Cost-effectiveness of pre-exposure prophylaxis for HIV prevention in men who have sex with men in the UK: a modelling study and health economic evaluation

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Summary

Background In the UK, HIV incidence among men who have sex with men (MSM) has remained high for several years, despite 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 uncertain.

Methods In this modelling study and economic evaluation, we calibrated a dynamic, individual-based stochastic model, the MSM HIV Synthesis Model, to multiple data sources (surveillance data provided by Public Health England and data from a large, nationally representative survey, Natsal-3) on HIV among MSM in the UK. We did a probabilistic sensitivity analysis (sampling 22 key parameters) along with a range of univariate sensitivity analyses to evaluate the introduction of a PrEP programme with sexual event-based use of emtricitabine and tenofovir for MSM who had condomless anal sexual intercourse in the previous 3 months, a negative HIV test at baseline, and a negative HIV test in the preceding year. The main model outcomes were the number of HIV infections, quality-adjusted life-years (QALYs), and costs.

Findings Introduction of such a PrEP programme, with around 4000 MSM initiated on PrEP by the end of the first year and almost 40 000 by the end of the 15th year, would result in a total cost saving (£1·0 billion discounted), avert 25% of HIV infections (42% of which would be directly because of PrEP), and lead to a gain of 40 000 discounted QALYs over an 80-year time horizon. This result was particularly sensitive to the time horizon chosen, the cost of antiretroviral drugs (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 is cost-effective and possibly cost-saving in the long term. A reduction in the cost of antiretroviral drugs (including the drugs used for PrEP) would substantially shorten the time for cost savings to be realised.

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Introduction

Sex between men is the predominant mode of HIV transmission in Europe and other high-income settings. In the UK, HIV incidence among men who have sex with men (MSM) has remained high, with around 3000 new HIV infections in 2014 and 2015, despite high levels of antiretroviral treatment (ART) coverage, virological suppression for those on treatment, and an expansion in HIV testing, although reports of numbers of new diagnoses suggest that there might have been recent declines. Additional prevention approaches are needed, of which a promising option is pre-exposure prophylaxis (PrEP) based on emtricitabine and tenofovir. This approach involves HIV-negative people taking the drug combination to reduce the risk of HIV infection. PrEP has been shown to be highly efficacious among MSM, whether used daily or in an event-based manner (ie, two pills 2–24 h before a sexual act, one for each consecutive day having condomless sex, for 2 days after the last sexual act), and effective in real-world conditions when used daily. However, when considering a PrEP programme in the UK for MSM, important questions are whether it is cost-effective from a health-system perspective (ie, the National Health Service [NHS] in the UK) and its budgetary impact. The aim of this study is to evaluate the cost-effectiveness of introducing event-based PrEP among MSM attending genitourinary medicine clinics in the UK in 2016. The choice of offering a sexual event-based PrEP regimen, rather than the daily regimen, was driven by the high efficacy of the event-based regimen reported in the IPERGAY study and its lower cost compared with the daily regimen. In the UK, there is a network of around 200 genitourinary medicine clinics, which offer sexual health advice, testing, treatment for sexually transmitted infections (STIs), and post-exposure prophylaxis (PEP) free of charge and confidentially to anybody. This network is envisaged to be the most pragmatic way of offering PrEP to MSM in the UK.

Methods

Study design

For this modelling study and health economic evaluation we used a dynamic individual-based simulation model (the HIV Synthesis Model), calibrated to the MSM HIV transmission model included in the National Institute for Health Research (NIHR) HIV Synthesis Model, to multiple data sources (surveillance data provided by Public Health England and data from a large, nationally representative survey, Natsal-3) on HIV among MSM in the UK. We did a probabilistic sensitivity analysis (sampling 22 key parameters) along with a range of univariate sensitivity analyses to evaluate the introduction of a PrEP programme with sexual event-based use of emtricitabine and tenofovir for MSM who had condomless anal sexual intercourse in the previous 3 months, a negative HIV test at baseline, and a negative HIV test in the preceding year. The main model outcomes were the number of HIV infections, quality-adjusted life-years (QALYs), and costs.

Findings

Introduction of such a PrEP programme, with around 4000 MSM initiated on PrEP by the end of the first year and almost 40 000 by the end of the 15th year, would result in a total cost saving (£1·0 billion discounted), avert 25% of HIV infections (42% of which would be directly because of PrEP), and lead to a gain of 40 000 discounted QALYs over an 80-year time horizon. This result was particularly sensitive to the time horizon chosen, the cost of antiretroviral drugs (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 is cost-effective and possibly cost-saving in the long term. A reduction in the cost of antiretroviral drugs (including the drugs used for PrEP) would substantially shorten the time for cost savings to be realised.

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Online See for appendix

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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 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 onward transmission. We combined search terms for PrEP (“pre-exposure prophylaxis”, “preexposure prophylaxis”, “PREP”, and “HIV”) with health economic terms (“cost”, “cost-effectiveness”, “cost effectiveness”, “ICER”, “cost-benefit”, “cost benefit”, “cost-utility”, “cost utility”, “health economics”, “economics”, and “economic evaluation”) and “transmission”. We found one report of a cost-effectiveness analysis of a PrEP programme among men who have sex with men (MSM) in the Netherlands. By use of a deterministic compartmental model calibrated to the Netherlands, the authors of this report concluded that the introduction of event-based PrEP in MSM in the Netherlands would be cost-effective at the current cost of emtricitabine and tenofovir over a 40-year time horizon. No such studies were done in the UK setting. The PROUD and IPERGAY trials showed that PrEP is highly efficacious and effective among MSM. We therefore 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, with similar eligibility criteria and assuming the programme will be delivered through the same system (genitourinary medicine clinics).

Added value of this study
Our study suggests that a PrEP programme offering sexual event-based use of emtricitabine and tenofovir to MSM results in a cost saving and a health benefit when considering an appropriately long time horizon (80 years). The patent protection on drugs used for PrEP expires in Europe in 2017–18 (a supplementary protection certificate for Truvada [Gilead Sciences, Foster City, CA, USA] expires in February, 2020). If the cost of antiretroviral drugs (used for PrEP and HIV treatment) is reduced from 2019 by 80%, introduction of such a PrEP programme would be cost-effective even when considering a 20-year time horizon.

Implications of all the available evidence
There is no doubt about the effectiveness of PrEP. Our work suggests that introduction of PrEP will—in addition to delivering a substantial health benefit—ultimately lead to a saving in costs, as a result of decreased numbers of men in need of lifelong HIV treatment. As antiretroviral drug patents expire over the next few years, the emergence of generic drugs might result in potentially large cost reductions for PrEP, and these reductions could help to limit the budget impact of PrEP and make it cost-effective over a relatively short time horizon.

epidemic in the UK that has previously been described in detail10 (see appendix p 1 for a brief description, pp 18–48 for details about the calibration, and pp 50–114 for full details). Ethical approval was not required for this work. A probabilistic sensitivity analysis was done to produce the main results, by sampling 22 key parameters (see appendix p 1 for the list of parameters sampled). 5965 simulations were done. 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 (five parameters); when estimating the incremental cost we considered the combination across all 22 parameters sampled in the probabilistic sensitivity analysis. The univariate sensitivity analyses were done by fixing the parameters that were sampled in the probabilistic sensitivity analysis.

PrEP policy options compared and main assumptions relating to PrEP
Two main scenarios were compared: one in which PrEP was not available and the other assuming that sexual event-based PrEP was introduced in April to June, 2016 (the proportion of pills taken was sampled; the mean corresponded to five pills per week). In both scenarios it was assumed that sexual behaviour, HIV testing behaviour, and the probability of initiating ART would remain at current levels. In the PrEP scenario, it was assumed that MSM were eligible for PrEP if they had a negative HIV test at PrEP initiation; they had reported condomless anal sexual intercourse in the previous 3 months (unless the only partner they had condomless sex with was a long-term partner virologically suppressed on ART); and they had an additional documented negative HIV test in the preceding year, similarly to the eligibility criteria for the PROUD study.18

The number of men eligible for PrEP in the UK, based on the above criteria, was estimated to be between 8400 and 12 200 (appendix p 2). This group was characterised (in the model) by an HIV incidence of around 2·0 per 100 person-years (90% range 0·7–4·3 per 100 person-years) in 2016, similar to the HIV incidence observed in repeat testers in genitourinary medicine clinics.19

Once PrEP has been started, we assumed that sexual event-based PrEP will be used in any subsequent 3-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; appendix p 128). However, men could restart PrEP with a mean
rate of 0.5 per year (a similarly wide variability is considered; appendix p 128) if having condomless sex again. We also assumed that the PrEP programme will be stopped if the overall HIV incidence in the MSM population drops below 1 in 1000 (ie, a decline of approximately five times compared with current HIV incidence).

We assumed that men on PrEP would be tested for HIV every 3 months, as recommended by the British Association for Sexual Health and HIV for MSM having condomless sex13 (and the US Centers for Disease Control and Prevention for people on PrEP14). 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 probabilistic sensitivity analysis) was assumed to be, on average 86%,10 reflecting both adherence and efficacy (the protection conferred when taken as prescribed).

### Outcomes and economic analysis

The main model outcomes were the number of HIV infections, quality-adjusted life-years (QALYs), and costs. In addition to the probabilistic sensitivity analysis, we did a range of univariate sensitivity analyses as outlined in the appendix (pp 3–6) to investigate the effect 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 probabilistic sensitivity analysis; appendix p 7). The cost (per year) of the antiretroviral drugs for treatment was assumed to be...
£6288 (Kevin Kelleher, London, personal communication [Freedom of Information request FOI-007334 made to NHS England]), whereas the mean cost (per year) of antiretroviral drugs for PrEP was £4331.15 The unit costs assumed (sampled in the probabilistic sensitivity analysis) are summarised in the appendix (pp 8–10) and were assumed to remain at the current level for the entire time horizon, although discounting was applied. In the base case, all costs and QALYs were discounted at an annual rate of 3.5%. A time horizon of 80 years was used, based on the National Institute of Health and Care Excellence (NICE) recommendations to consider a lifetime horizon.16

**Role of the funding source**

The National Institute for Health Research 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

In 2016, the year in which we assumed PrEP rollout would have started, the number of MSM living in the UK was estimated to be 725,200 (585,000 aged 15–64 years); 57,800 (53,900 aged 15–64 years) were estimated to be living with HIV and, with around 3,500 new HIV infections that year, HIV incidence was estimated to be around six per 1,000 person-years in MSM aged 15–64 years. We considered a PrEP programme for which uptake was such that, on average, around 4,000 MSM would initiate PrEP by the end of the first year, 16,600 would have ever been initiated on PrEP by the end of the fifth year (2020), and 38,900 by the 15th year (2030; figure 1A). This projection is considered to reflect a realistic gradual uptake. The mean time spent on PrEP among men initiated on PrEP is 4.5 years, according to this model.

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

The introduction of sexual event-based PrEP, by averting HIV infections (figure 1B, 1C), reduced the cumulative cost of HIV (table). Although 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 decline would occur around 10 years earlier if PrEP is introduced (figure 1D).

Figure 2 shows the undiscounted budget impact for HIV care and prevention (PrEP and PEP are included) for the next 80 years without the introduction of PrEP, with the introduction of PrEP, and their difference. The same estimate is presented assuming that the cost of antiretroviral drugs (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 antiretroviral drugs to treat people with HIV (44%) and on 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 30 years (figure 2A). With the introduction of PrEP (figure 2B), this peak is projected to occur 10 years earlier, in around 20 years.

The introduction of sexual event-based PrEP leads to an additional 40,000 discounted QALYs during an 80-year time horizon and a saving in costs (£1.0 billion discounted). Thus, during the 80-year time horizon, introduction of PrEP is cost-saving and therefore highly cost-effective. The cost-effectiveness plane (figure 3A) shows the uncertainty around our findings and the cost-effectiveness acceptability curve (figure 3B) shows that the probability of a PrEP programme being cost-effective is greater than 80% when considering a cost-effectiveness threshold greater than £20,000 per QALY gained (around 75% at £13,000 per QALY gained).

We did several one-way sensitivity analyses, summarised in figure 4 and described in the appendix (pp 3–6). In all sensitivity analyses related to costs (figure 4; S1–9), including analyses assuming the cost of daily PrEP rather than event-based PrEP, we found that during an 80-year time horizon the introduction of PrEP, as indicated, generates additional QALYs and is cost-saving.
Various other sensitivity analyses were considered (figure 4), including an effectiveness of 63% (the 90% lower confidence limit in the PROUD study,§ S10), assuming PrEP is used only in half of the 3-month periods when having condomless sex (S11), and assuming the proportion of condomless periods in which men initiated on PrEP have at least one condomless sex partner is 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 3-month periods when having at least one condomless sex partner, both the health benefits (23000 rather than 36000 discounted additional QALYs) and the cost savings (£673 million rather than £964 million) were considerably lower than they would have been if men used PrEP in 100% of 3-month periods when having condomless sex (S11).

Three other sensitivity analyses considered different sizes of the PrEP programme, either because of a lower (S13) or higher (S14) uptake than in the base case in the eligible population or by assuming that the size of the eligible population increases as a result of an assumed 15% of men who tested for HIV in the past year and who are having condomless sex coming forward for PrEP (S15). PrEP was cost-saving in all three scenarios: the larger the size of the PrEP programme, the larger the health benefit and cost savings.

In the context of higher background HIV incidence than in the base case (figure 4 [S16, S17]; appendix pp 14–17), the cost-effectiveness of introducing PrEP is even higher than in the base case, with more QALYs gained and greater savings in cost. However, if HIV incidence is lower than we have assumed in the base case
because of all people diagnosed with HIV starting treatment at diagnosis ($20), the introduction of PrEP is still cost-saving but the saving is slightly lower than in the base case. If the uptake of PrEP is concentrated in men at increased risk of contracting HIV ($19), the health benefit is slightly lower than in the base case because the size of the PrEP programme is smaller (appendix p 11), but the cost saving is even greater because 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 HIV incidence in the MSM population ($18) and in the context of MSM initiated on PrEP increasing, on average, by 25% the proportion of 3-month periods during which they have at least one condomless sex partner ($12) and having at least one condomless sex partner for life ($21). Even in these scenarios the introduction of PrEP was cost-effective.

Figure 5 shows how the cost-effectiveness of introducing PrEP varies according to different time horizons and different reductions in the cost of antiretroviral drugs. This evaluation 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 because of a moderate increase in sexual risk (appendix pp 14–17).

At the current cost of antiretroviral drugs, introduction of sexual event-based PrEP becomes cost-effective when considering a time horizon of 40 years or more. However, as the cost of antiretroviral drugs 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 antiretroviral drugs (for both PrEP and treatment) from 2019, PrEP would be cost-effective even when considering a 20-year time horizon (£6000 per QALY gained) and cost-saving during this time horizon if 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 STI diagnoses were reported among MSM in the UK. If there were to be 96 000 new STI diagnoses per year following the introduction of PrEP, its introduction would still be cost-saving if the average cost to treat an STI is £2000 or lower.

**Discussion**

The results of our modelling study and economic analysis suggest that the introduction of event-based PrEP among MSM in the UK with the eligibility criteria proposed is cost-saving and leads to health benefits, caused by a substantial reduction in HIV incidence among MSM. Our results are robust to substantial variations in the main assumptions. Although introduction of PrEP is cost-saving when considering 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 reach less than £13 000 per QALY gained.
Uptake of PrEP among the population eligible for it, and hence the size of the PrEP programme, is a crucial parameter for the budget impact of such a programme. Various surveys done in the UK among HIV-negative MSM reported that between 55% (among MSM who reported having sex without using a condom in the past 3 months and who had tested negative within the past 6 months; Ada Miltz, Fiona Lampe, Institute for Global Health, University College London, London, UK, personal communication) and 60% were interested in PrEP, 50% were willing to use it if it was available, and 2% had already used it. 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. Additionally, 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, as a result of greater numbers of men who are having condomless sex and have had a negative HIV test in the past year presenting for PrEP, introduction of PrEP has an even more important role in preventing HIV infections and is more cost-effective than the base case scenario.

In the main case scenario we assumed that HIV testing will continue at the current rate, since it is standard in health economic analyses to assume that the current situation will persist. However, testing rates have rapidly increased in the UK in 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 the number of new diagnoses has decreased in these clinics. Within our HIV Synthesis Model we predicted a decrease in HIV incidence as the proportion of people with HIV who are on ART increased because of increased testing and ART initiation at diagnosis, and we believe the observed decline 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 1 year in the number of different anal sex partners or in the proportion diagnosed with an STI, although the number of participants reporting receptive anal sex without a condom increased significantly. We investigated the effect of men starting PrEP increasing by 25% the proportion of 3-month periods in which they have at least one condomless sex partner and having at least one condomless sex partner in all subsequent 3-month periods; this assumption did not affect our main conclusions.

The reason why we observed a greater health benefit if people initiated on PrEP increasingly engage in condomless sex and use PrEP is that the greater the number of men using PrEP, the fewer the number of partnerships that are not protected by PrEP. In other words, those men who stay on PrEP for longer and continue having condomless sex are effectively protected from HIV when they have condomless sex partnerships, whereas if they had not started PrEP they would have a lifetime risk of contracting HIV.

Despite the strength of the evidence, one of the residual concerns about the introduction of PrEP is the potential spread of other STIs (including hepatitis C virus) 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 with the number of diagnoses in 2014) because of the introduction of PrEP, its introduction would still be cost-saving if the average cost to treat an STI is £2000 or lower.

The exact unit costs to the NHS for HIV drug treatment are confidential and it is uncertain by how much the cost of antiretroviral drugs will drop once the patents of antiretroviral drugs expire. The patent protection on drugs used for PrEP expires in Europe in 2017–18 (a supplementary protection certificate for Truvada [Gilead Sciences, Foster City, CA, USA] expires in February, 2020). It is expected that the cost of emtricitabine and tenofovir will decrease in the next 20 years, but there is uncertainty about reductions in the cost of other antiretroviral drugs used for treatment. In this regard we believe we have been conservative in using the cost of treatment from a Freedom of Information request (which is likely to be similar to the actual cost to the NHS) and the cost of Truvada for PrEP from the British National Formulary (since this was not available in the Freedom of Information request) and in assuming that the cost of emtricitabine and tenofovir and the cost of antiretroviral drugs used for treatment will decline by the same amount. These costs have a key role: the greater the reductions, the shorter the time horizon for PrEP to be cost-effective and cost-saving.

Cost-effectiveness analyses of PrEP introduction among MSM have been done in other high-income settings, including the USA, Australia, Canada, and the Netherlands. Most—but not all—analyses were done before the results of the PROUD and IPERGAY trials were reported and had therefore assumed a lower efficacy of PrEP than is now known, and most analyses considered a time horizon shorter than 80 years. The cost-effectiveness evaluation done in the Netherlands considered a time horizon of 40 years and concluded that the introduction of event-based PrEP in MSM in the Netherlands would be cost-effective at the current cost of emtricitabine and tenofovir, consistent with our findings for the UK.

Our study has several limitations. First, as with all mathematical models, the HIV Synthesis Model is a simplification of reality, and the uncertainty around our estimates is illustrated by considering the variation in the main assumptions. Second, the model estimates that around 80% of new HIV infections among MSM in the UK occur in men who are 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 engage in increased levels of condomless sex, the effect of PrEP could be even greater than was assumed in our modelling. Third, there is uncertainty over the parameter distributions to be used for the probabilistic sensitivity analyses, but we believe we have been conservative by choosing broad distributions, which means we could have conveyed more uncertainty than is actually present. Fourth, the population simulated by the model, because of computer capacity, is around 7% of the UK MSM population, which 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 the possibility that the variability reported is greater than the variability caused by the uncertainty in the parameters and the stochastic variability that would have been present 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 20 years, unless drug prices are substantially reduced.

Contributors
VC, AM, DD, SM, KJO, ONG, AN, MD, NF, GH, GC, YD, AR, and ANP contributed to the formulation of the research questions, provided critical input in the interpretation of results, and had substantial input in the drafting of the manuscript. VC and ANP worked on development and programming of the HIV synthesis model. VC did the modelling analysis. VC, AM, DD, SM, KJO, ONG, AN, MD, GC, AR, and ANP conceived and designed the experiments. VC and ANP did the experiments. VC, KJO, AM, ANP, ONG collected and defined the costs. VC and ANP analysed the data.

Declaration of interests
VC reports personal fees from Merck Sharp & Dohme (2015). SM was the principal investigator in the PROUD study, received entecavir and tenofovir free of charge, and received financial support for PROUD and personal fees from Population Council. ANP received personal fees from Gilead Sciences (2015), consultancy fees from GSK Biologicals (2012–14), and personal fees from AboVie (2013). AM has advised Gilead on a non-pecuniary basis (2015). MD received a grant from Gilead to investigate hepatitis C infection in the PROUD trial (2014). All other authors declare no competing interests.

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