Is Pre-Exposure Prophylaxis for HIV prevention cost-effective in men who have sex with men in the UK? A modelling and health economic evaluation

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ABSTRACT

Background: In the UK, HIV incidence among men having sex with men (MSM) remains high despite the widespread use of antiretroviral therapy and high rates of virological suppression. Pre-Exposure Prophylaxis (PrEP) has been shown to be highly effective in preventing further infections in MSM, but its cost-effectiveness is less certain.

Methods: A dynamic, individual-based stochastic model, the Synthesis model, was calibrated to multiple data sources on HIV among UK MSM. We evaluated the introduction of a PrEP programme with sexual event-based use of Emtricitabine/Tenofovir for MSM who had condomless anal intercourse in the previous three months, a negative HIV test at baseline, and a negative HIV test in the preceding year (similar to the eligibility criteria in the PROUD study).

Findings: The introduction of such a PrEP programme with around 4,000 MSM initiated on PrEP by the end of the 1st year and almost 40,000 by the end of the 15th year resulted in a total cost saving (£1·0 billion discounted) and led to a gain of 40,000 discounted quality adjusted life-years over an eighty-year time horizon. This result was particularly sensitive to the time horizon chosen, the cost of antiretrovirals (for treatment and PrEP), and the underlying trend in condomless sex.

Interpretation: This analysis suggests that the introduction of a PrEP programme for MSM in the UK could be cost-saving and produce better health outcomes over the long term. However, a reduction in the cost of antiretrovirals (including the drugs used for PrEP) significantly shortens the time for cost-effectiveness to be achieved.

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Research in context

Evidence before this study

Pre-Exposure Prophylaxis (PrEP) has been shown to be highly efficacious and effective. However, PrEP drugs are currently expensive in high income settings and the cost-effectiveness of offering PrEP as part of universal health care systems in such settings is unclear.

We searched PubMed for English-language studies published up to May 31, 2017, that estimated the cost-effectiveness of PrEP programmes, taking into account of onward transmission. We combined search terms for PrEP ("pre-exposure prophylaxis", "preexposure prophylaxis" "PREP" "HIV") with health economic terms ("cost", "cost-effectiveness", "cost effectiveness", "ICER", "cost-benefit", "cost benefit", "cost-utility", "cost utility", "health economics", "economics", "economic evaluation") and "transmission".

We found one report of cost-effectiveness analyses of PrEP programme among men having sex with men (MSM) in Europe: in the Netherland[1]. Using a deterministic compartmental model calibrated to the Netherlands, they concluded that the introduction of event-based PrEP in MSM in the Netherland would be cost-effective at the current cost of Emtricitabine/Tenofovir over a 40 year time horizon.

Added value of this study

The PROUD and IPERGAY trials demonstrated that PrEP is highly efficacious and effective among MSM. We used the effectiveness estimated in PROUD to evaluate the cost-effectiveness of a programme that will be delivered in the same population from which participants in the PROUD trial were recruited, using similar eligibility criteria and assuming it will be delivered through the same system (Genito Urinary Medicine clinics).
Our study suggests a PrEP programme with (sex) event-based use of Emtricitabine/Tenofovir being offered to MSM who had condomless anal intercourse in the previous three months, a negative HIV test at baseline, and a negative HIV test in the preceding year (similar to the eligibility criteria in the PROUD study) results in a saving in cost and a health benefit when considering an appropriately long time horizon (eighty years). The patent protection on drugs used for PrEP expires in Europe in 2017 - 2018 (a supplementary protection certificate for Truvada expires in February 2020)[2], if the cost of antiretroviral drugs (used for PrEP and treatment) are reduced from 2019 by 80%, the introduction of such a PrEP programme is cost-effective even when considering a twenty year time horizon.

Implications of all the available evidence

There is no doubt of the effectiveness of PrEP. Our work suggests that the introduction of PrEP will – in addition to delivering a substantial health benefit - ultimately lead to a saving in cost, due to the lower number of men in need of lifelong HIV treatment. As antiretroviral patents expire over the next few years, potentially large cost reductions in the drugs used for PrEP with the emergence of generics may occur and this would help to limit the budget impact of PrEP and make it cost-effective over a relatively short time horizon.

INTRODUCTION

Sex between men is the predominant mode of HIV transmission in Europe and other high income settings.[3] In the UK, HIV incidence among men having sex with men (MSM) has remained high (around 3,000 new HIV infections in 2014[4] and 2015[5,6], although with reports of somewhat lower levels in 2016[7]), despite high levels of antiretroviral treatment (ART) coverage, virological suppression for those on treatment and an expansion in HIV testing.[8,9] Alternative prevention approaches are needed, of which a promising option is Emtricitabine/Tenofovir-based Pre-Exposure Prophylaxis (PrEP). This involves HIV negative people taking the drug combination to reduce the risk of HIV infection. PrEP has been demonstrated to be highly efficacious among MSM, whether used daily[10] or event-based (i.e. two pills 2-24 hours before a sex act, one for each consecutive day having condomless sex, for two days after the last sex act),[11] and effective in real world conditions when used daily.[12]

However, when considering a PrEP programme in the UK for MSM, important questions are whether it is cost-effective from a health system (i.e. the National Health Service (NHS)) perspective and its budgetary impact. Therefore, the aim of this study is to evaluate the cost-effectiveness of introducing event-based PrEP among MSM attending Genito-Urinary Medicine (GUM) clinics in the UK in 2016. The choice of offering a sexual event-based PrEP regimen, rather than daily was driven by the high efficacy reported in the IPERGAY study[11] and the lower cost compared with daily regimen. In the UK, there is a network of around 200 GUM clinics, who offer sexual health advice, testing, treatment for sexually transmitted infections (STIs) and post-exposure prophylaxis (PEP) free and confidentially to anybody. This is envisaged to be the most pragmatic way of offering PrEP in the UK.

METHODS

A dynamic individual-based simulation model (the HIV Synthesis Model), calibrated to the MSM HIV epidemic in the UK that has previously described in detail,[5,8] was used to address this question (see Appendix I for a brief description, page 1, Appendix II for details on the calibration, page 18-48 and Appendix III for full details, page 50). A probabilistic sensitivity analysis (PSA) was conducted to produce the main results, by sampling twenty-two key parameters (see Appendix I page 1 for the list of parameters sampled). 5965 simulations were performed. To reduce the stochastic variability when presenting the main results, we divided each of these parameter distributions into tertiles and calculated the mean across simulations with the same combination of parameter tertiles. When estimating the health benefit we considered the combination of parameters affecting the HIV infections averted (5); while when estimating the incremental cost we considered the combination across all the parameters sampled in the PSA (22). The univariate sensitivity analyses were conducted by fixing the parameters that were sampled in the PSA.

PrEP policy options compared and main assumptions relating to PrEP

Two main scenarios were compared: one in which PrEP is not available and the other assuming that sexual event-based PrEP is introduced (the proportion of pills taken is sampled; the mean corresponds to 5 pills/week) in the second quarter of 2016. In both scenarios sexual behaviour, HIV testing behaviour, and the probability of initiating ART are assumed to remain at current levels. In the PrEP scenario, it was assumed that MSM were eligible for PrEP if: (a) they had a negative HIV test at PrEP initiation (b) they had reported condomless anal intercourse in the previous three months (unless the only partner they had condomless sex with was a long-term partner virologically suppressed on ART[13]), and (c) they had had an additional documented negative HIV test in the preceding year, very similarly to the PROUD study eligibility criteria.[12]
The current national number of men eligible for PrEP, based on the above criteria, has been estimated to be between 8,400 and 12,200 (See Appendix I, page 2). This group is characterised (in

the model) by an HIV incidence of around 2·0/100 person-years (90% range:0·7-4·3/100 person-years) in 2016, similar to the HIV incidence observed in repeat testers in GUM clinics.[14]

Once PrEP has been started, it is assumed sexual event-based PrEP will be used in any subsequent three month period when having condomless sex (unless the only condomless sex partner is a long term partner who is virologically suppressed on ART) unless there is a decision to interrupt it (mean rate of interruption of 0.1 per year, with wide variability considered, see Appendix IV page 128). However, mens can restart PrEP with a mean rate of 0.5 per year (similarly a wide variability is considered – see Appendix IV, page 128) if having condomless sex again. It is assumed that the PrEP programme will be stopped if the overall HIV incidence in the MSM population drops below 1/1000 (i.e. approximately a fivefold decline compared to current HIV incidence).

We assume that men on PrEP test for HIV every three months, as recommended by the British Association for Sexual Health and HIV for MSM having condomless sex[15] (and the US Centers for Disease Control and Prevention for people on PrEP[16]). In the eventuality that a person becomes HIV positive they would be diagnosed with HIV at the next test and PrEP would be stopped.

The effectiveness of PrEP (sampled in the PSA) was assumed to be on average 86%[12], reflecting both adherence and efficacy (the protection conferred when taken as prescribed).

Outcomes and Economic analysis

The main model outcomes are the number of HIV infections, quality adjusted life-years (QALYs), and costs. In addition to the PSA, a range of univariate sensitivity analyses were performed as outlined in the Appendix I (page 3-6) to investigate the impact of changes in key assumptions.

The utilities used to calculate the QALYs are age-adjusted and take into account the reduced quality of life of people diagnosed with HIV in different stages of infection (sampled in the PSA, see Supplementary Table 1 on page 7 of the Appendix I). The cost (per year) of the antiretroviral drugs for treatment is assumed to be £6,288[17], while the mean cost (per year) of antiretrovirals for PrEP is £4,331 [18]. The unit costs assumed (sampled in the PSA) are summarized in Supplementary Table 2 (page 8-10 of the Appendix I) and are assumed to remain at the current level for the entire time horizon, although discounting applies. In the base case, all costs and QALYs are discounted at an annual rate of 3·5%.[19] A time horizon of eighty years is used, given the National Institute of Health and Care Excellence recommendations considering a lifetime horizon.[19]

Role of the funding source
The NIHR had no role in study design, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Current situation and PrEP scale up

In 2016, the year in which it is assumed PrEP roll-out would have started, the number of MSM living in the UK is estimated to be 725,200 (585,000 aged 15-64); 57,800 (53,900 aged 15-64) are estimated to be living with HIV and, with around 3,500 new HIV infections that year, the HIV incidence rate is estimated to be around 6/1,000 person-years in MSM aged 15-64. We considered a PrEP programme where the uptake was such that on average around 4,000 MSM initiate PrEP by the end of the 1st year, and that by the end of the fifth (2020) and 15th years (2030) respectively 16,600

and 38,900 would have ever been initiated on PrEP respectively (See Figure 1a). This is considered to reflect a realistic gradual uptake. The mean time spent on PrEP among men initiated on PrEP is four and half years.

Epidemiological impact

Without the introduction of PrEP, HIV incidence is projected to decline due to the offer of earlier ART initiation and because of an increase in the number of MSM who become aware of their HIV status, induced by continuing HIV testing at the current rate. By introducing a PrEP programme as described above, over the next 80 years, 25% of the HIV infections among MSM living in the UK are predicted to be averted (with the specified distribution for the size of the PrEP programme; see Figure 1b and Table 1), 42% of which are directly due to people receiving PrEP and the remainder due to the prevention of onward transmission. As a consequence, PrEP would result in a gain of 220,000 quality adjusted life-years (QALYs - 40,000 with discounting) (see Table 1), corresponding to 5 QALYs gained per infection averted.

Economic impact

The introduction of event-based PrEP, by averting HIV infections (see Figure 1b and Figure1c), reduces the cumulative HIV cost (see Table 1). While the number of people living with HIV in care is projected to start declining in the mid 2050s, even if PrEP is not introduced, this would happen around ten years earlier if PrEP is introduced (See Figure 1d).

Figure 3 shows the undiscounted budget impact for HIV care and prevention (PrEP and PEP are included) over the next eighty years respectively without the introduction of PrEP, with the introduction of PrEP, and their difference. The same is presented assuming the cost of antiretrovirals (for PrEP and treatment) is reduced by 50% from 2019. In 2016, if PrEP is not introduced, 94% of the HIV budget is estimated to be spent on the cost of antiretroviral drugs to treat people with HIV (44%) and health care services for providing ART and treating clinical diseases (50%). The budget for HIV care, treatment, HIV testing and PEP for MSM in 2016 is estimated to increase from around £0·45 billion to reach its peak of around £0·85 billion in thirty years (See Figure 3a). With the introduction of PrEP (see Figure 3b), this peak is projected to happen ten years earlier, in around twenty years.

Cost-effectiveness evaluation

The introduction of event-based PrEP leads to an additional 40,000 discounted QALYs over an eighty-year time horizon and a saving in costs (£1·0 billion discounted). Thus, over the eighty-year time horizon PrEP introduction is cost saving, so highly cost effective. The cost-effectiveness plane (Figure 2a) illustrates the uncertainty around our findings and the cost-effectiveness acceptability curve the fact that the probability of a PREP programme being cost-effective is above 80% when considering a cost-effectiveness threshold greater than £20,000 per QALY gained (Figure 2b, around 75% at £13,000 per QALY gained).

We performed several one-way sensitivity analyses, summarized in Table 2 and described in the Appendix I (page 3). In all sensitivity analyses related to costs (Table 2; S1-S9), including assuming the cost of daily PrEP rather than event-based, we found that over an eighty-year time horizon the introduction of PrEP, as indicated, generates additional QALYs and is cost-saving.

A number of other sensitivity analyses were considered including: an effectiveness of 63% (the 90% lower confidence limit in PROUD[12]) (S10), assuming PrEP is used only in half of the three month

periods when having condomless sex (S11) and assuming the proportion of three month periods in which men initiated on PrEP have at least one condomless sex partner increased by 25% (S12). Our findings were robust to these variations and PrEP was still cost-saving and generated additional QALYs. However, if men who started PrEP only used it in 50% of three-month periods when having at least one condomless sex partner, both the health benefit (23,000 rather than 36,000 discounted additional QALYs) and the saving in cost (£673 million rather than £964 million) were considerably lower (S11).

Three other sensitivity analyses considered different sizes of the PrEP programme either due to a lower (S13) or higher (S14) uptake in the eligible population or by assuming that the eligible population increases due to an assumed 15% of men who tested in the last year and who are having condomless sex coming forward for PrEP (S15). PrEP is cost saving in these scenarios - the greater the size of the PrEP programme the larger the health benefit and the saving in cost.

In the context of higher background HIV incidence (Table 2;S16, S17; See also Supplementary Figure 1h -1m at page 14-17 of the Appendix I), the cost-effectiveness of introducing PrEP was even higher with more quality adjusted life-years gained and a greater saving in cost. On the other hand, if the HIV incidence is lower due to all people diagnosed with HIV starting treatment at diagnosis (S20), the introduction of PrEP is still cost-saving, but the cost saving is slightly lower. If the uptake of PrEP is concentrated in those at higher risk of contracting HIV (S19) the health benefit is slightly lower compared to the base case due to the fact that the size of the PREP programme is smaller (see Supplementary Figure 1b) but the saving in cost is even greater due to the fact it is a more efficient way of implementing PrEP. Finally, we considered the cost-effectiveness of PrEP in the context of the PrEP programme continuing, regardless of the HIV incidence in the MSM population (S18) and in the context of MSM initiated on PrEP increasing on average by 25% the proportion of three-month periods they have at least one condomless sex partner (S12) and having at least one condomless sex partner for life (S21). Even in these scenarios the introduction of PrEP was cost-effective. The reason why we observe a greater health benefit if people initiated on PrEP increase their condomless sex and use PrEP is that the greater the number of men using PrEP, the fewer the number of partnerships which are not protected by PrEP. In other words those men who stay on PrEP longer and continue having condomless sex are effectively protected from HIV when they have condomless sex partnerships, while if they had not started PrEP they would have a lifetime risk of contracting HIV.

Table 3 shows how the cost-effectiveness of introducing PrEP varies according to different time horizons and different reductions in the cost of antiretrovirals. This is done both in the base case scenario, where HIV incidence is predicted to drop even in the absence of PrEP, and in the context of the HIV incidence increasing due to a moderate increase in sexual risk(See Supplementary Figure 1h -1m at page 14-17 of the Appendix I).
At the current cost of antiretrovirals, the introduction of event-based PrEP becomes cost-effective when considering a time horizon of forty years or more. However, as the cost of antiretrovirals decreases the time horizon for the introduction of PREP to be cost-effective shortens. For example, when considering an 80% reduction in the cost of antiretrovirals (for both PrEP and treatment) from 2019, PrEP would be cost-effective even when considering a 20 year time horizon (£6,000/QALY gained) and cost-saving over this time horizon in the scenario where the HIV incidence is increasing.

Finally, we estimated the maximum cost to treat an STI at which the introduction of PrEP is still cost-effective, assuming a substantial increase in STIs. In 2014, 48,000 new STIs diagnoses were reported among MSM in the UK.[20] If there were to be 96,000 new STIs diagnoses per year following the introduction of PrEP, its introduction would still be cost saving if the average cost to treat an STI is £2,000 or less.

DISCUSSION

Our results suggest that the introduction of event-based PrEP among MSM in the UK with the eligibility criteria proposed is cost-saving, leading to a health benefit due to a substantial reduction in HIV incidence among MSM and a saving in cost. Our results are robust to considerable variations in the main assumptions. While PrEP introduction is cost saving taking an appropriately long time horizon, there are increases in overall costs for 20 years in our main results and it takes 40 years for the incremental cost effectiveness ratio to be below £13,000.

The uptake of PrEP among the population eligible for PrEP, and hence the size of the PrEP programme, is a crucial parameter for the budget impact of such a programme. A number of surveys conducted in the UK among HIV negative MSM reported that between 55%[21] (among men who reported sex without using condom in the past 3 months and who tested negative within the last six months) and 60%[22] were interested in PrEP, 50%[23] were willing to use it if available and 2% had already used it.[23] We found that the greater the size of the PrEP programme among men eligible the greater the health benefit. The saving in cost (we considered a maximum PrEP programme of 27,000 men at its peak) depends not only on the size but also on the risk of HIV acquisition in people receiving PrEP. In addition, the size of the PrEP programme will depend on whether men come forward for PrEP as it becomes available. Unfortunately, it is not possible yet to estimate this parameter with any degree of certainty. In the context of a larger PrEP programme, due to greater numbers of men having condomless sex and a previous HIV test in the last year presenting for PrEP, the introduction of PrEP plays an even more significant role in preventing HIV infections and is more cost-effective.

In the main case it is assumed that HIV testing will continue at the current rate, as it is standard in health economic analysis to assume the current situation will persist. However, testing rates have rapidly increased in the UK in the recent years, especially in some clinics and in combination with the offer of treatment at diagnosis (and to some extent the possibility of buying PrEP online) and a reduction in the number of new diagnoses has been observed in these clinics. Within our Synthesis model we do predict a drop in HIV incidence as the proportion of people with HIV who are on ART increased due to increased testing and ART initiation at diagnosis [5] and it is believed the observed drop in the number of new diagnoses is the result of a combination of interventions.

Within the PROUD trial, which was open-label, no significant difference was found at one year in the number of different anal sex partners or in the proportion diagnosed with an STI, although there was a significant increase in the number reporting receptive anal sex without a condom[12]. We investigated the impact of men starting PrEP increasing by 25% the proportion of three-month periods in which they have at least one condomless sex partner and having at least one condomless sex partner in all subsequent three month periods and this did not affect our main conclusions.

Despite the strength of evidence, one of the residual concerns regarding the introduction of PrEP is the potential spread of other STIs (including HCV) and the cost of their treatment. In our model the transmission of STIs and its treatment are not explicitly modelled. However, we found that if the annual number of STIs diagnosed doubled (compared to 2014) due to the introduction of PrEP, its introduction would still be cost saving if the average cost to treat an STI is £2,000 or less.

The exact unit costs the NHS pays for HIV drug treatment is confidential and it is uncertain by how much the cost of antiretroviral drugs will drop once the patent of the antiretrovirals expire. However, we can be confident that the cost of Emtricitabine/Tenofovir will decrease in the next 20 years, but there is more uncertainty over reductions in the cost for other antiretrovirals used for

treatment. In this regard we believe we have been conservative in using the cost of treatment from a Freedom of Information request (likely to be close to the actual cost for the NHS) and the cost of Truvada® for PREP from the British National Formulary (as this is not available in the FOI) and in assuming that the cost of Emtricitabine/Tenofovir and the cost of antiretrovirals used for treatment will decline by the same amount. These costs play a key role: the greater the reduction, the shorter the time horizon for PrEP to be cost-effective and cost-saving.

Cost-effectiveness analyses of PrEP introduction among MSM in other high-income settings have been conducted, including in the US,[24-27] Australia,[28] Canada,[29] and the Netherlands.[1] Most, but not all[27,29] were conducted before the PROUD and IPERGAY trials reported and had therefore assumed a lower efficacy of PrEP than we now consider to be the case, and most considered a shorter time horizon. The cost-effectiveness evaluation conducted in the context of the Netherlands[1] considered a time horizon of 40 years and concluded that the introduction of event-based PrEP in MSM in the Netherland would be cost-effective at the current cost of Emtricitabine/Tenofovir, consistent with our findings for the UK.

Our study has several limitations. First, as with all mathematical models, the Synthesis Model is a simplification of the reality and the uncertainty around our estimate is illustrated by considering variation in the main assumptions. Second, the model estimates that around 80% of new HIV infections among MSM in the UK come from men unaware of their HIV status. Part of the population unaware of their HIV positive status is a subgroup of people who are resistant to testing. However, if people who are unaware of their status are characterized by a higher level of condomless sex, the impact of PrEP could be even greater. Third, there is uncertainty over the parameter distributions to be used for the PSA, but we believe that we have been conservative by choosing broad distributions, which means we could have conveyed more uncertainty than there actually is. Forth, the population simulated by the model, because of computer capacity, is 1/15 of the UK MSM population and this increases the stochastic variability of our results. To tackle this issue we have presented the mean across simulations with the same combination of parameter tertiles. However, we cannot exclude that the variability reported is greater than the variability due to the uncertainty in the parameters and the stochastic variability if we had modelled the whole UK MSM population.
In conclusion, our analysis has shown that the introduction of PrEP in the proposed eligible population is cost-saving. However, commissioners will have to sustain an additional cost for the first twenty years, unless drug prices substantially reduce.

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Author Contributions

Contributed to the formulation of the research questions, had critical input into interpretation of results, and had substantial input into the drafting of the manuscript: VC, AM, DD, SM, KO, ONG, AN, MD, NF, GH, GC, VD, AR & AP. Worked on development and programming of the HIV Synthesis model: VC & AP. Performed the modelling analysis: VC. Conceived and designed the experiments: VC, AM, DD, SM, KO, ONG, AN, MD, GC, AR & AP. Performed the experiments: VC & AP. Collected and defined the cost: VC, KO, AM, AP, ONG. Analyzed the data: VC & AP.

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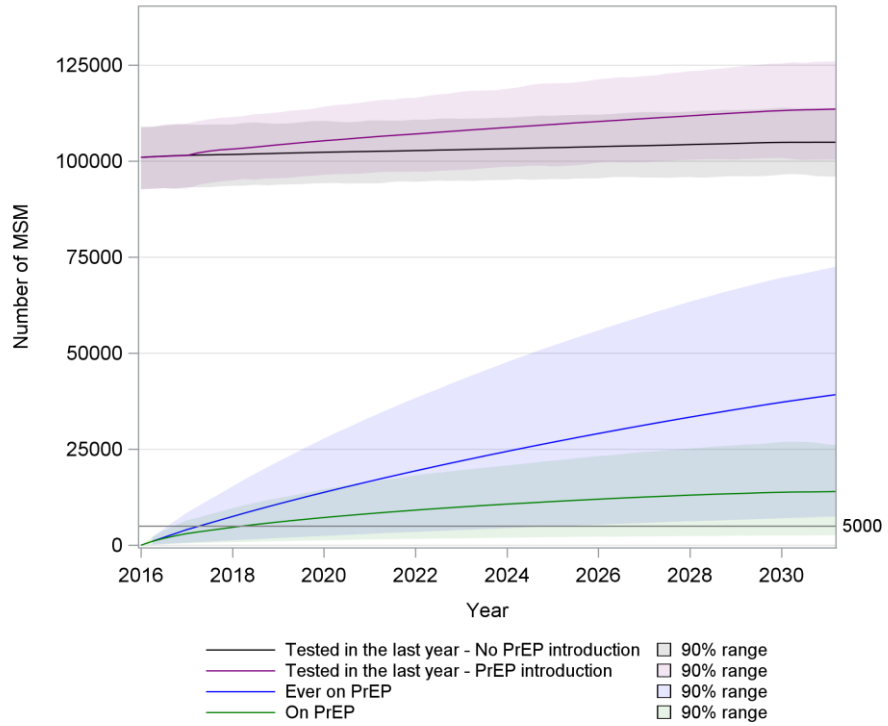
Competing interests:

VC reports personal fees from Merck Sharp & Dohme Limited (2015). SM who is the PI in the PROUD study, received drug free of charge and financial support for PROUD and personal fees from Population Council. AP reported personal fees from Gilead Sciences (2015), consultancy fees from GSK Biologicals (2012-2014) and personal fees from Abbvie (2013). AM has advised GILEAD on a non-pecuniary basis (2015). MD received a grant from Gilead to investigate hepatitis C in the PROUD trial (2014). No other authors have any competing interests

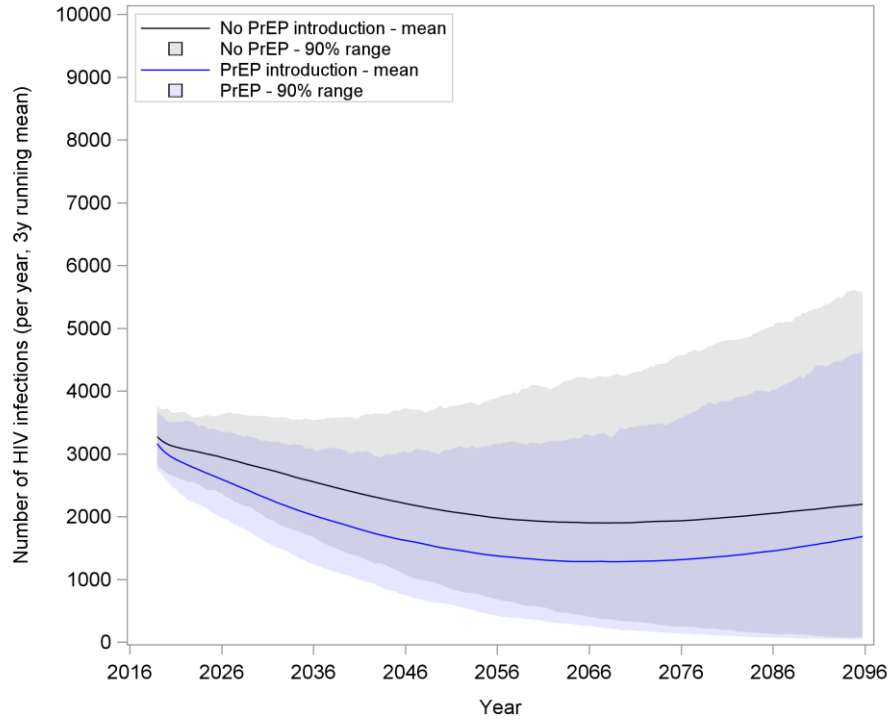
Ethics Statement: Ethical approval was not required for this work

Figure 1a. Projected mean (and 90% range) number of MSM aged 15-65 tested for HIV in the last year, initiated on PrEP (and alive) and currently on PrEP in the UK.



The trajectories presented are mean across means of simulations with the same PSA parameter tertiles.

Figure 1b. Projected mean (and 90% range) number of new HIV infections per year in the UK by PrEP policy scenario.



The trajectories presented are the three years running mean across means ofsimulations with the same PSA parameter tertiles.

Figure 1c. Mean (and 90% range) ratio of the projected cumulative number of HIV infections n the UK in the scenario with and without PrEP introduction

The trajectories presented are the three years running mean across means of simulations with the same PSA parameter tertiles.

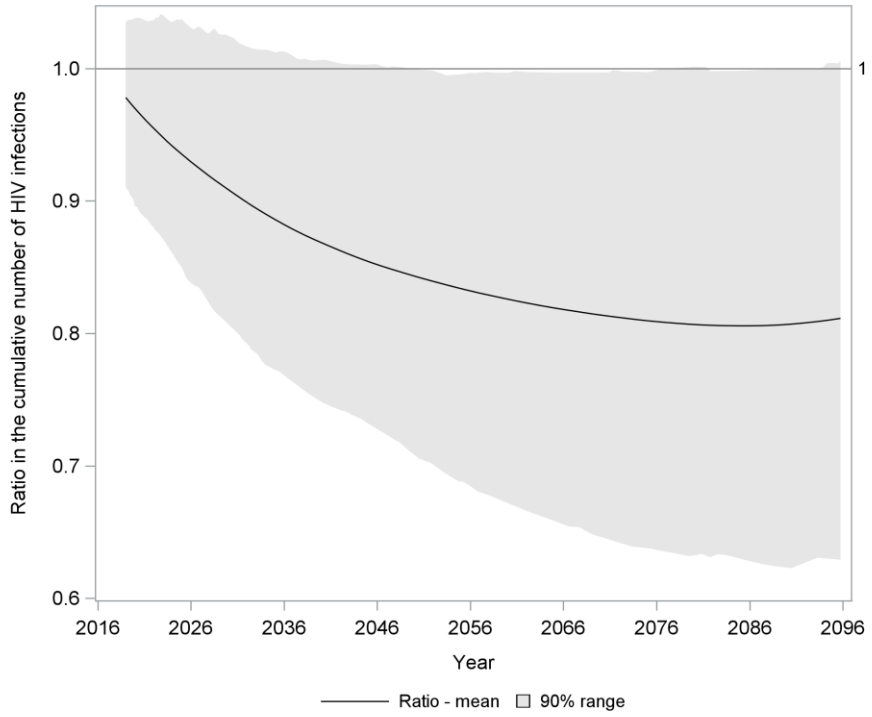


Figure 1d. Projected mean (and 90% range) number of MSM living with HIV (aged 15+) seen for HIV care per year in the UK, by PrEP policy scenario.

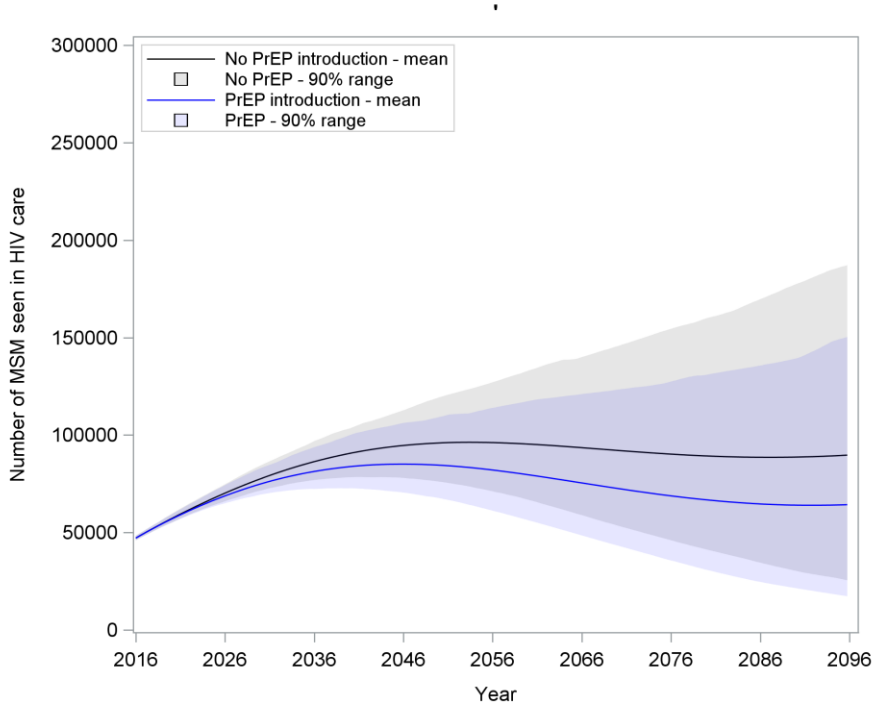


Table 1. Epidemiological impact – Cumulative mean^ number of HIV infections, quality adjusted life-years, and cost among MSM in the UK over eighty-year time horizon (2016-2096)

Mean (90% range)	**PrEP policy scenario**	
	No PrEP	**PrEP introduction**
HIV infections	178,900 (81,100; 323,300)	134,600 (61,700; 264,300)
HIV infections averted	-	44,300 (3,300; 97,600)
% of HIV infections averted	-	25%
QALYs (in 1,000)*	55,590 (55,030; 55,990)	55,810 (55,290; 56,120)
QALYs gained (in 1,000)*	**-**	220 (20; 430)
DiscountedQALYs (in 1,000)***	18,410 (18,330; 18,490)	18,450 (18,360; 18,510)
Discounted QALYs* gained (in 1,000)**	-	40 (4; 70)
Cost (in £ million)*	64,460 (24,070; 141,890)	56,440 (23,910; 126,050)
Discounted cost* (in £ million)**	20,640 (11,080; 36,220)	19,630 (11,390; 33,690)
Δ in discounted cost* (in £million)**	**-**	-1,000 (-4,900; 1,230)
Net monetary benefit* (in £million)**	**-**	1,490 (-1,360; 6,580)

MSM: men having sex with men; PrEP: Pre-Exposure Prophylaxis; QALYs: quality adjusted life-years;

^(range across means of simulations with the same combination of PSA parameter tertiles)

*(in all MSM, HIV+ and HIV-ve); **discounted at 3·5% per year; ***considering a cost-effectiveness threshold of £13,000 per QALY gained;

Figure 2a. Cost-effectiveness plane (each dot is the mean across simulations with the same PSA parameters tertiles)

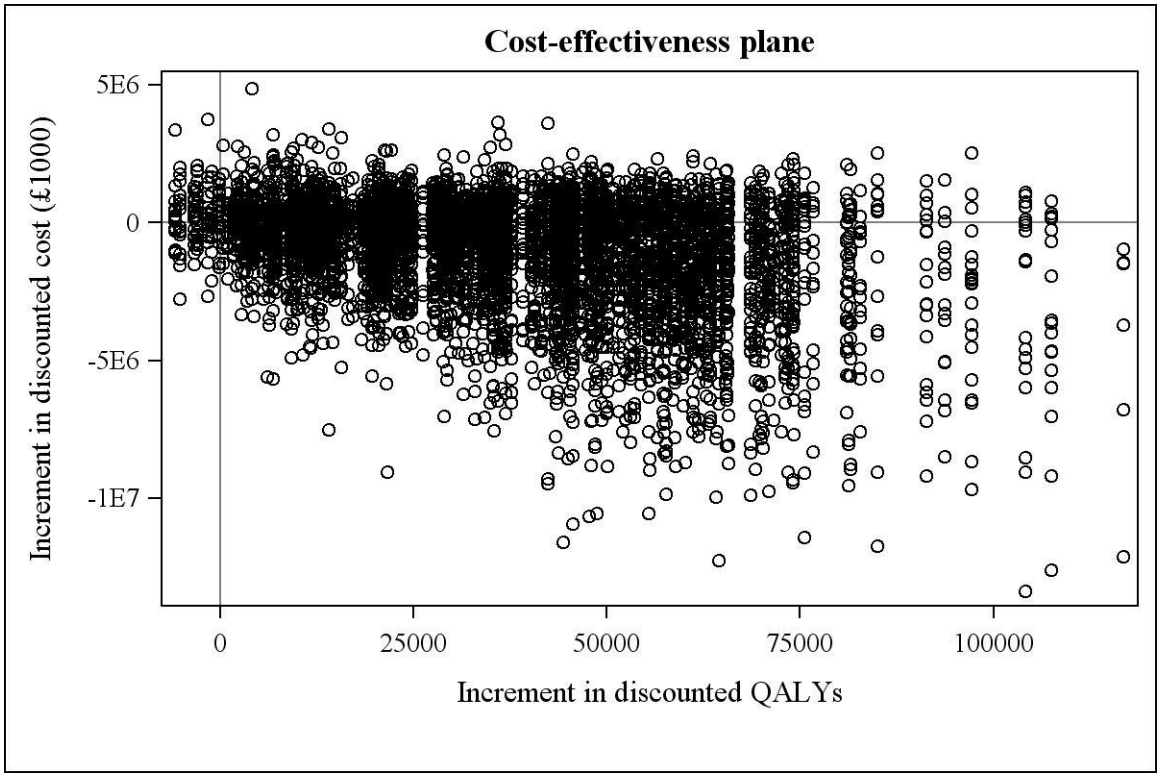


Figure 2b. Cost-effectiveness acceptability curve (CEAC) (based on mean across simulations with the same PSA parameters tertiles)

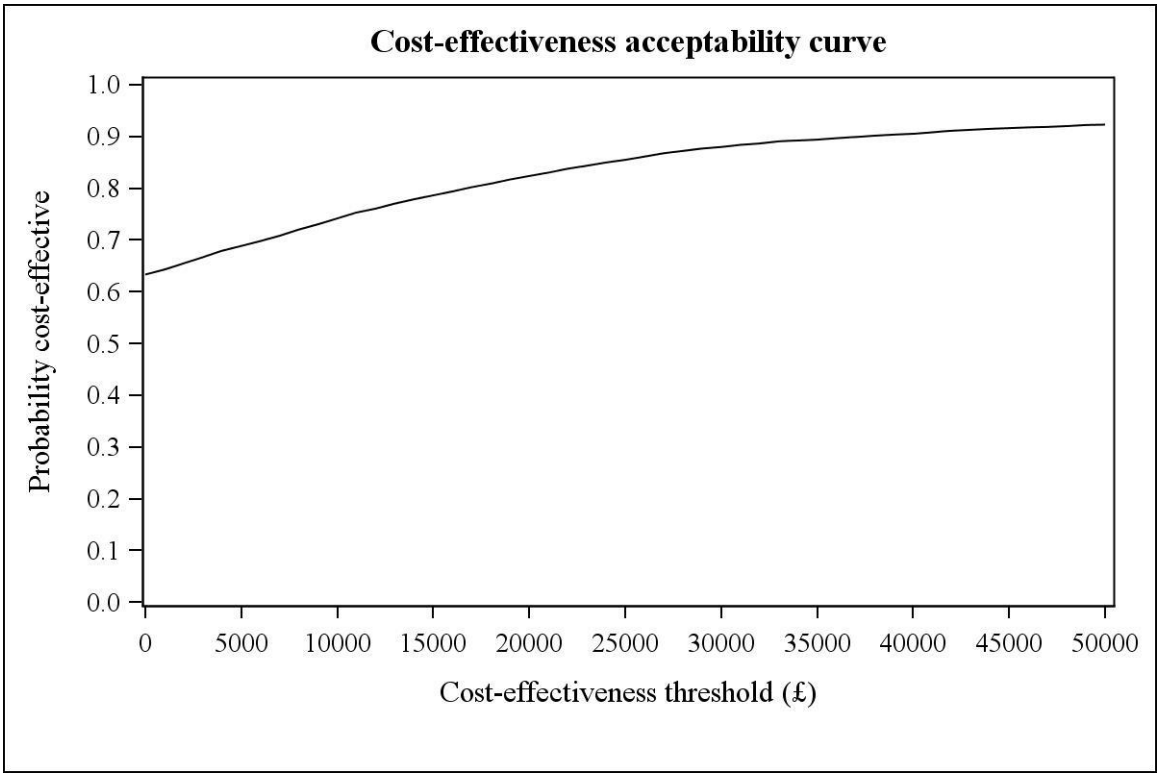
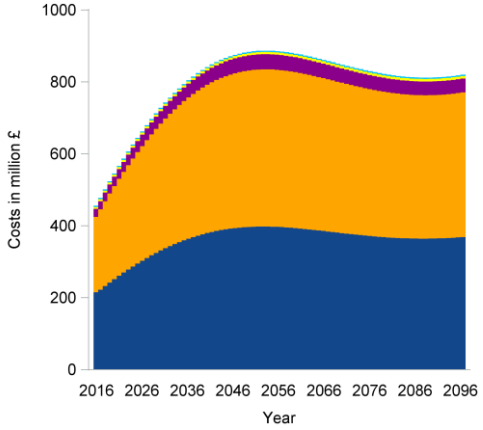
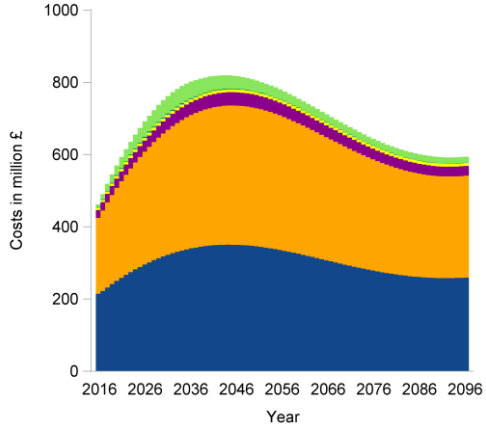


Figure 3. HIV care budget distribution (including PrEP and post-exposure prophylaxis; costs not discounted)

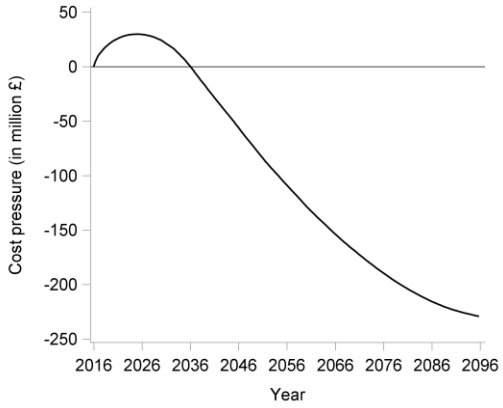
(a) Budget if PrEP is not introduced (Current cost of ARVs)



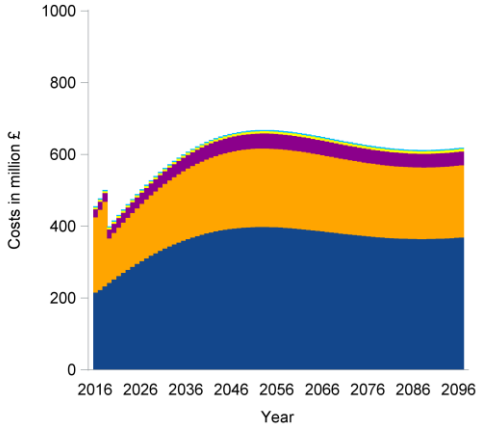
(b) Budget with the introduction of PrEP (Current cost of ARVs)



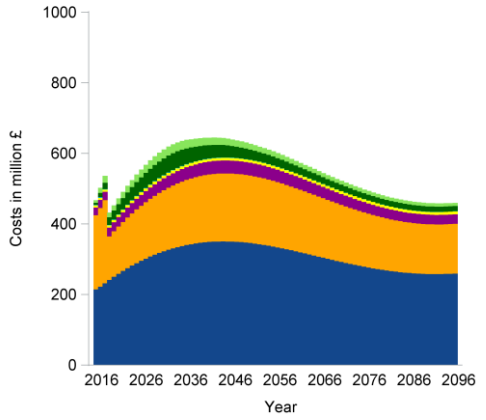
(c) Difference in the budget if PrEP is introduced vs no (Current cost of ARVs; b minus a)



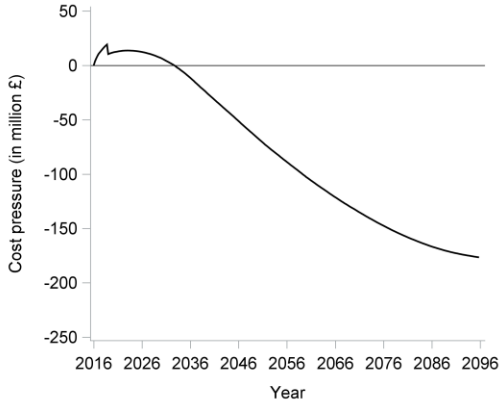
(d) Budget if PrEP is not introduced (50% reduction in ARVs cost)



(e) Budget with the introduction of PrEP (50% reduction in ARVs cost)



(f) Difference in the budget if PrEP is introduced vs no (50% reduction in ARVs cost; e minus d)



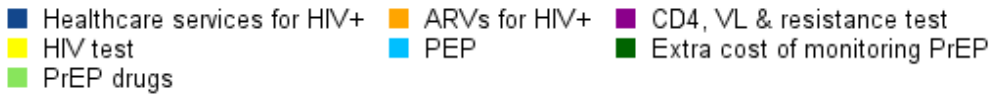


Table 2. Sensitivity analyses. Difference in discounted QALYs and discounted cost* over eighty-year time horizon for MSM in the UK by potential implementation of PrEP with current cost of ARVs and with an 80% reduction from 2019.

The reduction in cost of ARVs refers to ARVs used for treatment and as PrEP and the reduction is from 2019 (the year after Emtricitabine/Tenofovir patent expires in Europe), reflecting the potential reduction due to price discounts and use of generic drugs (See section "*Sensitivity analyses*" in the Appendix for detailed description).

		QALYs gained (thousands, discounted)*	Difference in discounted cost (£ million)*		ICER (£ per QALY gained)	
			Current cost of ARVs	80% reduction in ARVs cost	Current cost of ARVs	80% reduction in ARVs cost
Base case		36	-964	-919	dominant	dominant
Sensitivity on costs	**S1. No healthcare care cost for MSM living with HIV undiagnosed**		-912	-867	dominant	dominant
	S2. Daily PrEP use**		-662	-850	dominant	dominant
	S3. BNF cost for ART**		-1,615	-1,118	dominant	dominant
	S4. BNF cost for ART & Daily PrEP use**		-1,313	-1,050	dominant	dominant
	S5. Tenofovir cost instead of Emtricitabine/Tenofovir**		-1,615	-1,118	dominant	Dominant
	S6. 20% reduction in Emtricitabine/Tenofovir cost***		-1,138	NC	dominant	NC
	S7. 50% reduction in Emtricitabine/Tenofovir cost***		-1,400	NC	dominant	NC
	S8. 80% reduction in Emtricitabine/Tenofovir cost***		-1,662	NC	dominant	NC
	S9. PrEP used 50% of days at a cost of £4,008 per 365 pills******		-1,305	-997	dominant	dominant
S10. PrEP Effectiveness 63%		33	-746	-791	dominant	dominant

S11. PrEP used only in 50% of 3 months with ≥1 CLS partner	23	-673	-614	dominant	dominant
S12. 25% increase in the proportion of three month periods in which MSM initiated on PrEP have ≥1 CLS partner	41	-774	-938	dominant	dominant
S13. Low uptake (Correlation as in the base case)	8	-249	-230	dominant	dominant
S14. High uptake (Random)	50	-1,177	-1,187	dominant	dominant
S15. 15% of men who had a test in the last year and who are having CLS come forward for PrEP	69	-1,894	-1,661	dominant	dominant
S16. No change in ART eligibility criteria in 2016^,^^	49	-1,380	-1,209	dominant	dominant
S17. Gradual increase in CLS^^	74	-2,472	-1,996	dominant	dominant
S18. PrEP programme continues indefinitely	37	-331	-775	dominant	dominant
S19. Probability of initiating PrEP for people with 1 CLS partner of 0.01 rather than 0.3	31	-984	-839	dominant	dominant
S20. Immediate ART initiation for all people diagnosed	35	-869	-846	dominant	dominant
S21. MSM initiated on PrEP have ≥1 CLS partner for life (as long as the PrEP programme is running)	59	-1,139	-1,324	dominant	dominant

ARVs: antiretrovirals; ART: antiretroviral therapy; BNF: British National Formulary; CLS: condomless sex; ICER: incremental cost-effectiveness ratio; MSM: men having sex with men; NC: not calculated, as the result will be the same as other sensitivity analyses in the table; PrEP: Pre-Exposure Prophylaxis; QALYs: quality adjusted life-years;

*compared to the scenario without PrEP; **See Supplementary Table 2 at page 7 of the Appendix;***from 2019;^ the probability per 3 months of starting PrEP if the CD4 is above 350 cells/mm^3 is 0·025, rather than 0·15 per 3 month. ^^The comparator to calculate QALYs averted, difference in cost and ICER is the same scenario but without the introduction of PrEP;****The assumption of a cost of £4,008 for 365 pills rather than £4,331, as reported in the BNF 2015, was considered because the average cost for one year of antiretroviral treatment per person in London is £4,741 (Source: Freedom of Information Request). Most regimen would contain Truvada, so given the cheapest cost of the third agent is Lamivudine which is available as generic at a cost of £733 we wanted to consider the maximum cost of Truvada being 4,008 (£4,741-£733)

■ cost-saving (leading to a health benefit and saving in cost); ■ cost-effective (incremental cost-effectiveness ratio [ICER] below £13,000/QALY gained);
■ border-line cost-effective (ICER between £13,000-£30,000/QALY gained); ■ not cost-effective (ICER above £30,000/QALY gained);

Table 3. Cost-effectiveness evaluation by length of time horizon considered and reduction in the cost of antiretrovirals from 2019 in the context of the HIV incidence declining (base case) and increasing.

The reduction in cost of ARVs refers to ARVs used for treatment and as PrEP. Supplementary Figure 1h at page 14 of the Appendix I describes the simulations in which HIV incidence is increasing

ICER (£ per discounted QALY gained)		Time horizon (years)							
		10	20	30	40	50	60	70	80
Base case (HIV incidence declining)									
Current cost of ARVs		559,000	113,000	28,000	dominant	dominant	dominant	dominant	dominant
Reduction in the cost of ARVs	**10%**	510,000	100,000	22,000	dominant	dominant	dominant	dominant	dominant
	20%	461,000	86,000	17,000	dominant	dominant	dominant	dominant	dominant
	30%	412,000	73,000	11,000	dominant	dominant	dominant	dominant	dominant
	40%	363,000	60,000	6,000	dominant	dominant	dominant	dominant	dominant
	50%	314,000	46,000	200	dominant	dominant	dominant	dominant	dominant
	60%	265,000	33,000	dominant	dominant	dominant	dominant	dominant	dominant
	70%	216,000	19,000	dominant	dominant	dominant	dominant	dominant	dominant
	80%	167,000	6,000	dominant	dominant	dominant	dominant	dominant	dominant
	90%	118,000	dominant	dominant	dominant	dominant	dominant	dominant	dominant
HIV incidence increasing									
Current cost of ARVs		367,000	82,000	14,000	dominant	dominant	dominant	dominant	dominant
Reduction in the cost of ARVs*	**10%**	335,000	72,000	10,000	dominant	dominant	dominant	dominant	dominant
	20%	302,000	62,000	5,000	dominant	dominant	dominant	dominant	dominant
	30%	269,000	51,000	1,000	dominant	dominant	dominant	dominant	dominant
	40%	237,000	41,000	dominant	dominant	dominant	dominant	dominant	dominant
	50%	204,000	31,000	dominant	dominant	dominant	dominant	dominant	dominant
	60%	171,000	20,000	dominant	dominant	dominant	dominant	dominant	dominant
	70%	139,000	10,000	dominant	dominant	dominant	dominant	dominant	dominant
	80%	106,000	dominant	dominant	dominant	dominant	dominant	dominant	dominant
	90%	73,000	dominant	dominant	dominant	dominant	dominant	dominant	dominant

ARVs: antiretrovirals; ICER: incremental cost-effectiveness ration; PrEP: Pre-exposure prophylaxis; QALYs: quality adjusted life-years;

■ cost-saving (leading to a health benefit and saving in cost); ■ cost-effective (incremental cost-effectiveness ratio [ICER] below £13,000/QALY gained); ■ border-line cost-effective (ICER between £13,000-£30,000/QALY gained); ■ not cost-effective (ICER above £30,000/QALY gained);

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