7906–14 519)	4984 (4825–5000)	4986 (4851–5000)
MSM on PrEP 31-12-2027 (*n*)	5932 (3417–8664)	7302 (4077–10 275)	4746 (3513–5000)	4896 (4225–5000)
Cost effectiveness results, cumulative 2018—2027				
Incremental costs HIV treatment[b] (million euros)	−64.8 (−122.7 to −23.3)	−63.2 (−118.4 to −22.9)	−48.2 (−86.6 to −20.5)	−43.5 (−79.7 to −17.5)
Incremental costs HIV monitoring (million euros)	−4.1 (−7.5 to −1.6)	−4.0 (−7.4 to −1.5)	−3.1 (−5.3 to −1.4)	−2.8 (−4.9 to −1.2)
Costs PrEP medication (million euros)	22.0 (12.8–33.3)	25.5 (14.8–38)	14.6 (10.9–18.5)	14.9 (11.3–18.6)
Costs PrEP monitoring (million euros)	39.2 (25–53.1)	45.5 (29.1–60.2)	26.0 (22.8–27.3)	26.2 (24.4–27.3)
Other costs (million euros)	4.1 (−3.0 to 12.1)	5.3 (−1.6 to 13.7)	3.1 (−2.9 to 9.4)	4.4 (−0.4 to 10.3)
Total incremental costs (million euros)	−3.7 (−44.4 to 19.6)	9.2 (−23.7 to 31.4)	−7.6 (−41.3 to 15.2)	−0.8 (−33.5 to 21.8)
QALYs gained	1482 (426–3570)	1380 (367–3443)	1116 (324–2511)	901 (207–2205)
ICER	217.4 (−29 752.5 to 31 923)	11 996 (−16 355 to 56 518)	−5575 (−46 281 to 29 978)	2967 (−48 965–63 577)
Cost saving (%)[c]	52	23	64	49
Cost effective (%)[c]	92	73	94	80
Not-cost effective (%)[c]	8	26	6	20

CAI, condomless anal intercourse; ICER, incremental cost-effectiveness ratio; PrEP, preexposure prophylaxis; QALY, quality-adjusted life-year; RC, risk compensation.
[a]The cumulative number of averted HIV infections from 2018 to 2027 compared with simulations without PrEP.
[b]Extra costs made in simulations with the PrEP programme compared with simulations without PrEP. Negative numbers indicate costs saved.
[c]Interventions are cost-effective if the ICER is less than 20 000 euros per QALY gained. If a simulation is cost-saving (negative incremental costs with QALYs gained, it is also considered cost-effective.
[e]Results of the PrEP programme uncapped in size and without risk compensation (RC).
[f]Results of the PrEP programme uncapped in size, but with risk compensation (75% increase in the probability of CAI per sex act, among PrEP users).
[g]Results of the PrEP programme with capped size (2.5% of MSM), without risk compensation.
[h]Results of the PrEP programme with capped size (2.5% of MSM) and with risk compensation (75% increase in probability of CAI per sex act, among PrEP users).

With risk compensation, the HIV incidence rate was 0.084 infections per 100PY in 2027, lower than the standard PrEP scenario. Slightly more HIV infections were averted with risk compensation: 3550 (Table 1). Gonorrhoea prevalence was reduced compared with the situation without PrEP, but this was higher than in the standard PrEP scenario, at 0.212% in 2027. The PrEP programme with risk compensation was larger than without risk compensation: in 2027, there were 7302 and 5932 PrEP users, respectively (Table 1 and Figure A7 in Supplement, http://links.lww.com/QAD/B630), as CAI with a casual partner and having had a gonorrhoea diagnosis were eligibility criteria. The savings made in HIV monitoring and treatment were similar to those with the standard programme, whereas the incremental costs by the PrEP programme were higher: €25.5 million for PrEP medication and €45.5 million for monitoring (cumulative over 2018–2027). The scenario with risk compensation was less likely to be cost-effective than the standard PrEP programme: PrEP was cost-effective in 73% of simulations (23% cost-saving) (Table 1).

Capped size scenario

Capping the PrEP programme size to 2.5% of MSM (5000 MSM) not only reduced the programme size but also decreased HIV and *N. gonorrhoeae* transmission, compared with the standard PrEP scenario (Table 1). This smaller programme cost less and led to fewer savings in HIV treatment and monitoring. This scenario was cost-effective in 94% of simulations (64% cost-saving).

Capped size with risk compensation scenario

HIV incidence rate decreased to 0.141 infections per 100PY in the scenario with capped size and risk

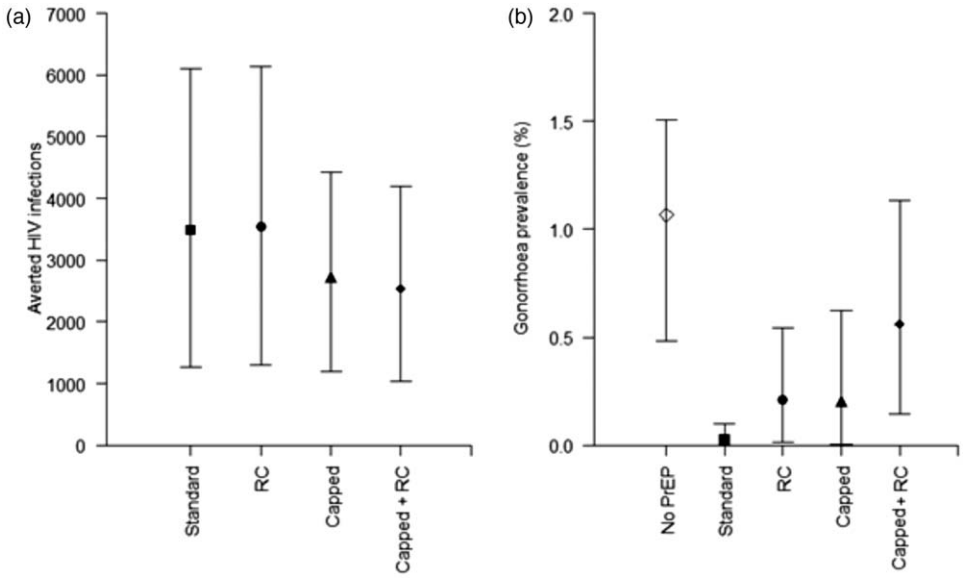

Fig. 1. Cumulative number of averted HIV infections in 2018–2027 and gonorrhoea prevalence in 2027. (a) Cumulative number of averted HIV infections with different PrEP scenarios compared with the scenario without PrEP from 2018 to 2027. (b) Prevalence of gonorrhoea on 31 December 2027 in the MSM population. Scenarios shown are: no PrEP (open diamond); standard PrEP scenario (square); risk compensation scenario (circle); capped size scenario (triangle); capped size with risk compensation scenario (diamond). Symbols show the mean, whiskers show the 95% uncertainty interval. PrEP, preexposure prophylaxis; RC, risk compensation.

compensation (Table 1). The reduction in HIV incidence and gonorrhoea prevalence was less in this scenario than in the capped size without risk compensation scenario because of the difference in the probability of CAI. In the uncapped with risk compensation scenario, the increase in CAI was compensated by the increased number of PrEP users, leading to a larger decrease in HIV incidence and gonorrhoea prevalence with risk compensation than without. This scenario was cost-effective in 80% of simulations (49% cost-saving). This scenario was less likely to be cost-saving than the capped programme without risk compensation, but more likely to be cost-saving than the standard programme with risk compensation .

Sensitivity analyses

In the scenario where PrEP had no effect on HIV acquisition, 1219 HIV infections were averted (Table 2). Gonorrhoea prevalence was reduced almost as much as with the standard PrEP scenario (because of gonorrhoea testing and treatment offered during PrEP controls) but not exactly the same, as the numbers of PrEP users in the two scenarios were not the same.

With a lower PrEP effectiveness (64%), fewer HIV infections were averted and the ICER was higher than in the standard scenario, but PrEP was cost-effective in 75% of the simulations and cost-saving in 21% of simulations. Alternatively, with a higher effectiveness of PrEP (96%), more HIV infections were averted by 2027. The costs for HIV medication and care were more reduced, whereas the PrEP programme costs were comparable. The programme was cost-effective in 97% of simulations and cost-saving in 63% of simulations.

If the probability of an eligible MSM to start PrEP was lower (50%), the PrEP programme would be smaller resulting in lower costs of PrEP medication and monitoring. Although fewer savings were made in HIV medication and care, this scenario was more likely to be cost-saving than the standard PrEP scenario.

With a higher increase (200%) in the probability of CAI per sex act, men on PrEP had a median of 15 (IQR: 6–28) CAI acts per 3 months in 2018. The number of PrEP users was 12 306 in 2018, decreasing slowly to 9986 in 2027. This number was considerably higher than that with the standard scenario (with or without risk compensation). This expanded programme resulted in more averted HIV infections than both the standard PrEP scenario and the scenario with risk compensation . However, the total costs of the PrEP programme surpassed the savings made in HIV treatment and care, resulting in an ICER of €58 558 per QALY gained; this scenario was cost-effective in 35% of simulations (3% cost-saving).

Assuming an 80% reduction in costs of antiviral agents for treatment, resulted in an ICER of €35 550 per QALY gained; this scenario was cost-effective in only 21% of simulations and it was not cost-saving in our simulations. Using the same discounting rate of 3.5% for both costs and QALYs resulted in similar economic results, as for the

Table 2. Sensitivity analyses for effects and costs of preexposure prophylaxis programmes, the Netherlands, 2018–2027 (mean and 95% uncertainty interval).

	Higher effectiveness of PrEP[e]	Lower effectiveness of PrEP[f]	No effectiveness of PrEP[g]	Lower starting probability[h]	More risk compensation[i]
Epidemiological results					
HIV incidence 2017 (infections per 100PY)	0.292 (0.130–0.498)	0.292 (0.130–0.498)	0.292 (0.130–0.498)	0.292 (0.130–0.498)	0.292 (0.130–0.498)
HIV incidence 2027 (infections per 100PY)	0.078 (0.033–0.131)	0.118 (0.042–0.207)	0.213 (0.075–0.392)	0.133 (0.045–0.250)	0.079 (0.032–0.138)
Cumulative averted HIV infections[a] 2018–2027 (n)	3734 (1405–6587)	2946 (1030–5205)	1219 (295–2319)	2789 (949–4939)	3591 (1325–6240)
Percent of cumulative HIV infections 2018–2027 averted	64% (16–72%)	46% (33–58%)	21% (10–31%)	49% (38–57%)	63% (55–72%)
Gonorrhoea prevalence 31-12-2017 (%)	0.782 (0.334–1.242)	0.782 (0.334–1.242)	0.782 (0.334–1.242)	0.782 (0.334–1.242)	0.782 (0.334–1.242)
Gonorrhoea prevalence 31-12-2027 (%)	0.026 (0.000–0.108)	0.022 (0.000–0.098)	0.019 (0–0.068)	0.097 (0.004–0.289)	0.584 (0.170–0.978)
MSM on PrEP 31-12-2018 (*n*)	11 042 (7656–13 647)	11 032 (7675–13 670)	11 011 (7707–13 701)	8433 (5720–10 530)	12 306 (8289–15 591)
MSM on PrEP 31-12-2027 (*n*)	5836 (3369–8494)	6174 (3525–9126)	6889 (3803–10 275)	4337 (2560–6285)	9986 (5961–13 733)
Cost effectiveness results, cumulative 2018–2027					
Incremental costs HIV treatment[b] (million euros)	−70.4 (−132 to −25.5)	−52.2 (−101 to −17.7)	−12.2 (−34.8 to 1.4)	−53.4 (−102.5 to −17.1)	−61.1 (−115.2 to −21.7)
Incremental costs HIV monitoring (million euros)	−4.4 (−8 to −1.7)	−3.4 (−6.3 to −1.2)	−1.1 (−2.6 to −0.1)	−3.4 (−6.3 to −1.1)	−3.9 (−7.1 to −1.5)
Costs PrEP medication (million euros)	21.9 (12.7–33)	22.3 (13–33.9)	23.3 (13.3–35.5)	15.9 (9.3–23.8)	31.5 (18.6–46.7)
Costs PrEP monitoring (million euros)	39.1 (24.8–52.7)	49.9 (25.6–54.1)	41.7 (26.5–56.7)	30.2 (19.3–40.6)	56.1 (36.5–73.8)
Other costs (million euros)	4.8 (−2.8 to 14.1)	2.6 (−3.9 to 10.2)	−2.2 (−6.7 to 2.1)	3.0 (−2.8 to 10.7)	7.7 (1.8–16.0)
Total incremental costs (million euros)	−9.1 (−52.6 to 15.5)	9.2 (−22.6 to 28.5)	49.5 (30.5–78.3)	−7.7 (−41.3 to 13.2)	31.5 (−0.6 to 57.4)
QALYs gained	1562 (440–3771)	1271 (376–2960)	652 (200–1288)	1222 (353–2918)	1180 (156–3254)
ICER	−4452 (−38 520 to 22 900)	12 118 (−14 507 to 51 679)	101 053 (30 962–272 703)	−4699 (−39 494 to 23 521)	58 558 (−832 to 236 049)
Cost saving (%)	63	21	0	64	3
Cost effective (%)[c]	97	75	0	96	35
Not cost-effective (%)[c]	3	25	100	4	65

CAI, condomless anal intercourse; ICER, incremental cost-effectiveness ratio; PrEP, preexposure prophylaxis; QALY, quality-adjusted life-year; RC, risk compensation.
[a]The cumulative number of averted HIV infections from 2018 to 2027 compared with simulations without PrEP.
[b]Extra costs made in simulations with the PrEP programme when compared with simulations without the PrEP programme. Negative numbers indicate costs saved.
[c]Interventions are cost-effective if the incremental cost is less than 20 000 euros per QALY gained.
[e]Simulations with a PrEP effectiveness of 96% per sex act instead of 86%.
[f]Simulations with a PrEP effectiveness of 64% per sex act instead of 86%.
[g]Simulations with a PrEP effectiveness of 0% per sex act instead of 86%.
[h]Simulations where men with an indication for PrEP have 50% probability of starting with PrEP instead of 75%.
[i]Simulations with a per sex act 200% increase in probability of condomless anal intercourse among PrEP users instead of 75%.

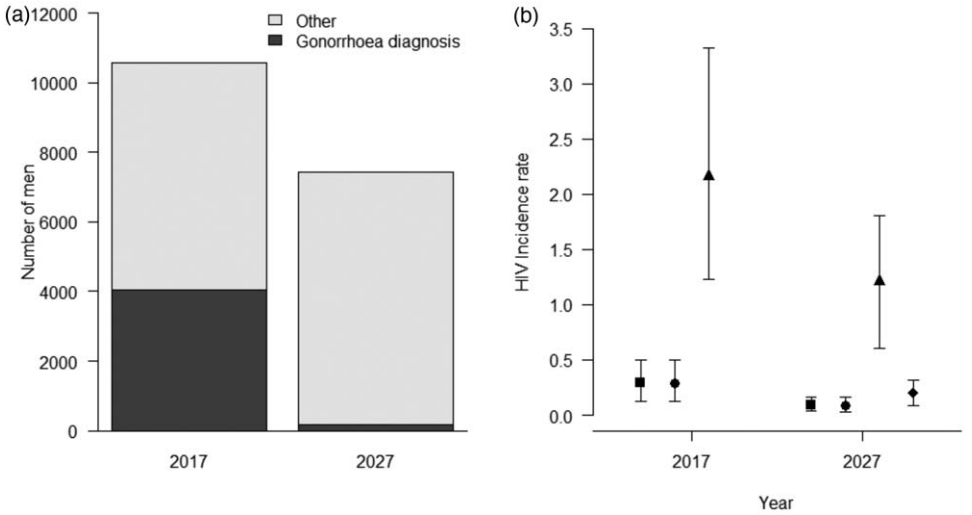

Fig. 2. Eligibility for preexposure prophylaxis and HIV incidence rates in the standard preexposure prophylaxis scenario. (a) The number of MSM that are eligible for PrEP at the time of an HIV/STI test in 2017 and 2027. The upper, lighter part shows the number of men who were eligible because of other criteria than having had a gonorrhoea diagnosis. The lower, darker part shows the number of men who were eligible as they had a gonorrhoea diagnosis, possibly in combination with other criteria. (b) HIV incidence rates in 2017 and 2027 in infections per 100 person-years for the following groups: total MSM population (square); MSM not on PrEP (circle); MSM not taking PrEP, but eligible (triangle); MSM on PrEP (diamond). Symbols show the mean, whiskers show the 95% uncertainty interval. PrEP, preexposure prophylaxis; RC, risk compensation.

standard scenario (Table B12, http://links.lww.com/QAD/B630).

Discussion

This study explored the cost-effectiveness of PrEP accounting for the impact of a PrEP programme on gonorrhoea. Our results showed that a national PrEP programme could be cost-effective and could result in considerable reductions in both HIV and *N. gonorrhoeae* transmission. Generally, HIV incidence decreased when more men used PrEP, regardless of risk compensation. Gonorrhoea prevalence dropped because men on PrEP were tested every 3 months and treated if positive, thus reducing onward transmission. This reduction, however, was smaller with risk compensation. Risk compensation and smaller reductions in gonorrhoea prevalence led to higher numbers of PrEP users.

An important finding of our study is that small reductions in condom use counterintuitively led to slightly less new HIV infections. This can be explained by the fact that reduced condom use resulted in more MSM engaging in CAI every year and hence more MSM being eligible to start or continue PrEP; this led to a higher number of MSM on PrEP and, hence, higher number of MSM being protected against acquisition of HIV. That compensated the increased 'opportunities' to get infected with HIV because of reduced condom use, as the latter was rather small. Another important result of our study is that although the total costs of a PrEP programme may be high, these costs may be lower than the savings that can be made in HIV care because of the decreased number of HIV infections, making the programme cost-saving. Nevertheless, if condom use is considerably reduced, resulting in higher numbers of PrEP users, the costs of the programme may outweigh the savings in HIV care, making the programme not cost-effective. Furthermore, our calculations confirm the fears that the costs of PrEP monitoring (excluding PrEP medication) can be extremely high; looking at the total costs, cumulative over the whole Dutch MSM population and over the 10-year period 2018–2027, we found that, the cumulative costs for PrEP monitoring may surpass the cumulative costs for PrEP medication.

Our findings are in agreement with those from earlier work. An earlier cost-effectiveness analysis for a Dutch PrEP programme for MSM using a compartmental model with only HIV, annual costs of HIV care (cART and monitoring) of €12 468–13 505 and annual costs of PrEP (medication and monitoring) of €7400 found PrEP to be cost-effective over a 40-year time-horizon [8]. That study, however, did not take into account changes in sexual risk behaviour, and did not follow Dutch guidelines as those were published around the same time, when deciding whom to give PrEP. Cambiano *et al.* used an agent-based model and assumed that MSM could start with PrEP if they had CAI in the 3 months prior to a negative HIV test and men on PrEP were tested 3-monthly. They used a higher price for

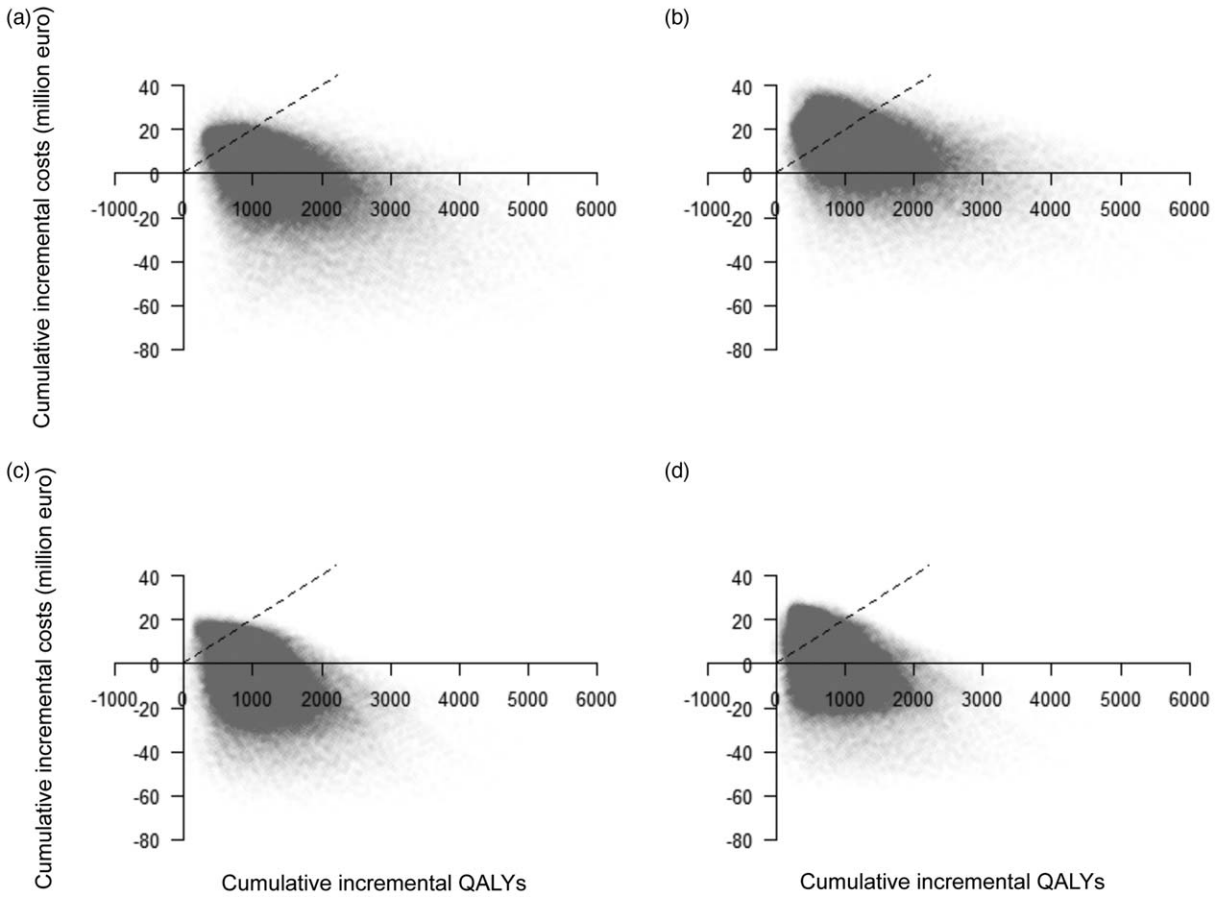

Fig. 3. Cost effectiveness planes of four preexposure prophylaxis scenarios. (a) Standard PrEP scenario, (b) risk compensation scenario, (c) capped size scenario, (d) capped size and risk compensation scenario. The x-axis shows the cumulative incremental quality-adjusted life-years (QALYs), over 2018–2027, of the respective PrEP scenario compared with the scenario without PrEP. The y-axis shows the cumulative incremental costs over 2018–2027 made in the respective PrEP scenario compared with the scenario without PrEP in million euros. Dashed line shows the threshold of 20 000 euros per QALY gained, below which an intervention is cost-effective. Lower right quadrant shows cost-saving simulations. Per scenario 100 000 cost-effectiveness ratios were calculated. PrEP, preexposure prophylaxis.

PrEP (£4331 for 1 year), £6288 for 1 year of ART, and found PrEP to be cost-effective over an 80-year time-horizon [19]. A compartmental model study of MSM based on American data calculated PrEP to be not cost-effective with an ICER of $353 739 per QALY, over a 20-year time-horizon [20]. That study assumed a price of US$ 22 per day for PrEP drugs, but a lower PrEP effectiveness of 73% and it did not target MSM at high risk for HIV, but all HIV-susceptible MSM. In a study for high-risk MSM in New York, a price of US$ 31 per day for PrEP drugs and lifetime cART costs of US$ 343 130 per treated individual were used. The study found PrEP to be cost-saving over a 5-year horizon, if the effectiveness of PrEP is 70% for those with good adherence, 50% for those with bad adherence, and assuming only 33% of MSM on PrEP having good adherence [21]. That study also pointed out that MSM not on PrEP also benefit from lower HIV incidence rates caused by PrEP.

We showed that even with decreased condom use, 3-monthly testing (provided for PrEP monitoring) can result in considerable reductions in gonorrhoea prevalence; this effect was also found in another study using a model for chlamydia and gonorrhoea transmission after the introduction of PrEP [4]. We found that risk compensation can result in higher numbers of PrEP users, which is in agreement with results from [4].

Our modelling and cost-effectiveness study has several strengths. First of all, we developed an advanced agent-based model that accounts also for transmission of *N. gonorrhoeae*, in addition to HIV. That is important as risk compensation because of PrEP provision could result in increases in other STIs [6] and as changes in gonorrhoea could lead to changes in the size of the PrEP programme. Our results show that the number of PrEP-eligible MSM may decline in time, most likely because of the decline in gonorrhoea prevalence (Fig. 2a), which is one of the PrEP

eligibility criteria. The decline in number of PrEP user results, in turn, in variations in the costs and effects of the programme. Second, we used an activity-based costing approach to identify all costs related to a complete PrEP programme, including PrEP medication, initial controls to establish PrEP eligibility, and regular PrEP controls, according to the Dutch guidelines. Another strength of our study is that we assessed the individual contribution of PrEP medication, PrEP monitoring, HIV medication (cART), and monitoring of those in care to the total costs of the programme (Tables 1 and 2).

Nevertheless, our study also has some limitations. We assumed that MSM can only start PrEP if they present themselves for an HIV/STI test and meet one of the criteria for PrEP. We assumed there was no change in testing behaviour among MSM not on PrEP, whereas more MSM might get an HIV/STI test in order to join the PrEP programme. For the moment, no major changes in HIV/STI testing have been observed in the Netherlands, as PrEP was recommended for MSM in 2018, Noneligible MSM might falsely report CAI and receive PrEP; that could increase the ICER, as the costs would increase, but the effects would hardly change. However, we expect that if only limited numbers of noneligible MSM will use PrEP. which will not affect its cost-effectiveness. Finally, we did not account for the possibility to use event-driven PrEP.

In conclusion, our study suggests that a nationwide PrEP programme targeted to MSM at high risk for HIV can have a substantial impact on HIV and gonorrhoea transmission. The more MSM are included in the programme, the larger the effect on HIV incidence rate and the more HIV infections can be averted over 10 years. The costs of such a programme can be substantial but most likely less than the savings in costs of HIV care, thus the program is likely to be cost-effective and even cost-saving. Even with small reductions in condom use, the programme can be cost-effective. Therefore, implementation of a nation-wide PrEP programme, with proper medical guidance and monitoring, is expected to reduce HIV and gonorrhoea transmission and to be cost-effective.

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Conflicts of interest

There are no conflicts of interest.

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