Discussion paper: Estimates of the number of people eligible for PrEP in Australia, and related cost-effectiveness.

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1 Introduction

In late 2015, AFAO commissioned the Kirby Institute for Infection and Immunity in Society at the University of New South Wales to provide updated estimates of the number of people who would need to be on PrEP in Australia to realise PrEP's potential to reduce HIV notifications. The researchers were also asked to model the cost effectiveness of PrEP. The paper was informed by technical experts drawn from community, clinical and social research and other stakeholders.

This report lays out estimates of eligibility for HIV pre-exposure prophylaxis (PrEP) in gay men in Australia, following the Australasian Society for HIV Medicine (ASHM) Australian Commentary on the US Public Health Service Clinical Practice Guidelines on Prescribing PrEP (http://arv.ashm.org.au/arv-guidelines/prep-resources-for-clinicians). These guidelines are hereafter referred to as the ASHM commentary. The document also lays out cost-effectiveness estimates based on these eligibility estimates and scenarios of coverage, adherence and pace of scale up**.** Given the lack of precise estimates of some at-risk populations, it also provides information on the plausible ranges of these estimates.

The main purpose of this document is to provide the latest available estimates to inform the work of stakeholders working in this field, including but not limited to advocacy organisations, policy makers, funders, the pharmaceutical industry, the TGA and the PBAC.

2 Estimating the population eligible for PrEP

a) Background

Following the approval by the US FDA of HIV PrEP in July 2012, the US Centres for Disease Control (CDC) published PrEP clinical practice guidelines in 2014. These guidelines recommended HIV PrEP consisting of co-formulated tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) for adults at "substantial risk" of HIV infection. Among men who have sex with men, this was loosely defined by the CDC as those with an HIV positive partner, or with a recent bacterial sexually transmitted infection (STI), or with a high number of sex partners, or with a history of inconsistent or no condom use, or with a history of commercial sex work. Initial US estimates were that this would comprise about 25% of sexually active men who have sex with men (Smith et al., 2015). A 2014 study in San Francisco based on local behavioural surveillance data estimated that 64% of HIV negative sexually active men who have sex with men in that setting would meet the CDC PrEP criteria, but that only 15% of these men were actually using PrEP (Snowden et al., 2017).

Australian researchers and clinicians first considered state-based PrEP guidelines soon after the publication of the CDC guidelines in 2014. In NSW, a multi-disciplinary group was tasked by NSW Health with developing state-based guidelines. The researchers, clinicians and community representatives on this group were concerned that the US behavioural PrEP eligibility criteria for men who have sex with men were too widely defined and did not adequately contextualise high HIV risk behaviour. Initial guidelines used data on HIV incidence from Australia's most recent HIV risk factor cohort study, the Health in Men cohort (HIM) study conducted in Sydney, NSW (Poynten et

al., 2010). Although follow-up in that study ceased in 2007, the annual number of diagnoses in MSM in NSW remained roughly stable to 2016. In the HIM study, the HIV incidence in sexually active gay men overall was 0.78 per 100 person years, but there were easily identifiable subgroups of gay men who had an incidence of HIV of at least 2% per year (the subgroup with the highest HIV incidence was men with a diagnosis of rectal gonorrhoea in the last 6 months, who had an HIV incidence of 7.0 per 100 person-years (Jin et al., 2010). These data were then adjusted to form clinically meaningful and easily measurable risk behaviours which could comprise a pragmatic definition of high-risk which would determine eligibility, as outlined in Table 1 below.

Table 1: Factors associated with high risk of HIV acquisition among MSM in the Health in Men (HIM) study, Australia, 2001-07, and their translation into eligibility criteria for PrEP in Australia[1].

Findings of the HIM study		PrEP eligibility criteria
High–risk factor	**HIV incidence per 100 person years (95% confidence interval)**	
A regular sexual partner of an HIV-positive man with whom condoms were not consistently used in the last six months	5.36 (2.78-10.25)	A regular sexual partner of an HIV-infected men (***not on treatment and/or detectable viral load***) with whom condoms were not consistently used in the last three months
At least one episode of receptive unprotected anal intercourse with any casual HIV-infected or unknown HIV status male partner during the last six months	2.31 (1.48-3.63)	At least one episode of receptive condomless anal intercourse (CLAI) with any casual HIV-infected male partner or a male partner of unknown HIV status in the last three months
Rectal gonorrhoea diagnosis in last six months	7.01 (2.26-21.74)	Rectal gonorrhoea, rectal chlamydia or *infectious syphilis* diagnosis in the last three months or at screening for PrEP
Rectal chlamydia diagnosis in last six months	3.57 (1.34-9.52)	
Methamphetamine use in last six months	1.89 (1.25-2.84)	Methamphetamine use in last three months

[1]Table adapted from draft ASHM HIV Pre-Exposure Prophylaxis: Clinical Guidelines, 2017

At the outset, it was recognised that in defining high risk there were differences between ***research-measured*** risk factors such as in the HIM study data and ***clinically pragmatic*** measures of high risk. The most important of these differences was that while the research and behavioural surveillance measures generally related to a 6-month period, clinicians recommended that measures for clinical use should relate to a 3-month period to facilitate assessment and initiation of PrEP, and follow up with 3 monthly monitoring and drug supply. This means that exact estimates of the populations at high-risk are not possible as some form of assumption is required to make the data from Australian behavioural surveillance data fit the data required for estimation of clinically meaningful "high-risk" groups. Using a 3-month period of risk instead of the research-based 6-month period of risk would tend to lead to some over-estimation of populations at risk of PrEP.

b) Initial (2015) PrEP eligibility estimates

In 2015, the Kirby Institute undertook estimates of the number of gay men in Australia at high risk to HIV infection eligible for PrEP. These estimates were based on definitions of high HIV risk contained

in the NSW PrEP guideline which were later adapted for ASHM's commentary. The initial estimates were based on the following data points and calculations.

1. The Australian Bureau of Statistics (ABS) reports the population of males aged 16 to 69 in 2015 to be 8,287,110.
2. In the population-based Second Australian Study of Health and Relationships (ASHR2, conducted in 2012-2013), the proportion of men aged 16 to 69 who identified as gay was 1.88%, equivalent to 155, 798 gay men in 2015. (Men who identified as bisexual (1.3% of the sample) were not included in estimates of PrEP eligibility, because it was felt that such men would be much less likely to be prepared to present to a doctor and discuss their homosexual behaviour in a way which would be required for PrEP access. In addition, behavioural data on bisexual men, while being relatively limited, suggest that bisexual men have lower HIV risk behaviour than gay-identifying men. In EPIC-NSW, 95% of participants identify as gay compared to 4% who identify as bisexual (unpublished data), further supporting the presumption that few bisexual-identifying men will present for PrEP.
3. At the end of 2014, 20 537 MSM were living with HIV (uncertainty range 18,797 – 22,892)
4. In ASHR2, among gay-identified men aged 16 to 69, 81.9% reported same-sex sexual experiences in the last 12 months, leaving 110,779 sexually active HIV negative gay men.

Further calculations of numbers of men eligible for PrEP are based on this estimate of **110,779** sexually active HIV negative gay men aged 16-69 in Australia in 2015.

Estimates of gay men in categories who have specific risk criteria were based on behaviours and STI history reported by sexually active men in the gay community periodic surveys (GCPS). The GCPS forms the basis of Australia's behavioural surveillance for HIV risk behaviours. Surveys are conducted in gay community settings in the major cities of Australia annually or biennially, and data used in this report were from 2015 or the most recent year for those jurisdictions which do not conduct the survey annually.

As receipt of PrEP under the guidelines was conditional on the likelihood that risk behaviour would continue (and was not only in the past), it was felt that a measure of likely future behaviour was required. There was no direct research measure of this measure of future behaviour, but in the 2015 estimates Australian Gay Community Periodic Survey data on having at least 10 casual partners in the last 6 months were used in the estimates as a rough indicator of men who may be likely to have continuing risk. This is likely to have led to a degree of under-estimation of the populations at risk (some men who acquire HIV have fewer than 10 casual partners in a 3- or 6-month period).

Using this methodology, and based on the behavioural risk factors described in Table 2 (see below), Kirby estimated that 12% of sexually active gay men in Australia would be eligible for PrEP (equivalent to 13293 men). This figure was used as a key input to estimate the number of high risk MSM eligible for PrEP through access studies commenced in 2016 in NSW (EPIC), Victoria (PrEPX) and Queensland (QPrEP).

c) Updated 2017 estimation of PrEP eligibility

To inform future PBAC submissions and further initiatives to provide PrEP in Australia, the Kirby Institute and the Centre for Social Research on Health has developed a new estimate of the number

of MSM at high risk of HIV. The key change has been to modify the criteria to be more clinically pragmatic, and less restrictive using updated data sources. This has drawn on many inputs including the following

1. Experience from Australian clinical access studies currently providing PrEP to around 7000 individuals at high risk to HIV in NSW, Victoria and Queensland. The most advanced of these, EPIC-NSW, had by June 2017 recruited about 2500 participants more than the original estimate of 3700 and continues to recruit 50-80 new participants each week, albeit at a rate greatly reduced from the rate in early 2016 when 100-150 participants per week were enrolled. Victoria reached its estimate of 2600 participants in the PrEPX study and the study was expanded to allow more enrolment.
2. Experience from comparable settings who are rapidly rolling out PrEP, notably in France, and the USA (California, New York, Washington State) that in 2015-2016 roll-out of PrEP to gay men had considerably accelerated.
3. Draft updated PrEP eligibility criteria contained in clinical guidance provided by ASHM which recommended more practitioner discretion in applying the high-risk guidelines.
4. WHO guidelines, which recommend PrEP in populations with an HIV incidence of 3% per year or more. In fact, we chose risk groups, based on HIM study data, with an annual HIV incidence of more than approximately 2%, as in Australia there are few easily-identifiable subgroups of gay men with an incidence of more than 3%.
5. The position of PBAC in the response to Gilead's unsuccessful PBAC PrEP submission that further applications for PrEP listing on the PBS should not seek to unreasonably limit the eligible population.

In addition, new estimates of MSM living with HIV were released in the Kirby Institute 2016 annual surveillance report (ASR), and these were 7.1% lower than those in the 2015 ASR. These estimates were that an estimated 19, 067 MSM were living with HIV (uncertainty limits of 16 944 – 21 341), leaving a central estimate of 136,731 HIV negative gay men.

In summary, these new eligibility estimates are substantially higher than the previous estimates, relating to the adjustments of initial calculations in the table below, the use of more updated risk estimates from the gay community periodic surveys (GCPS).

It is important to acknowledge that behaviour change in the community would also lead to changes in the proportion of gay men who are eligible for PrEP.

Table 2: Differences between 2015 estimates of PrEP eligibility and updated estimates.

	Initial 2015 estimates of high-risk gay men eligible for PrEP (based on available 2014/15 data)	**Updated estimates of high-risk gay men eligible for PrEP (based on 2015/16 data)**
Population of MSM living with HIV	20,537(Kirby ASR 2015)	19,067 (Kirby ASR 2016)
Population of sexually active HIV negative MSM aged 16-69	110,779	111,983
Risk behaviour requirements (last 6 months, from gay community periodic surveys)		
Requirement for ongoing risk	For each category below, men also were required to have at least 10 casual partners in the last 6 months	No requirement: it is assumed that men who have the risk factors below are likely to have ongoing risk.
Receptive condomless anal intercourse with casual partners	Often	>= one episode (15.4%)
Methamphetamine use	Monthly or more	>= once (9.2%)
CLAI with regular partner who has detectable viral load	At least once	At least once (no change) (0.1%)
Anal STI or syphilis	Any STI	Any STI plus a rectal swab or a syphilis test (10.5%)
Results		
Number of gay men eligible for PrEP under high-risk criteria	13,293	31,502
Percent of sexually active gay men eligible for PrEP under high-risk criteria	12%	28%

Medium risk: The draft *ASHM HIV Pre-Exposure Prophylaxis Clinical Guidelines, 2017* also contain two medium risk criteria. The guidelines recommend that PrEP be considered in men reporting these behaviours. These are:

1. Reporting more than one episode of anal intercourse during the last 3 months when condoms broke or slipped off during intercourse (HIV incidence in HIM of 1.3 per 100py).

2. For uncircumcised men only, having at least one episode of insertive condomless anal intercourse where the serostatus of partner is not known or is HIV-positive (HIV incidence in HIM of 1.7 per 100 person-years).

There are difficulties in estimating the proportion of the population who would fit these categories. Regarding condom breakage, data on breakage during anal intercourse in Australia are sparse. Unpublished data from the Health in Men study suggest this occurs in about 1% of HIV negative gay men in a 6-month period, but this is almost entirely in men who report one of the high-risk criteria above. Thus, this criterion is unlikely to add substantially to the total pool of men requiring PrEP, unless condom breakage/slippage is over-reported.

Based on reasonable estimates of the proportion of uncircumcised men, which is much higher in younger than older men, about 2% of gay men might fit into this category, but again, many of these men are likely to report a high-risk behaviour.

Overall, it is unlikely that more than 4% of sexually active gay men would fit into this medium-risk category.

Heterosexual people and injecting drug users: The draft ASHM HIV Pre-Exposure Prophylaxis Clinical Guidelines, 2017 recommend PrEP in heterosexual people and injecting drug users only in very limited circumstances. These are likely to involve very small numbers and we have not made formal estimates of eligibility under these criteria.

Box 1: Risk criteria for MSM to identify their eligibility for PrEP, from DRAFT 2017 Australasian Society for HIV Medicine HIV Pre-exposure Prophylaxis Clinical Guidelines.

<table>
<tr><td colspan="3">A. High risk – recommend prescribing daily PrEP if the patient acknowledges</td></tr>
<tr><td>Having had any of the following in the last 3 months
At least one episode of condomless anal intercourse with a regular HIV + partner (not on treatment and/or detectable viral load)
At least one episode of receptive CLAI with any casual HIV + male partner or a male partner of unknown status
Rectal gonorrhoea, rectal chlamydia or infectious syphilis diagnosis (during the last 3 months or at screening for PrEP)
Methamphetamine use which may lead to an increased risk of HIV acquisition</td><td>AND</td><td>Being likely to have in the next 3 months
(indicating sustained risk)
Multiple events of condomless anal intercourse (CLAI)
With or without sharing intravenous drug equipment</td></tr>
<tr><td colspan="3">B. Medium risk – consider prescribing daily PrEP, based on case by case approach if discussion reveals</td></tr>
<tr><td>Having had any of the following in the last 3 months
More than one episode of anal intercourse when proper condom use was not achieved (e.g. condom slipped off or broke) where the serostatus of partner was not known, or was HIV + and not on treatment or with a detectable viral load
(if patient uncircumcised) more than one episode of insertive CLAI where the serostatus of partner was not known, or was HIV + and not on treatment or with a detectable viral load</td><td>AND</td><td>Being likely to have in the next 3 months
(indicating sustained risk)
Multiple events of condomless anal intercourse (CLAI)
With or without sharing intravenous drug equipment</td></tr>
<tr><td colspan="3">Case by case approach
If, based on a complete sexual and drug-using history, and the personal circumstances of the patient, the doctor believes they are likely be at high-risk of HIV, then PrEP prescription may be considered despite the absence of the high- or medium risk factors above.</td></tr>
</table>

3 Cost-effectiveness analyses

a) Possible proportions of gay men receiving PrEP

A range of scenarios are possible with respect to use of PrEP at the population level. As the likely numbers of recipients who receive PrEP based on heterosexual behaviour or IDU is believed to be small, we have confined these analyses to gay identifying men. We do not believe high levels of uptake are likely in bisexual men (1.3% of adult males aged 16-69), for reasons outlined above, and as supported by the fact that only 4% of participants in EPIC NSW enrolled in 2016 identified as bisexual. The following categories were developed. Although further categories could be added, we believe this gives us a reasonable range based on current calculations of those at risk.

Table 3: PrEP usage scenarios for cost-effectiveness analysis.

PrEP usage scenarios	Percentage of high risk gay men who receive PrEP (approximately 28% of gay men)	Percentage of medium risk gay men who receive PrEP (approximately 4% of gay men)	Percentage of all other gay men who receive PrEP. (approximately 68% of gay men)	Scenario name
Use only in high-risk gay men, lowest uptake	30%	0%	0%	Scenario30-0-0
Use only in high-risk gay men, medium levels of uptake	60%	0%	0%	Scenario60-0-0
Use only in high-risk gay men, highest plausible uptake	90%	0%	0%	Scenario90-0-0
High uptake in high risk, low uptake in medium risk	90%	20%	0%	Scenario90-20-0
High uptake in high risk, medium-high uptake in medium risk	90%	60%	0%	Scenario90-60-0
High uptake in high risk, some uptake in both medium and low uptake	90%	20%	10%	Scenario90-20-10
High uptake in high risk, higher uptake in medium and low risk	90%	60%	30%	Scenario90-60-30
90% of gay men use PrEP, regardless of risk	90%	90%	90%	Scenario90-90-90

b) Cost-effectiveness

The detailed methods used to determine cost-effectiveness of PrEP as a public health intervention are detailed in the Appendix. The following is a summary. All monetary values are given in Australian dollars.

(i) Summary of methods

- We developed a HIV transmission mathematical model and determined what impact PrEP would have on reducing HIV among Australian gay men in a range of usage scenarios (Table 3, see above) and willingness to pay thresholds, and initially assumed the following: 1) PrEP unit cost is $10,249; 2) scale up occurred over a 3-year period; 3) high adherence (90%) resulting in very high efficacy (99%) and 4) no reduction in condom use.
- We assumed the current estimated PrEP unit cost is $10,249 based on the 2015 dispensed price for maximum quantity (DPMQ) of tenofovir with emtricitabine on the Pharmaceutical Benefits Scheme website (see Tables A2-A5 in the Appendix). The actual amount paid by government is commercial-in-confidence. We assessed lower unit costs needed for PrEP to be cost-effective.
- We assumed three years for scale up to reach the usage coverage levels based on the clinical capacity and experience of rolling out PrEP programs in jurisdictions during 2016, and assessed the impact of scaling up in shorter periods.
- A high level of 90% adherence was assumed based on emerging evidence from Australian demonstration projects, including measures based on biological assays in the PRELUDE study which were presented at the ASHM conference in 2016 (Zablotska, 2016). We also assessed the impact of PrEP if there were lower levels of adherence (70%, 50% and 30%) and assumed efficacy at these lower levels based on the Anderson et al study [18] which estimated an HIV-1 risk reduction of 99% for seven doses per week, 96% for four doses per week, and 76% for two doses per week.
- We estimated the unit cost required for the PrEP intervention to become cost-effective at $30,000, $60,000 and $90,000 willingness-to-pay thresholds (Table 4, see below) as well as the total cost (Table 5, see below). Willingness-to-pay thresholds are a subjective value determining whether a program is 'cost effective' or if it is 'cost effective' to switch from one program to another and reflects the maximum amount the health sector is willing to pay to procure a good or avoid something undesirable. These three thresholds were selected to encompass a broad range of potential outcomes as the Pharmaceutical Benefits Advisory Committee (PBAC) does not use a specific cost-effectiveness threshold for inclusion onto the PBS.
- Based on data from the Gay Periodic Survey, at baseline we assumed 47% and 42% of high-risk gay men taking PrEP used condoms with casual and regular partners respectively, and assessed the impact if condom use decreased by 10%, 30% and 50% (for those taking PrEP and overall).

(ii) Projected impact of PrEP on reductions in new HIV infections

The HIV model showed that PrEP interventions are projected to have a large impact on new HIV infections over 2016-2030 particularly if a high coverage is reached in the high-risk gay men, who make up 28.2%, or 31,700 (range: 25,400-38,100) of HIV-negative gay men (Table A7 and Figure A8 in the Appendix). Expanding PrEP to medium-risk gay men reduces new infections minimally due to

the relatively small population size of medium risk men, as defined in the ASHM guidelines. Expanding PrEP to low-risk gay men does result in some additional new infections averted but this is small relative to the population size (67.8% of all HIV-negative gay men).

(iii) Cost-effectiveness considering different PrEP usage scenarios

Table 4 shows the PrEP unit cost needed for difference usage scenarios to be cost-effective and willingness to pay thresholds. Table 5 shows the total costs of these scenarios to the health system at the $60,000 willingness to pay threshold.

The current estimated PrEP unit cost (of $10,249) would need to fall by 26-47% for the scenarios in which PrEP is used only by high-risk gay men to be cost-effective (Table 4). This would result in an incremental cost per annum of $8,214,000-$18,421,000 considering 9,450-28,350 gay men will receive it in 2016.

For the **Scenario90-0-0** (where coverage in restricted to 90% of high-risk men only) the unit cost would need to be $5,420 (incremental cost per annum of $18,421,000), ranging from $4,090 to $6,740 for the lower and upper thresholds, respectively (Table 4).

For the **Scenario90-20-10** where PrEP is provided to 90% of high-risk men, 20% of medium risk men and 10% of low-risk men, PrEP unit cost would have to fall to $4,120, or total incremental costs per year of $20,554,000 (Table 5).

In a scenario where PrEP coverage further expands to medium-risk men (**Scenario90-60-0**) the unit cost needs to be $4,920, and when it expands to medium and low risk gay men (**Scenario90-60-30**), the unit cost would need to be $2,860 to be cost effective, or total incremental costs per year of $22,169,000 (Table 5).

Finally, in a scenario where 90% of all gay men (high, medium and low) received PrEP (**Scenario90-90-90**, the PrEP unit cost would have to fall to below $1,700 per year, or total incremental costs per year of $25,733,000 for all men (Table 5).

PrEP is more cost-effective if it is prioritized to men at highest risk of HIV. When coverage is expanded from **Scenario90-0-0** to medium-risk men (**Scenario90-60-0**) the unit cost needed to be cost effective drops only moderately by $500. However, when coverage is expanded from **Scenario90-0-0** to low-risk risk men (**Scenario90-60-30**), the unit price needs to drop considerably, by $2,560 to be cost effective.

Table 4: PrEP unit cost required per year to be cost effective at three different willingness-to-pay thresholds, for all the usage scenarios. Ranges available in Table A7 of the appendix.

Percent of gay men receiving PrEP, by HIV risk			**Willingness to pay threshold (median)**		
High-risk	Medium-risk	Low-risk	30k per QALY	60k per QALY	90k per QALY
30%	0%	0%	$5,690	$7,580	$9,480
60%	0%	0%	$4,780	$6,350	$7,920
90%	0%	0%	$4,090	$5,420	$6,740
90%	20%	0%	$3,970	$5,250	$6,530
90%	60%	0%	$3,730	$4,920	$6,100
90%	20%	10%	$3,120	$4,120	$5,100
90%	60%	30%	$2,150	$2,860	$3,560
90%	90%	90%	$1,300	$1,700	$2,110

Table 5: Total costs to health system.

Percent of gay men receiving PrEP, by HIV risk			**Unit cost to be cost-effective at 60k per QALY (median)**	**Average annual incremental cost 2016-2030 (nearest $1000, median)**
High-risk	**Medium-risk**	**Low-risk**		
30%	0%	0%	$7,580	$8,214,000
60%	0%	0%	$6,350	$14,310,000
90%	0%	0%	$5,420	$18,421,000
90%	20%	0%	$5,250	$18,548,000
90%	60%	0%	$4,920	$18,865,000
90%	20%	10%	$4,120	$20,554,000
90%	60%	30%	$2,860	$22,169,000
90%	90%	90%	$1,700	$25,733,000

(iv) Variation in cost-effectiveness estimates considering scenarios of unit cost, adherence, usage patterns, speed of scale up and condom use

a. ***Unit cost:*** If we assumed the agreed generic price of PrEP is $1000 per unit (around 10% of the current PBS cost), then all the PrEP scenarios would be cost—effective, and the Scenario90-0-0 would be cost-saving (see Appendix Figure A11).

b. ***Adherence:*** Reducing adherence to moderate levels only slightly reduces the epidemiological impact of the PrEP intervention. This is because PrEP efficacy does not reduce substantially until the number of pills taken per week falls below three with efficacy remaining at 75% even if only two pills are taken per week (assumed efficacy for 7, 5, 3, 1 pills per week is 99%, 97%, 90%, 77%, 45% respectively; Figure A7 in the Appendix). Given efficacy is maintained despite a lower adherence, this has the effect of greatly increasing the cost-effectiveness of PrEP (as the PrEP costs are lower as men require fewer pills per year) (Figure A12 and Table A8 in the Appendix). If a lower adherence reflected men were taking PrEP on 'demand' then such a scenario would be even more cost-effective (as long as PrEP was taken at the appropriate time, so that high levels of efficacy are maintained).

c. ***Condom use:*** If the presence of a PrEP program reduces the level of condom use in gay men taking PrEP, then we project only a small increase in new infections overall (compared to the no risk compensation scenario) and a corresponding small reduction in cost-effectiveness (Figures A13-A14 in the Appendix). This is because at high adherence PrEP is highly effective at preventing HIV transmission and essentially replaces the need for condoms with respect to reduction in HIV transmission risk. However, such a scenario would likely lead to an increase in other sexually transmitted infections (not costed here). If there is a reduction in condom use across all gay men, even in those not taking PrEP—potentially due to a general belief of lower risk—then the effect of PrEP will be reduced slightly but will not counteract the overall benefits of PrEP (Figures A13-A14 and Table A9 in the Appendix).

d. ***Scale up duration:*** Taking less than three years to reach the intervention coverage increases the impact and cost-effectiveness of PrEP interventions. This highlights the importance of scaling up PrEP programs as fast as possible to maximize the benefit (Figure A15 and Table A10 in the Appendix).

4 References

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5 Appendix – detailed modelling methods and further results

To evaluate the cost-effectiveness of providing PrEP in Australia we applied a previously developed HIV transmission model. The model is a general dynamic, population-based compartmental model based on a precursor of the Optima HIV model [1] known as Prevtool. The Prevtool model has been used to evaluate the cost-effectiveness and return on investment of HIV programs in a number of settings [2–4]. We developed a version of Prevtool which incorporated all the features of Optima (as described in detail elsewhere [1]) and to specifically evaluate the impact and cost-effectiveness of HIV interventions (such as PrEP) in Australia. All analyses and results were obtained using Matlab 2014a with figures produced using R version 3.3.0 in Rstudio 1.0.44 using ggplot 2.2.0. Full details of the software used, fully reproducible code, and input data spreadsheets are available from on request in line with recommended reproducibility guidelines for computational methods [5].

a) Model summary

Our model partitions the overall Australian population by population group and by HIV health state. For each population group the model tracks the people living with HIV (PLHIV) across four stages of CD4 count: >500, 350–500, 200–349, and < 200, cells per microliter. The key steps of the HIV diagnosis and care cascade are included: from infection to diagnosis, initiation of first-line anti-retroviral therapy (ART), treatment failure, subsequent lines of therapy, and HIV/AIDS-related or other death. HIV infections occur through the interaction between different populations by regular, casual, or commercial (including transactional) sexual partnerships, through sharing of injecting equipment. The rate that uninfected individuals become infected depends on the number and type of risk events (such as condomless sexual intercourse or sharing of syringes) to which individuals are exposed in each period (either within their population groups or through interaction with other population groups) and the infection probability of each event. The value of this transmission rate varies across CD4 count compartments (indirectly reflecting the higher viral load at early and late stages of infection) and differs for different modes of transmission (intravenous drug injection with a contaminated needle–syringe, penile–vaginal intercourse or penile-anal intercourse), and by interventions and treatment [6–8]. We did not consider mother-to-child transmission for this analysis.

We partitioned the Australian population into 11 sub-populations:

- Female sex workers;
- Clients of female sex workers;
- Sexually active gay men at low-risk of infection;
- Sexually active gay men at medium-risk of infection;
- Sexually active gay men at high-risk of infection including those who inject drugs;
- Males who inject drugs;
- females who inject drugs;
- Other males 16-69 years old;

- Other females 16-69 years old;
- Males older than 69 years; and
- Females older than 69 years.

We assume sexual activity begins at 16 years of age and people are no longer at risk of HIV infection after 69 years of age. This is based on available behavioural data from the 2014 Australian Survey of Sex and Relationships study which recruited 16-69-year-olds and because very few HIV notifications occur in people over 70 years old (only 1.3% of notifications occurred in the 70+ age group in 2015) [9,10]. Individuals are assigned to a given population group based on their dominant risk of acquiring HIV — however cross-modal types of transmission are captured by setting relevant behavioural parameters to nonzero values (e.g., some gay men may also inject drugs). The first nine populations include people younger than 70 years of age. People in these populations move in to the 70+ population groups as they age and are assumed to be no longer at risk of acquiring HIV. For this analysis, we focus on the low, medium and high-risk gay male sub-populations as the Australian Society of HIV Medicine (ASHM) draft PrEP guidelines focus on these populations (see Table 3 in the main text). The other populations are included in the model to ensure it captures the overall HIV epidemiology and matches data for national HIV indicators [10].

Estimates for the population size of each sub-population come from various sources. We used the definition and population estimate for high, medium, and low risk gay men in 2015 as per the 2017 estimates in the main text. The sizes of the male and female population who inject drugs were based on recent estimates of the number of people who have injected drugs in the previous 12 months (NDARC estimates under review). There are no official estimates for number of FSW and clients in Australia. We used an estimate of 30,000 FSW based on expert opinion and assumed 2% of 15-69 year old males based on 2014 Australian Survey of Sex and Relationships data for men who had paid for sex in the previous 12 months [11]. Finally, estimates for the general population younger and older than 70 years came from the Australian Bureau of Statistics using the June estimate for each year (series no: 3101059 released December 2016; http://www.abs.gov.au/AUSSTATS/abs@.nsf/mf/3101.0) with adjustments for the at-risk population estimates.

b) Model calibration

Using available demographic, epidemiological, behavioural, and clinical data, we calibrated the model to reflect the HIV epidemic in Australia over 2000-2015 and future trends up to 2030 (corresponding to the period of analysis). The purpose of calibration is to ensure the simulated epidemic over 2000-2025 appropriately represents the HIV epidemic and trends in Australia. We primarily used notifications data from the National HIV Registry and estimates from Australia's HIV Cascade over 2000-2015 using the methodology and data sources described in the 2016 Annual Surveillance Report [10]. Australia has limited information on HIV prevalence and incidence for specific populations, but we calibrated the model to produce reasonable estimates of these indicators based on survey data [10,12,13] and HIV cascade estimates [10]. Estimates of new infections from back-projection models using CD4 count at diagnosis generally align with notifications [14–16].

To calibrate the model, we used a two-stage process. First, we calibrated the model to

- prevalence estimates for each population;
- the number of notifications of HIV (overall and male-to-male sex for all GBM, injecting drug use for PWID, and other for the remaining populations);
- the overall estimate for number of people living with diagnosed HIV;
- the overall estimate for the number of people taking ART;
- the coverage of ART in people living with diagnosed HIV;
- the estimated population sizes for each gay man risk group;
- maintain background PrEP use at 3% (in line with 2015 estimates [17]); and
- produce new infections after 2015 that remain stable or slightly decline assuming effective ART reduces transmission probability by ~90%.;

by hand-tuning the model parameters and visual inspection. We then used the manually calibrated simulation to produce an ensemble of 50 simulations by fitting the model to the simulated prevalence for each population, the simulated number of overall new infections, the simulated overall number of diagnoses and the simulated overall number on treatment from the manually fitted simulation. The resulting fits were obtained automatically using a semi-Bayesian process with empirical estimates for the model parameter values interpreted in Bayesian terms as prior distributions. This process was repeated until we obtained an ensemble distribution with a median and mean aligned with the hand-tuned fitted simulation.

Figures A1 to A6 show the resulting simulated epidemic projections compared to available data. The figures show a single “best fit” simulation from the hand-tuned model calibration compared to the median and mean for an ensemble of simulations (used to reflect the uncertainty in these estimates). We generated all the results from this analysis using the 50 ensemble simulations using the median values and range.

Figure A1: Calibration of model to the number of diagnoses in gay men, PWID, and other populations. Data points represent notifications data in the National HIV registry. The solid lines are the corresponding median estimates and the shading shows the range for the ensemble simulations. (Left) Simulated new diagnoses for overall, gay men, PWID and other populations the solid curves represent the median values of the ensemble simulations with shading showing the range. (Right) New diagnoses for the overall population with the black line for the hand-tuned simulation and the blue and red lines are the median and mean of the ensemble simulations respectively.

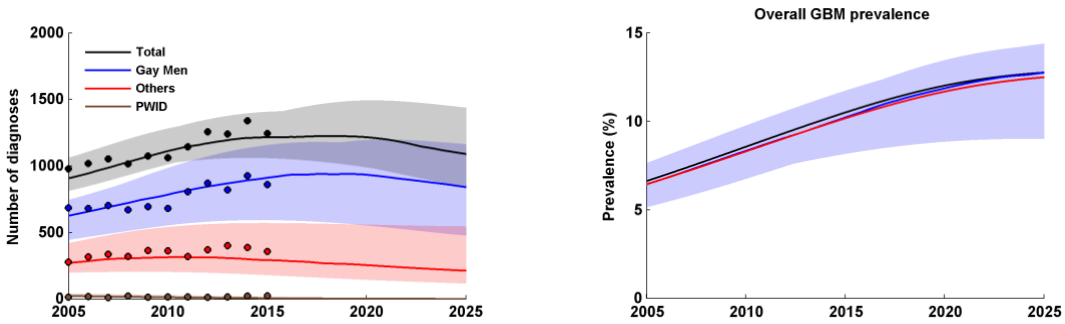


Figure A2: Calibration of the model to the number of people living with diagnosed HIV (PLDHIV). Data points represent estimates from Australia's HIV cascade. The black line is the hand-tuned simulation and the blue and red lines are the median and mean of the ensemble simulations respectively.

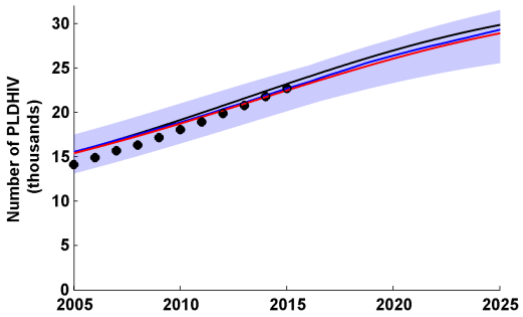


Figure A3: Calibration of the model to the estimated number of people on ART (left) and ART coverage for PLDHIV (right) in Australia. The black discs represent available data or estimates. Data for the number of people taking ART are from AHOD 2000-2012 and the PBS 2013-2014. The number of people taking ART divided by the estimate for PLDHIV from the HIV cascade gives the datum for treatment coverage. The black line is the hand-tuned simulation and the blue and red lines are the median and mean of the ensemble simulations respectively.

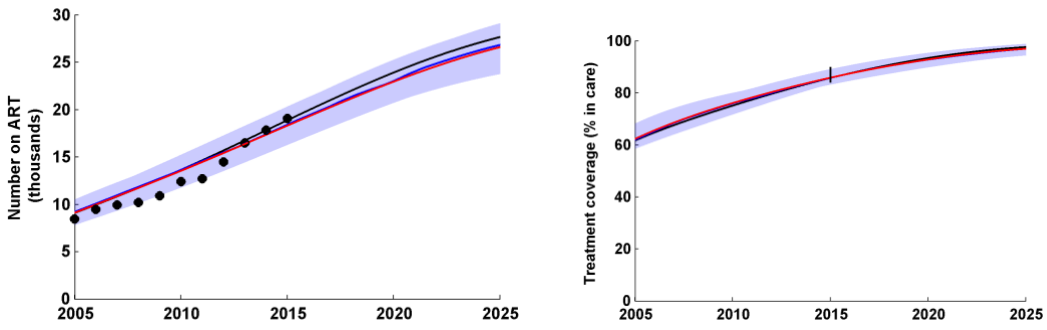


Figure A4: Simulated HIV prevalence in GBM by at-risk category (left) and in the overall GBM population (right) in Australia. There are no specific data available to inform the model calibration. The model calibration aimed to reflect expected prevalence in this population. (Left) The solid lines are the corresponding median estimates and the shading shows the range for the ensemble simulations. (Right) The black line is the hand-tuned simulation and the blue and red lines are the median and mean of the ensemble simulations respectively.

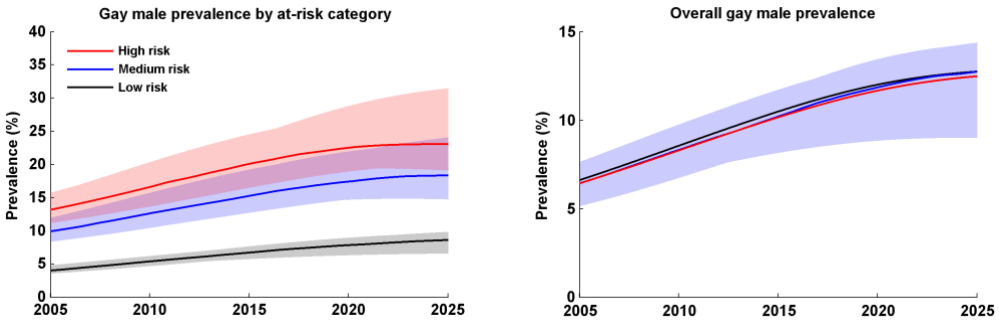


Figure A5: **Calibration of model to HIV prevalence in non-GBM populations.** Black points represent available HIV prevalence estimates from other models, available surveys, other data sources or expert opinion. Lines attached to these discs represent broad uncertainty bounds. The solid curve is the corresponding model simulation. Note prevalence data points for CSW, Males 70+, and Females 70+ are assumptions used for guidance. The black line is the hand-tuned simulation and the blue and red lines are the median and mean of the ensemble simulations respectively.

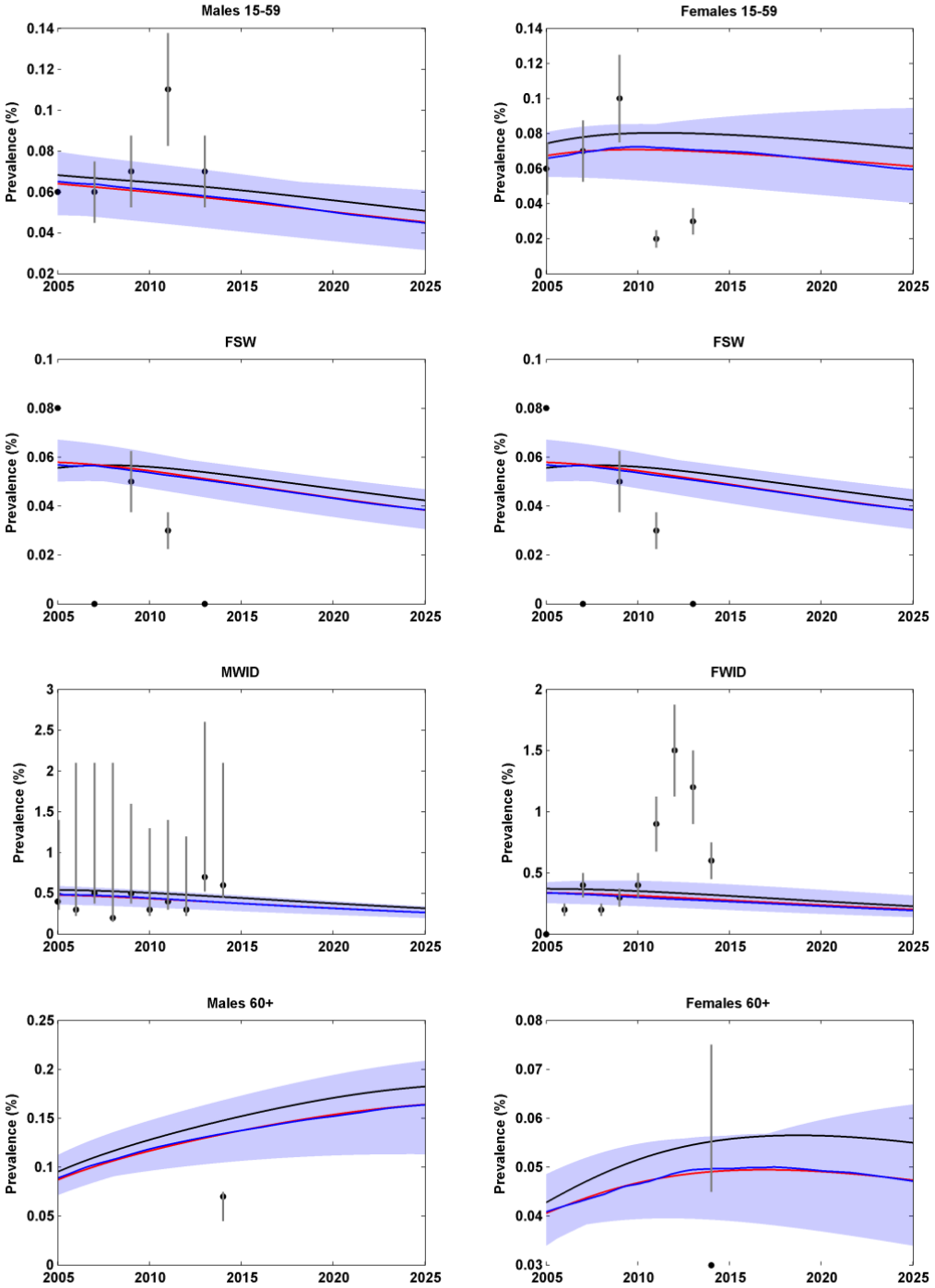
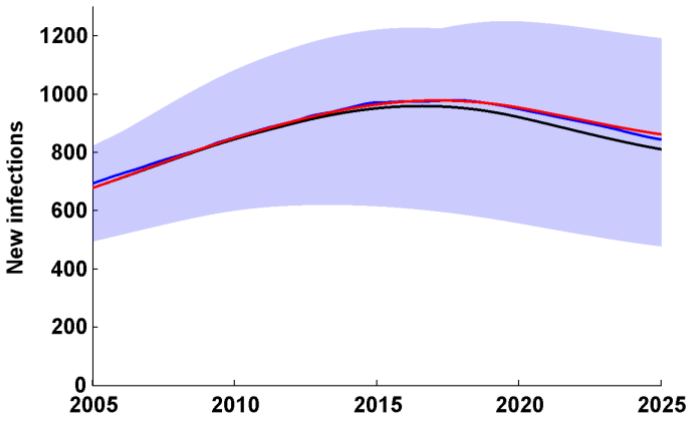


Figure A6: Simulated new HIV infections in Australian gay men. There is no specific data available to inform the model calibration to new infections. The model calibration aimed to reflect expected proportion of new infections in gay men and align roughly with total diagnoses, which other models have indicated align with new infections [10] . The black line is the hand-tuned simulation and the blue and red lines are the median and mean of the ensemble simulations respectively.



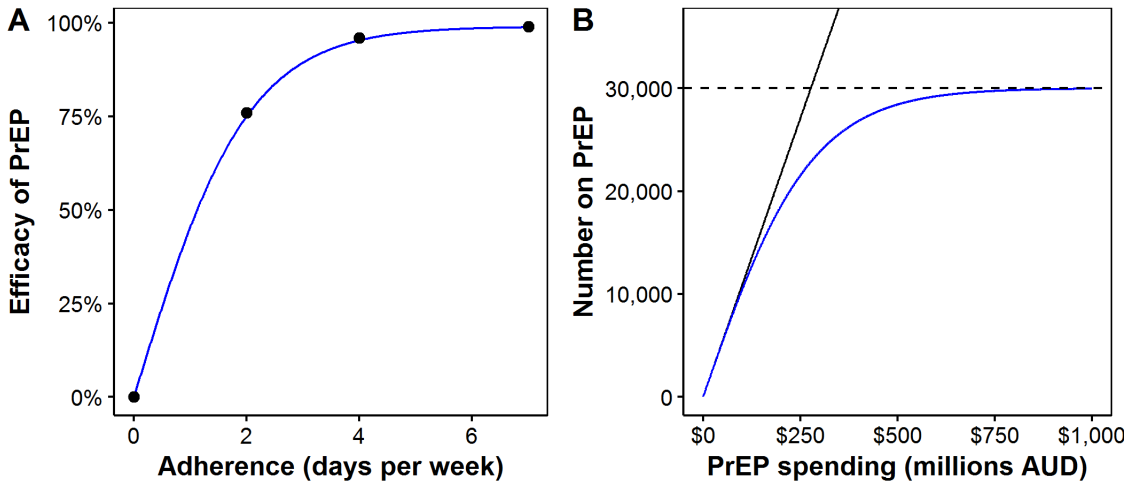
c) PrEP implementation and efficacy assumptions

The model implements a PrEP program by specifying the coverage and adherence level in each population allowing prioritization and variation of use across different populations. Adherence is specified by the average number of pills taken per week and determines the population use-efficacy based on results from the Anderson et al study [18]. That study estimated an HIV-1 risk reduction of 76% for two doses per week, 96% for 4 doses per week, and 99% for 7 doses per week of emtricitabine/tenofovir disoproxil fumarate. Our model uses a fitted logistic curve to this data to give the PrEP efficacy for any adherence level between 0 and 7 does of PrEP per week (as shown in Figure A7). Our model can use marginal unit costs based on a maximum possible coverage level; however, for this analysis we simply assume a fixed unit cost per person per year for all coverage levels.

The model also considers the scale-up of PrEP programs by specifying the number of years required for each population to reach the program coverage. For the intervening years, we assume a linear interpolation between the year the program starts and the year the program coverage is reached. For each population, the background PrEP coverage is maintained even if a PrEP program does not prioritize that population. Once the program coverage is reached we assume it is maintained at the same level into the future. For this analysis, we only consider PrEP programs for the gay populations for the 2016-2030 period.

Risk compensation is also captured in the model through changes in population level condomless anal intercourse. For each population receiving PrEP, a relative reduction in condomless anal intercourse within the population can be specified to capture likely risk compensation effects due to PrEP.

Figure A7: PrEP efficacy and spending relationships. A) Relationship between PrEP efficacy and number of pills taken per week. Data points correspond to the results from Anderson et al [18]. The blue line is a fitted exponential curve. B) Relationship between total PrEP program spending and the number of people taking PrEP (blue line). The line plateaus when it reaches the maximum coverage (black dashed line). The black line gives the number on PrEP if the unit cost is used (as for this analysis) which corresponds to about $300 million per year to provide PrEP to 30,000 men.



d) Cost-effectiveness calculations

We conducted the cost-effectiveness calculations using the same costing approach as Schneider et al [19] with prices updated to 2015 values in Australian dollars. We estimated the annual operating cost of a PrEP program prioritizing GBM living in Australia using a health provider perspective. For the susceptible GBM population receiving PrEP in the model, patient monitoring costs included HIV antibody testing and screening for sexually transmitted infections every 3 months and monitoring serum creatinine levels every 3 months. We based the cost of PrEP on the 2015 dispensed price for maximum quantity (DPMQ) of tenofovir with emtricitabine on the Pharmaceutical Benefits Scheme website (http://www.pbs.gov.au/pbs/home)—with costs associated with receiving PrEP adjusted to population adherence level in the model. Table A1 shows the resulting annual unit cost for providing PrEP at 100% adherence (one pill per day) with the full cost calculations available in Tables A2-A5 in section 5f. PrEP and ART costs. The product of population coverage, size of the susceptible population, the PrEP unit cost, and population adherence level, then gives the annual PrEP program cost for each year.

We also included the cost of HIV-related medical care and treatment after infection for all HIV-positive people in the model. Published DPMQs on the PBS website (http://www.pbs.gov.au/pbs/home) informed the cost of ART. The S100 Highly Specialized Drugs private cost figures were used for all treatment costs. The model includes first line ART, second line and lines of ART, and treatment failure. We estimated the cost of providing first and higher lines of ART using estimated annual costs for first and second line ART per patient per year (as the model only considers first and second or higher line ART separately). People experiencing treatment failure are assumed to be taking ART (but ineffectively) at a cost given by the weighted average of the first and second (and higher) line costs and the proportion of people on each line. To the annual treatment costs, we added the estimated cost of routine medical and laboratory testing and

hospitalization costs using the Medicare Benefits Schedule [41] and National Hospital Cost Data Collection cost weights [42]. We estimated healthcare use from Australian guidelines. Table A1 provides the estimated costs used for this analysis with the complete detail on all cost inputs provided in Tables A2-A6 in section 5f.

We estimated the cost-effectiveness of PrEP programs using quality of life estimates for people living with HIV and AIDS. For our analysis, we used the utility estimates from the meta-analysis of Tengs and Lin [20]. The authors report pooled utility estimates of 0.70 for patients with AIDS, 0.82 for patients with symptomatic HIV, and 0.94 for asymptomatic HIV patients. We mapped the health states "CD4+≥500 cells/μL" and "CD4+ 350–499 cells/μL" to the utility for asymptomatic infection, "CD4+200–349 cells/μL" to symptomatic infection, and "CD4+<200 cells/μL" to AIDS in our analysis.

For our analysis, we estimated simulation ensemble median and range for the total quality adjusted life years (QALY) gained, incremental PrEP program costs, incremental cost of providing care and treatment to HIV-positive people, and the incremental cost per QALY gained over 2016-2030 using a discounting rate of 5%. All costs are reported in Australian dollars (A$). We used the cost per QALY gained as the incremental cost-effectiveness ratio (ICER) for comparison to a specified cost-effectiveness threshold. The Pharmaceutical Benefits Advisory Committee (PBAC) does not use a specific cost-effectiveness threshold for inclusion onto the PBS. Analyses of past decisions suggest successful applications have an ICER of A$50-80,000 with wide variation depending on other factors (personal communication). We considered willingness-to-pay threshold of A$30,000, A$60,000 and A$90,000 for this analysis.

Table A1: Summary of model PrEP parameters and cost assumptions.

Parameter	Estimate	Source/Notes
Gay male populations sizes in 2015 (HIV-positive and HV-negative)		
High-risk gay men	Total: 38,200 Range: 30,600-45,900 % all HIV-negative gay men: 28.2%	See main text; assumed range of +/- 20%
Medium-risk gay men	Total: 5,100 Range: 4,100-6,100 % all HIV-negative gay men: 4 %	See main text; assumed range of +/- 20%
Low-risk gay men	Total: 80,300 Range: 64,200-96,400 % all HIV-negative gay men: 67.8%	See main text; assumed range of +/- 20%
PrEP parameters		
Current PrEP coverage— Percentage of high-risk gay men who are taking PrEP in 2015— and efficacy	3% (Range: 1-5%) at 85% efficacy	GCPS: PrEP use by non-HIV-positive men in 6 months prior (Sydney, 2015). Assumed only in high-risk and at lower adherence and efficacy as not part of a formal PrEP program. Efficacy based on the Partners PrEP study [21]
Efficacy of PrEP at full adherence (7 pills per week) during program implementation	99%	Anderson et al. [18]
Utilities		
Uninfected	1.0	Assumption
Untreated CD4 ≥ 500 cells/μL	0.935	[28–32]
Untreated CD4 350-499 cells/μL	0.935	
Untreated CD4 200-349 cells/μL	0.818	
Untreated CD4 < 200 cells/μL	0.702	
Annual costs for HIV-negative person taking PrEP		
PrEP drug cost	$9,604	PBS item: 6468; Table A2
Monitoring cost (PrEP related)	$645	See Table A3
Annual cost of care for diagnosed HIV-positive people		
Medical costs at CD4 ≥ 500 cells/μL	$2,791	See Table A5
Medical costs at CD4 ≥ 500 cells/μL	$3,914	
Medical costs at CD4 ≥ 500 cells/μL	$3,914	
Medical costs at CD4 ≥ 500 cells/μL	$7,870	
Annual drug costs for diagnosed HIV-positive people taking ART		
Drug cost: first line	$9,257	See Table A4

Drug cost: second and higher lines	$19,364	Based on cost of second line ART in Table A4
Discounting		
Costs	5%	Assumption
Outcomes	5%	Assumption

e) PrEP scenarios

We investigated the impact of PrEP programs using several theoretical simulation scenarios. In these scenarios, we change the PrEP model parameters for each gay male population from their baseline values in the fitted ensemble simulations. We assume only HIV-negative men are eligible for PrEP, and gay men with undiagnosed HIV are tested and diagnosed during PrEP pre-screening in line with the Australian Society of HIV Medicine PrEP guidelines. The specific scenarios we ran for this analysis are described in Table 3 of the main text. These scenarios focus on variations in prioritization and coverage within gay men with 90% adherence, a three-year program scale-up, and no risk compensation for each population. Costs associated with each scenario were discounted at 5% per annum. We gave each scenario a short name for reporting purposes. We compared the results of these scenarios to the baseline scenario where all model parameters remain at their fitted values over 2016-2030 to determine the impact and cost-effectiveness of PrEP. We consider the scenario Scenario90-60-30 to reflect the maximum realistic coverage for each at-risk GBM population and the Scenario90-90-90 scenario to be the theoretical maximum across the entire population.

To explore the impact of adherence, risk compensation, and program scale-up on the impact and cost-effectiveness of PrEP we ran a series of scenarios varying associated model parameters for the SenarioCov90-0-0 scenario. The results of this one-way analysis are provided as supplementary material.

f) PrEP and ART costs

The following tables show the costing methodology used for this analysis. These costs and calculations have been updated to 2015 prices (as of January 2016). Number per year = tablets per day * 365/max quantity. Resulting cost per patient per year is obtained by number per year * DPMQ * % coverage.

Table A2: Annual cost of tenofovir and emtricitabine.

	Number per year	**DPMQ AUS $**	**Max Quantity**	**Cost per patient per year, 2015 AUS $**	**Reference [a]**
Tenofovir and emtricitabine Pack size = 30 Tablet 300/200 mg per day Dose = 1 tablet per day	6.09	$1,577.13	60	$9,604.72	PBS item: 10347N

Abbreviations: AUS $, Australian dollar; DPMQ, dispensed price for maximum quantity; mg, milligrams; PBS, pharmaceutical benefits scheme

Notes: [a] DPMQ published on www.pbs.gov.au/, last accessed January 2016.

Table A3: Annual cost of patient monitoring for individuals receiving PrEP.

Routine medical					
	Number per year	**Unit cost, 2015 AUS $**	**% of patients receiving item per year**	**Baseline estimate**	**Reference** [a]
General-practitioner consultation	4.0	$37.05	50%	$74.10	MBS Item 23
Specialist consultation	4.0	$64.20	50%	$128.4	MBS Item 116
Routine laboratory					
Serum creatinine	4.0	$8.25	100%	$33.00	MBS Item 66500
STD screen: syphilis, hepatitis B, hepatitis C, and HIV.	4.0	$47.35	100%	$189.4	MBS Item 69413
STD screen: chlamydia trachomatis	4.0	$24.40	100%	$97.6	MBS Item 69316
STD screen: gonorrhoea.	4.0	$30.50	100%	$122	MBS Item 69317
Total				**$644.50**	

Abbreviations: AUS $, Australian dollar; HIV, human immunodeficiency virus; MBS, Medicare benefits schedule; STD, sexually transmitted disease

Notes: a) Benefits published on http://www.health.gov.au/internet/mbsonline/publishing.nsf/Content/Medicare-Benefits-Schedule-MBS-1, last accessed January 2016. Greatest percentage benefit assumed.

Table A4: Annual cost of antiretroviral therapy. Number per year = tablets per day * 365/max quantity. Resulting cost per patient per year is obtained by number per year * DPMQ * % coverage.

	Number per year	DPMQ AUS $	Max Quantity	% of patients receiving item per year	Cost per patient per year, 2013 in AUD	Reference
First-Line						
Nevirapine Pack size = 60 Tablet 200 mg Dose = 200 mg 2 per day	6.09	$418.95	120	100%	$2,551.41	PBS item: 10304H
Lamivudine Pack size = 60 Tablet 150mg Dose = 150mg 2 per day	6.09	$325.87	120	100%	$1,984.55	PBS item: 10348P
Zidovudine Pack size = 100 Tablet 100mg Dose = 600mg per day	5.48	$861.65	400	100%	$4,721.84	PBS item: 10266H
Total					**$9,257.80**	
Second-line						
Boosted Protease Inhibitor:						
Ritonavir boosted lopinavir Pack size = 120 Tablet 50/200 mg Dose = 100/400mg 2 per day	6.09	$1,416.93	240	100%	$8,629.10	PBS item: 10272P
Two nucleoside analogues:						
Tenofovir and emtricitabine Pack size = 30 Tablet 300/200 mg per day Dose = 1 tablet per day	6.09	$1,577.13	60	100%	$9,604.72	PBS item: 10347N
Maraviroc Pack size = 60 Tablet 150mg Dose = 150 mg 2 per day	6.09	$1,882.33	120	10%	$1,146.34	PBS item: 10318C
Total					**$19,380.16**	
Third-line						
Darunavir Pack size = 60 Tablet = 600mg Dose = 1200mg per day	6.09	$2,144.35	120	100%	$13,059.09	PBS item: 10329P

Ritonavir Pack size = 30 Tablet 100mg Dose = 100mg 2 per day	1.01	$1,029.09	720	100%	$1,039.38	PBS item: 10273Q
Etravirine Pack size = 60 Tablet = 200 mg Dose = 200mg 2 per day	6.09	$1,279.93	120	100%	$7,797.77	PBS item: 10301E
Raltegravir Pack size = 60 Tablet = 400 mg Dose = 400 x2 per day	6.09	$1,378.03	120	100%	$8,392.20	PBS item: 10286J
Maraviroc Pack size = 60 Tablet 150mg Dose = 150 mg 2 per day	6.09	$1,882.33	120	10%	$1,146.34	PBS item: 10318C
Total					**$31,434.78**	
Fourth-line						
Darunavir Pack size = 60 Tablet = 600mg Dose = 1200mg per day	6.09	$2,144.35	120	100%	$13,059.09	PBS item: 10329P
Ritonavir Pack size = 30 Tablet 100mg Dose = 100mg 2 per day	1.01	$1,029.09	720	100%	$1,039.38	PBS item: 10273Q
Tenofovir and emtricitabine Pack size = 30 Tablet 300/200 mg per day Dose = 1 tablet per day	6.09	$1,577.13	60	100%	$9,604.72	PBS item: 10347N
Enfuvirtide Pack size = 60 vials Injection = 90mg Dose = 90 mg x2 per day	6.09	$4,472.93	120	50%	$13,619.07	PBS item: 10365M
Total					**$37,322.26**	

Abbreviations: AUS $, Australian dollar; DPMQ, dispensed price for maximum quantity; PBS, pharmaceutical benefits scheme; mg, milligrams

Notes: [a] Costs are assumed to be the DPMQ published on www.pbs.gov.au/, last accessed January 2016.

Table A5: Annual medical cost of HIV-infected individual in 2015 A$.

CD4 >500					**Cost per patient per year, 2015 A$**			
Routine medical								
		No. Per Year [a]	**Unit cost, 2015 A$**	**% of patients receiving item per year**	**Baseline estimate**	**Low estimate**	**High estimate**	**Reference [b]**
General-practitioner consultations	Baseline	5.9	$37.05	50%	$109.29			MBS Item 23
	Low estimate	5.3	$37.05	50%		$98.12		
	High estimate	6.7	$37.05	50%			$124.12	
Specialist consultations	Baseline	5.9	$64.20	50%	$189.39			MBS Item 116
	Low estimate	5.3	$64.20	50%		$170.13		
	High estimate	6.7	$64.20	50%			$215.07	
Routine laboratory								
HIV viral load		2	$153.25	100%	$306.50	$306.50	$306.50	MBS Item 69378
Full blood examination		2	$14.45	100%	$28.90	$28.90	$28.90	MBS Item 65070
CD4 T cell lymphocyte count and percent		2	$167.75	100%	$335.50	$335.50	$335.50	MBS Item 71141
Genotypic testing for HIV		0	$690.80	0%	$0.00	$0.00	$0.00	MBS Item 69380
Liver enzymes/renal		1	$15.05	100%	$15.05	$15.05	$15.05	MBS Item 66512
Glucose/lipids		1	$9.95	100%	$9.95	$9.95	$9.95	MBS Item 66503
Hospitalizations								
	Baseline	0.1669	$10,766	100%	$1,796.84			AR-DRG: S65C, HIV-RELATED DISEASES -CSCC
	Low estimate	0.1669	$2,046.26	100%		$341.52		AR-DRG: S60Z, HIV, Same day
	High estimate	0.1669	$43,431.2	100%			$7,248.67	AR-DRG: S65A, HIV-RELATED DISEASES +CCC
Total cost (per year)	**Baseline**				**$2,791.42**			
	Low estimate					**$970.17**		
	High estimate						**$8,283.76**	
CD4 350-499								

Routine medical								
General-practitioner consultations	Baseline	6.6	$37.05	50%	$122.27			MBS Item 36
	Low estimate	5.1	$37.05	50%		$94.48		
	High estimate	8.6	$37.05	50%			$159.32	
Specialist consultations	Baseline	6.6	$64.20	50%	$211.86			
	Low estimate	5.1	$64.20	50%		$163.71		
	High estimate	8.6	$64.20	50%			$276.06	
Routine laboratory								
HIV viral load		2	$153.25	100%	$306.50	$306.50	$306.50	MBS Item 69378
Full blood examination		2	$14.45	100%	$28.90	$28.90	$28.90	MBS Item 65070
CD4 T cell lymphocyte count and percent		2	$167.75	100%	$335.50	$335.50	$335.50	MBS Item 71141
Genotypic testing for HIV		0	$690.80	0%	$0.00	$0.00	$0.00	MBS Item 69380
Liver enzymes/renal		2	$15.05	100%	$30.10	$30.10	$30.10	MBS Item 66512
Glucose/lipids		2	$9.95	100%	$19.90	$19.90	$19.90	MBS Item 66503
Hospitalizations								
	Baseline	0.2656	$10,766	100%	$2,859.44			AR-DRG: S65C, HIV-RELATED DISEASES -CSCC
	Low estimate	0.2656	$2,046.26	100%		$543.49		AR-DRG: S60Z, HIV, Same day
	High estimate	0.2656	$43,431.2	100%			$11,535.33	AR-DRG: S65A, HIV-RELATED DISEASES +CCC
Total cost (per year)	**Baseline**				**$3,914.47**			
	Low estimate					**$1,522.58**		
	High estimate						**$12,691.61**	
CD4 200-349								
Routine medical								
General-practitioner consultations	Baseline	6.6	$37.05	50%	$122.27			MBS Item 36
	Low	5.1	$37.05	50%		$94.48		
	High	8.6	$37.05	50%			$159.32	

Specialist consultations	Baseline	6.6	$64.20	50%	$211.86			
	Low	5.1	$64.20	50%		$163.71		
	High	8.6	$64.20	50%			$276.06	
Routine laboratory								
HIV viral load		3	$153.25	100%	$459.75	$459.75	$459.75	MBS Item 69378
Full blood examination		3	$14.45	100%	$43.35	$43.35	$43.35	MBS Item 65070
CD4 T cell lymphocyte count and percent		3	$167.75	100%	$503.25	$503.25	$503.25	MBS Item 71141
Genotypic testing for HIV		0	$690.80	0%	$0.00	$0.00	$0.00	MBS Item 69380
Liver enzymes/renal		3	$15.05	100%	$45.15	$45.15	$45.15	MBS Item 66512
Glucose/lipids		3	$9.95	100%	$29.85	$29.85	$29.85	MBS Item 66503
Hospitalizations								
	Baseline	0.2656	$10,766	100%	$2,859.44			AR-DRG: S65C, HIV-RELATED DISEASES -CSCC
	Low estimate	0.2656	$2,046.26	100%		$543.49		AR-DRG: S60Z, HIV, Same day
	High estimate	0.2656	$43,431.2	100%			$11,535.33	AR-DRG: S65A, HIV-RELATED DISEASES +CCC
Total cost (per year)	**Baseline**				**$3,914.47**			
	Low estimate					**$1,522.58**		
	High estimate						**$12,691.61**	
CD4 <200								
Routine medical								
General-practitioner consultations	Baseline	6	$37.05	50%	$111.15			MBS Item 36
	Low estimate	4.8	$37.05	50%		$88.92		
	High estimate	7.9	$37.05	50%			$146.35	
Specialist consultations	Baseline	6	$64.20	50%	$192.60			
	Low estimate	4.8	$64.20	50%		$154.08		
	High estimate	7.9	$64.20	50%			$253.59	
Routine laboratory								
HIV viral load		4	$153.25	100%	$613.00	$613.00	$613.00	MBS Item 69378
Full blood examination		4	$14.45	100%	$57.80	$57.80	$57.80	MBS Item 65070

CD4 T cell lymphocyte count and percent		4	$167.75	100%	$671.00	$671.00	$671.00	MBS Item 71141
Genotypic testing for HIV	Baseline	1	$690.80	100%	$695.80	$695.80	$695.80	MBS Item 69380
Liver enzymes/renal		4	$15.05	100%	$60.20	$60.20	$60.20	MBS Item 66512
Glucose/lipids		4	$9.95	100%	$39.80	$39.80	$39.80	MBS Item 66503
Hospitalizations								
	Baseline	0.5042	$10,766	100%	$5,428.21			AR-DRG: S65C, HIV-RELATED DISEASES -CSCC
	Low estimate	0.5042	$2,046.26	100%		$1,031.72		AR-DRG: S60Z, HIV, Same day
	High estimate	1.0321	$43,431.2	100%			$44,825.34	AR-DRG: S65A, HIV-RELATED DISEASES +CCC
Total cost (per year)	**Baseline**				**$7,869.56**			
	Low estimate					**$3,412.32**		
	High estimate						**$47,362.88**	

Abbreviations: AUS $, Australian dollar; DPMQ, dispensed price for maximum quantity; HIV, human immunodeficiency virus; MBS, Medicare benefits schedule; mg, milligrams

Notes: [a] References 1-3

[b] MBS benefits published on http://www.health.gov.au/internet/mbsonline/publishing.nsf/Content/Medicare-Benefits-Schedule-MBS-1, last accessed January 2016. Greatest percentage benefit assumed. Costs per AR-DRG from round 14 NHCDC costs weights (for 2009-2010) published on http://www.health.gov.au/internet/main/publishing.nsf/Content/health-casemix-data-collections-about, last accessed January 2016. Costs per AR-DRG were inflated to current AUD from Dec 2010 to Dec 2015 using the quarterly health CPI from the ABS (28.4536%)

g) Main Results and Figures

Table A6: ***Summary table of results for main PrEP scale-up scenarios***. Median and range for the 50 ensemble simulations. Incremental costs are calculated by subtracting the costs for the baseline scenario. Negative values correspond to the specified scenario have lower costs than the baseline scenario. All values rounded to the nearest 10.

Scenario	Infections averted (Undiscounted)	QALYs gained (Discounted)	Incremental PrEP costs (discounted)	Incremental ART costs (discounted)	Incremental cost (discounted)	Cost per QALY gained
Scenario30-0-0	4720 (2510-6440)	2190 (1160-2840)	$344,458,170 ($200,179,720-$509,346,430)	$-133,361,830 ($-173,303,590-$-68,967,440)	$205,242,910 ($111,520,410-$360,722,570)	102440 (39490-162870)
Scenario60-0-0	7790 (4170-10670)	3830 (2060-4990)	$726,237,770 ($425,931,130-$1,067,103,970)	$-236,755,840 ($-305,605,710-$-125,064,360)	$476,225,550 ($271,550,470-$803,625,710)	134950 (57250-206840)
Scenario90-0-0	9540 (5160-13080)	4940 (2690-6450)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-310,304,340 ($-398,217,340-$-166,796,370)	$778,135,040 ($446,727,460-$1,280,440,160)	170160 (77110-253570)
Scenario90-20-0	9580 (5170-13110)	4960 (2700-6470)	$1,150,143,630 ($678,001,300-$1,672,707,570)	$-312,091,040 ($-400,428,280-$-167,325,490)	$820,230,500 ($471,700,980-$1,325,311,870)	178690 (81520-261840)
Scenario90-60-0	9650 (5190-13170)	5010 (2720-6510)	$1,241,103,440 ($729,468,090-$1,765,466,660)	$-315,606,710 ($-404,772,700-$-168,375,980)	$909,548,450 ($521,722,560-$1,415,206,620)	195770 (90280-278240)
Scenario90-20-10	9830 (5340-13440)	5130 (2820-6700)	$1,555,547,120 ($1,042,427,950-$2,037,523,180)	$-325,189,680 ($-415,027,110-$-175,343,230)	$1,233,828,360 ($826,696,530-$1,681,756,670)	245490 (141760-358820)
Scenario90-60-30	10350 (5660-14110)	5460 (3050-7180)	$2,439,733,900 ($1,809,919,040-$2,860,133,580)	$-348,237,310 ($-446,318,830-$-191,681,130)	$2,089,480,860 ($1,574,783,750-$2,485,738,910)	379470 (258790-605800)
Scenario90-90-90	11330 (6440-15660)	6270 (3650-8360)	$4,811,273,040 ($3,998,583,440-$5,665,224,660)	$-406,933,180 ($-518,013,420-$-233,622,020)	$4,403,443,470 ($3,709,987,260-$5,340,664,580)	694590 (533950-1164600)

Table A7: PrEP unit cost required for scenario to be cost-effective for a given willingness-to-pay threshold (A$ per QALY gained). For each scenario and cost-effectiveness threshold, the table shows the median value and range (minimum and maximum) from the simulation ensemble.

Scenario	$30,000 per QALY gained	$60,000 per QALY gained	$90,000 per QALY gained
Scenario30-0-0	$5,690 ($4,250-$9,240)	$7,580 ($5,610-$12,430)	$9,480 ($6,960-$15,620)
Scenario60-0-0	$4,780 ($3,600-$7,840)	$6,350 ($4,730-$10,500)	$7,920 ($5,860-$13,170)
Scenario90-0-0	$4,090 ($3,110-$6,730)	$5,420 ($4,070-$8,990)	$6,740 ($5,030-$11,240)
Scenario90-20-0	$3,970 ($3,030-$6,520)	$5,250 ($3,970-$8,700)	$6,530 ($4,900-$10,890)
Scenario90-60-0	$3,730 ($2,890-$6,140)	$4,920 ($3,780-$8,190)	$6,100 ($4,670-$10,250)
Scenario90-20-10	$3,120 ($2,250-$4,570)	$4,120 ($2,980-$6,100)	$5,100 ($3,710-$7,630)
Scenario90-60-30	$2,150 ($1,420-$2,900)	$2,860 ($1,880-$3,870)	$3,560 ($2,350-$4,830)
Scenario90-90-90	$1,300 ($790-$1,580)	$1,700 ($1,040-$2,100)	$2,110 ($1,290-$2,610)

Figure A8: Impact of PrEP on new infections in gay men 2015-2030 for maximum coverage scenarios compared to the status quo scenario. The lines correspond to the median of the simulations. The shading shows the range in new infections for all simulations. A) shows the impact when prioritizing at high-risk gay men only (Scenario90-0-0) B) shows impact when both high and medium-risk gay men are prioritized (Scenario90-60-0) C) when all gay men are prioritized (Scenario90-60-30). D) shows the impact of PrEP for the median values in A) blue line, B) green line and C) purple line.

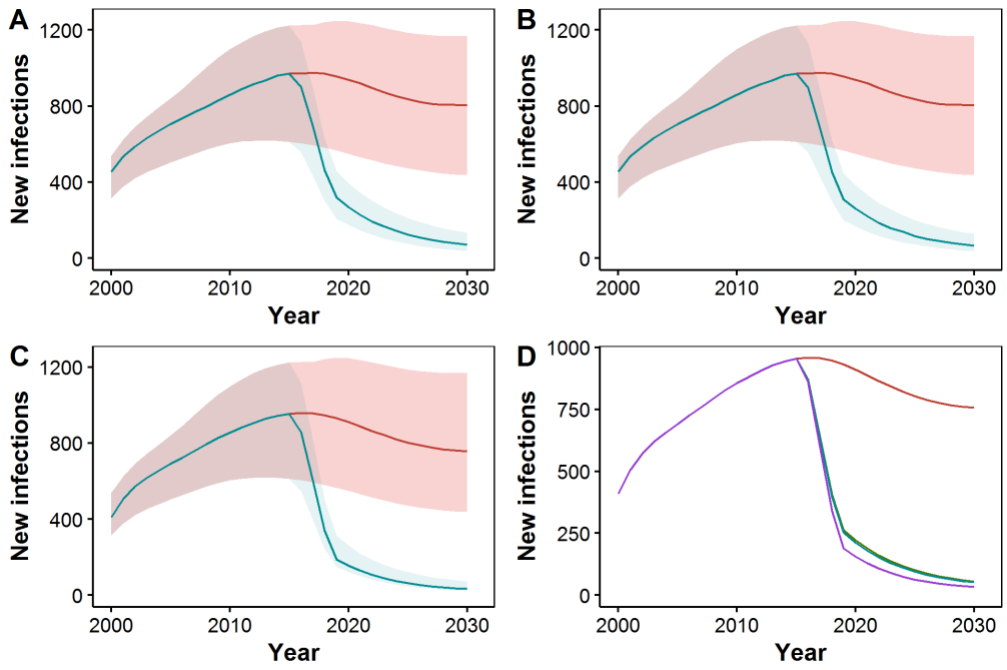


Figure A9: Total infections averted (top), and associated ICER (with 5% discounting) compared to the baseline scenario (bottom) for all scenarios over 2016-2030. For each scenario, the points correspond to the median value with the error bar range corresponding to the minimum and maximum from the simulation ensemble.

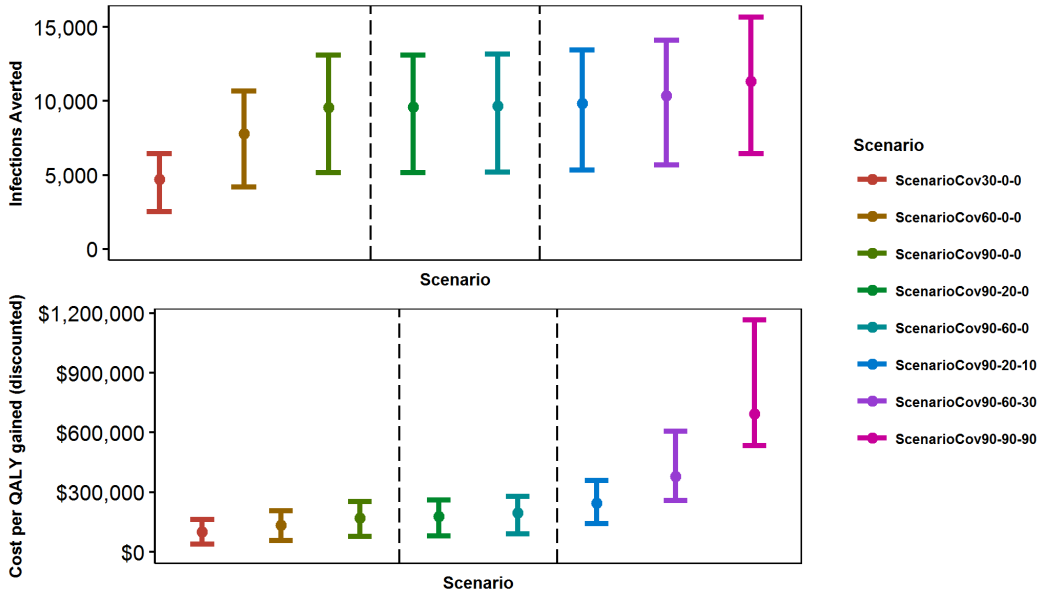


Figure A10: **PrEP unit cost required for each usage scenario to be cost-effective for a given willingness-to-pay threshold (AUD per QALY gained).** For each scenario, the points correspond to the median value with the error bar range corresponding to the minimum and maximum from the simulation ensemble.

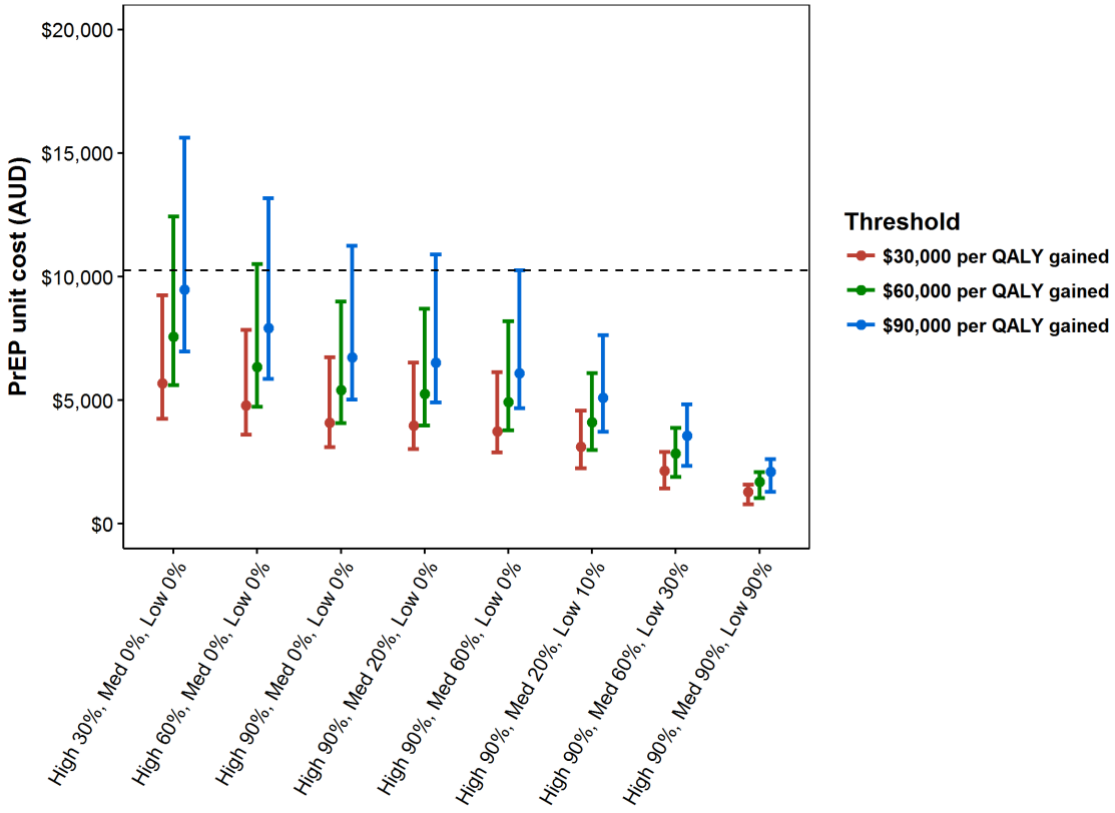
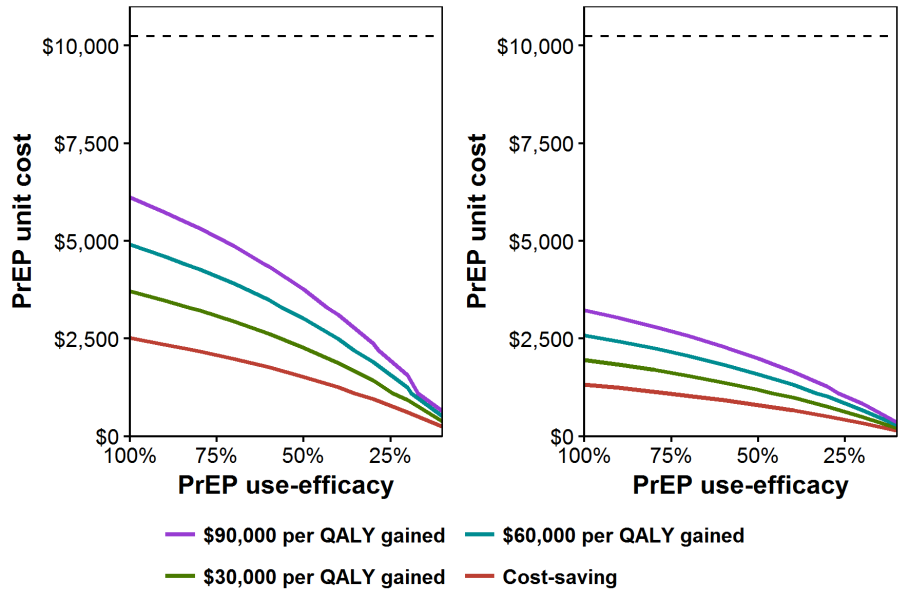


Figure A11: Resulting ICER fitted to median estimates for all simulations as PrEP unit cost and use efficacy is varied for Scenario90-0-0 (left) and Scenario90-60-30 (right). Dashed line shows the current PrEP unit cost.



h) Additional Scenario and Sensitivity results

(i) Impact of Adherence

Figure A12: Effect of variation in PrEP adherence in the ScenarioCoc90-0-0 scenario (90% adherence). (A) Median change in new infections over 2016-2030 for each scenario, (B) median and range in cumulative infections over 2016-2030 for each scenario and (C) median and range in the ICER over 2016-2030 for each scenario.

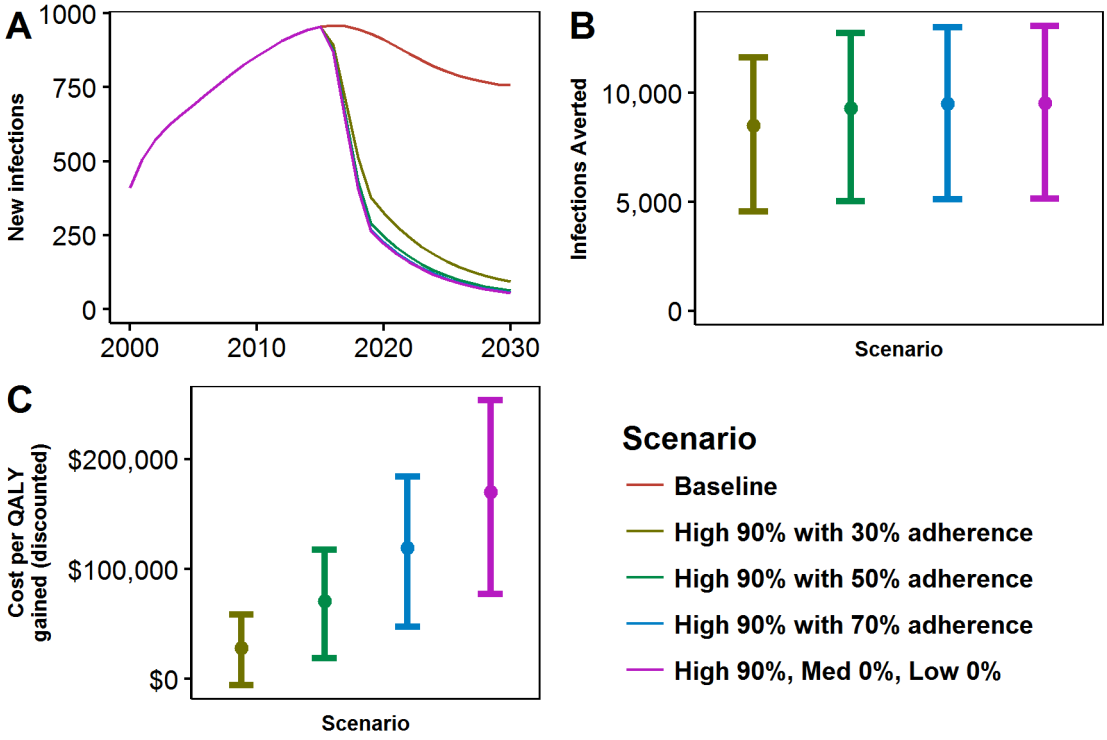


Table A8: Summary table of results for variation in PrEP adherence scenarios. Median and range for the 50 ensemble simulations. Incremental costs are calculated by subtracting the costs for the baseline scenario. Negative values correspond to the specified scenario have lower costs than the baseline scenario. All values rounded to the nearest 10.

Scenario	Infections averted (Undiscounted)	QALYs gained (Discounted)	Incremental PrEP costs (discounted)	Incremental ART costs (discounted)	Incremental cost (discounted)	Cost per QALY gained
Scenario90-0-0 with 30% adherence	8500 (4560-11640)	4240 (2290-5540)	$368,992,340 ($217,022,340-$541,114,080)	$-263,702,500 ($-339,702,360-$-140,003,980)	$115,965,320 ($-31,462,790-$247,446,530)	27970 (-5680-58400)
Scenario90-0-0 with 50% adherence	9310 (5020-12760)	4770 (2600-6240)	$615,243,670 ($361,855,580-$902,231,330)	$-299,123,650 ($-384,236,900-$-160,303,260)	$311,250,010 ($119,299,240-$568,857,550)	71010 (19130-117380)
Scenario90-0-0 with 70% adherence	9500 (5130-13020)	4900 (2670-6410)	$861,880,660 ($506,916,970-$1,263,911,860)	$-308,064,180 ($-395,419,260-$-165,491,990)	$537,370,320 ($302,936,760-$920,488,070)	119470 (47430-183900)
Scenario90-0-0	9540 (5160-13080)	4940 (2690-6450)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-310,304,340 ($-398,217,340-$-166,796,370)	$778,135,040 ($446,727,460-$1,280,440,160)	170160 (77110-253570)

(ii) Impact of risk compensation

Figure A13: Effect of reductions in condom use for men taking PrEP in the Scenario90-0-0 scenario (no change in condom use). (A) Median change in new infections over 2016-2030 for each scenario, (B) median and range in cumulative infections over 2016-2030 for each scenario and (C) median and range in the ICER over 2016-2030 for each scenario.

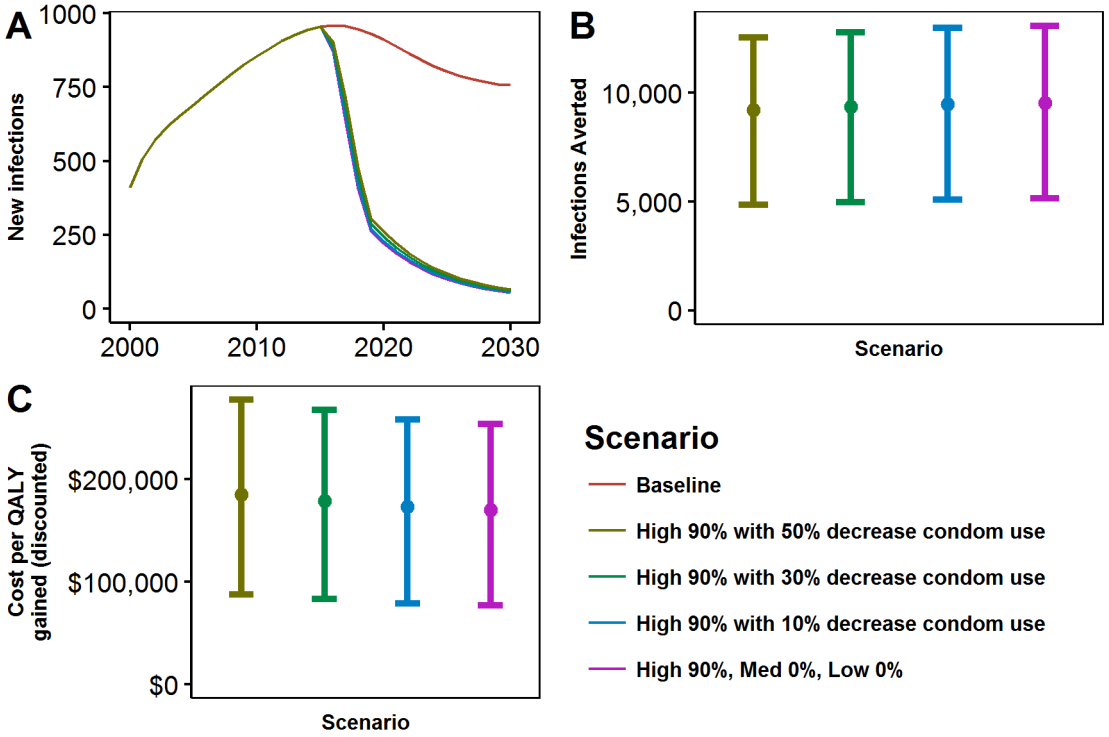


Figure A14: Effect of reductions in condom use for all gay men in the Scenario90-0-0 scenario (no change in condom use). (A) Median change in new infections over 2016-2030 for each scenario, (B) median and range in cumulative infections over 2016-2030 for each scenario and (C) median and range in the ICER over 2016-2030 for each scenario.

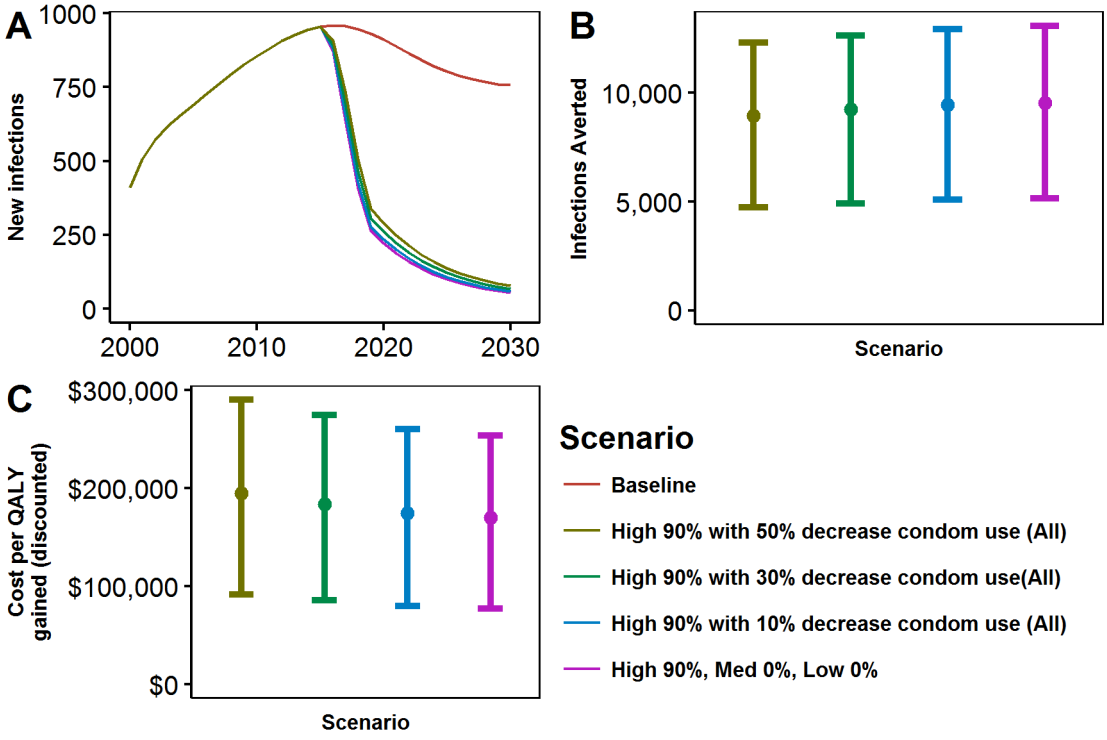


Table A9: Summary table of results for reductions in condom use scenarios. Median and range for the 50 ensemble simulations. Incremental costs are calculated by subtracting the costs for the baseline scenario. Negative values correspond to the specified scenario have lower costs than the baseline scenario. All values rounded to the nearest 10.

Scenario	Infections averted (Undiscounted)	QALYs gained (Discounted)	Incremental PrEP costs (discounted)	Incremental ART costs (discounted)	Incremental cost (discounted)	Cost per QALY gained
Scenario90-0-0 with 50% decrease in condom use (all gay men)	8950 (4750-12300)	4470 (2380-5860)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-279,499,160 ($-360,228,030-$-144,433,440)	$811,358,620 ($479,360,410-$1,315,474,620)	194800 (91730-290380)
Scenario90-0-0 with 30% decrease in condom use (all gay men)	9230 (4920-12620)	4660 (2510-6100)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-292,328,320 ($-375,770,540-$-153,586,520)	$797,774,140 ($465,936,470-$1,301,139,680)	184000 (85400-274330)
Scenario90-0-0 with 10% decrease in condom use (all gay men)	9440 (5080-12930)	4850 (2630-6340)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-304,396,410 ($-390,848,150-$-162,460,890)	$784,585,180 ($453,010,030-$1,287,235,350)	174370 (79730-260100)
Scenario90-0-0 with 50% decrease in condom use (men taking PrEP)	9210 (4870-12540)	4620 (2460-6030)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-289,528,120 ($-371,877,940-$-149,870,260)	$798,818,340 ($470,977,000-$1,305,218,450)	185320 (87520-277680)
Scenario90-0-0 with 30% decrease in condom use (men taking PrEP)	9350 (4990-12760)	4760 (2550-6200)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-298,451,710 ($-382,607,060-$-156,777,610)	$790,407,350 ($461,040,990-$1,295,128,080)	178920 (83100-267440)
Scenario90-0-0 with 10% decrease in condom use (men taking PrEP)	9480 (5100-12980)	4880 (2650-6370)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-306,396,930 ($-393,077,310-$-163,501,590)	$782,180,600 ($451,421,550-$1,285,277,440)	172970 (79030-258010)
Scenario90-0-0	9540 (5160-13080)	4940 (2690-6450)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-310,304,340 ($-398,217,340-$-166,796,370)	$778,135,040 ($446,727,460-$1,280,440,160)	170160 (77110-253570)

(iii) Effect of program scale up

Figure A15: Effect of changing the scale-up period for the ScenarioCoc90-0-0 scenario (3-year scale-up). (A) Median change in new infections over 2016-2030 for each scenario, (B) median and range in cumulative infections over 2016-2030 for each scenario and (C) median and range in the ICER over 2016-2030 for each scenario.

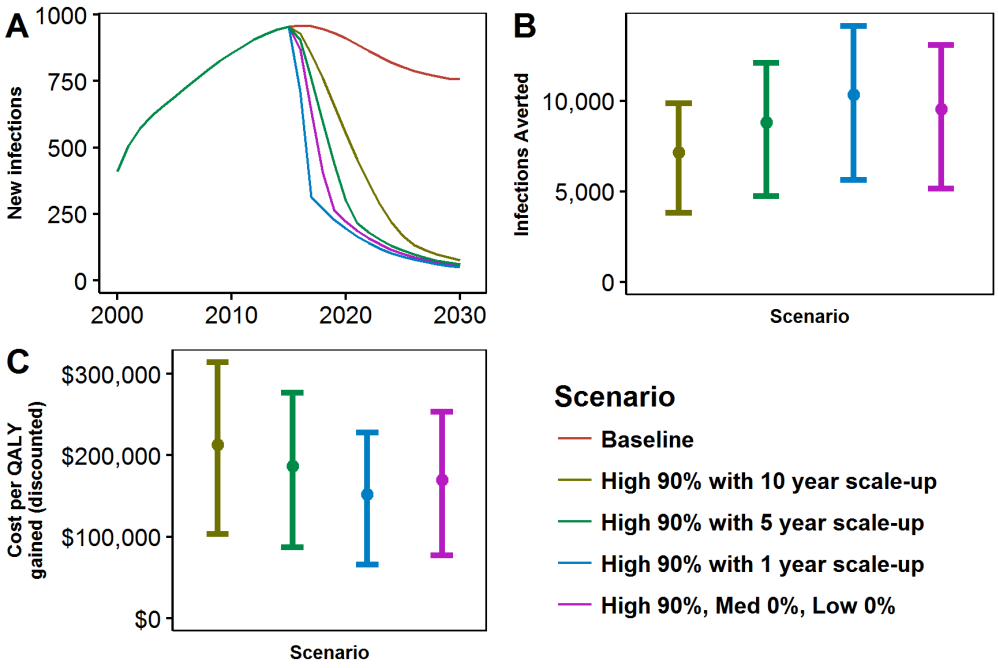


Table A10: Summary table of results for scale-up scenarios. Median and range for the 50 ensemble simulations. Incremental costs are calculated by subtracting the costs for the baseline scenario. Negative values correspond to the specified scenario have lower costs than the baseline scenario. All values rounded to the nearest 10.

Scenario	Infections averted (Undiscounted)	QALYs gained (Discounted)	Incremental PrEP costs (discounted)	Incremental ART costs (discounted)	Incremental cost (discounted)	Cost per QALY gained
Scenario90-0-0 with 10-year scale-up	7170 (3820-9870)	2990 (1610-3940)	$779,824,240 ($458,657,570-$1,143,575,640)	$-172,761,480 ($-223,935,760-$-90,139,110)	$593,277,560 ($347,276,620-$951,953,340)	213350 (103610-314370)
Scenario90-0-0 with 5-year scale-up	8810 (4730-12080)	4230 (2300-5550)	$1,009,573,830 ($593,785,910-$1,480,492,680)	$-258,102,960 ($-332,461,380-$-137,102,500)	$732,994,160 ($424,583,560-$1,193,339,360)	186690 (87120-276950)
Scenario90-0-0 with 1-year scale-up	10340 (5630-14150)	5800 (3190-7540)	$1,213,229,000 ($713,566,670-$1,779,143,510)	$-376,373,010 ($-480,604,610-$-205,254,660)	$813,573,380 ($461,091,410-$1,358,509,810)	152350 (66080-227640)
Scenario90-0-0	9540 (5160-13080)	4940 (2690-6450)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-310,304,340 ($-398,217,340-$-166,796,370)	$778,135,040 ($446,727,460-$1,280,440,160)	170160 (77110-253570)

(iv) Effect of variation in PrEP program coverage

Figure A16: Effect of variation in coverage when prioritizing at-high-risk gay men (assuming 90% adherence, 3-year scale-up and no reduction in condom use). (A) Median change in new infections over 2016-2030 for each scenario, (B) median and range in cumulative infections over 2016-2030 for each scenario, (C) median and range in incremental PrEP program costs over 2016-2030 for each scenario, (D) median and range in incremental treatment costs over 2016-2030 for each scenario, and (E) median and range in the ICER over 2016-2030 for each scenario.

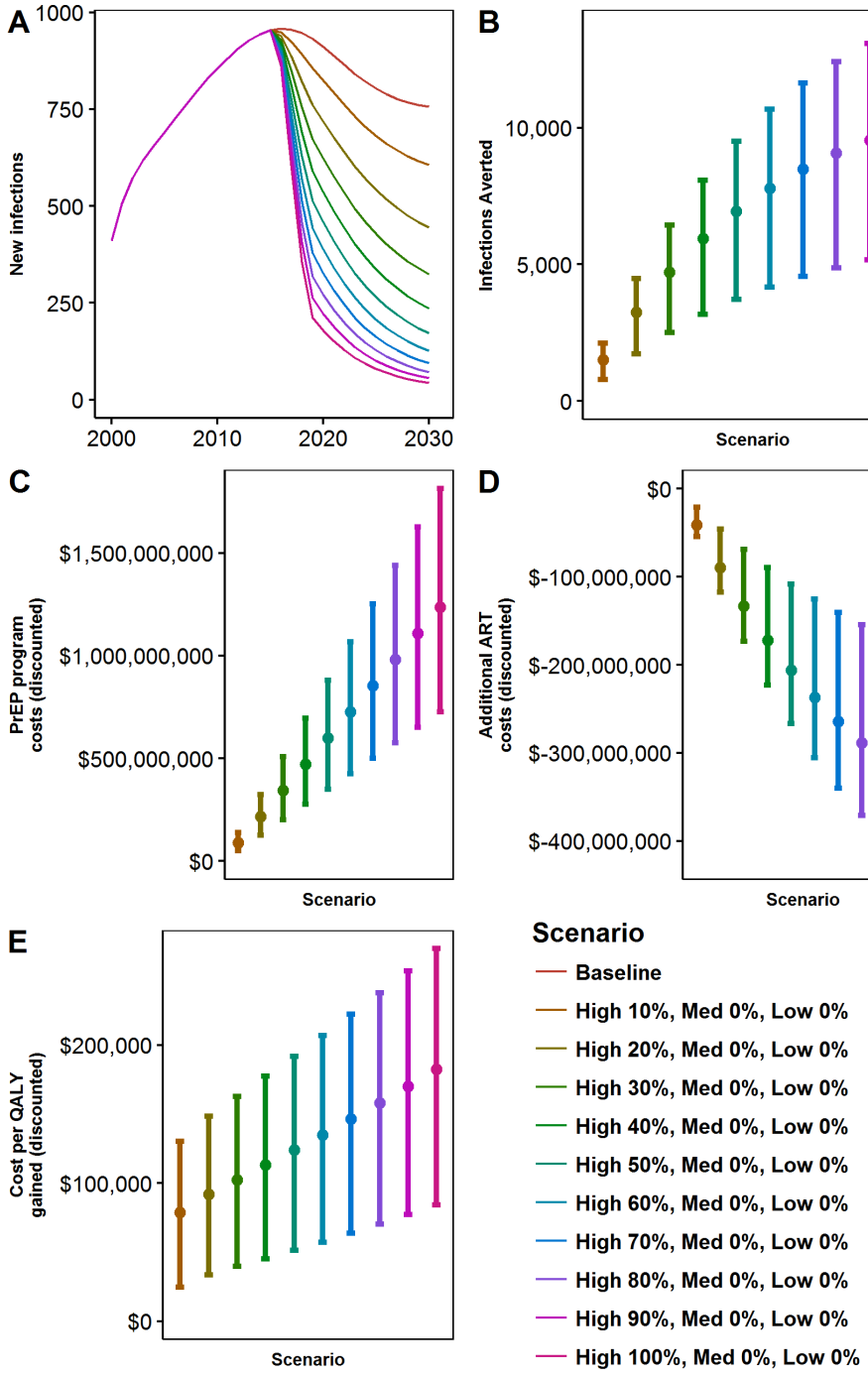


Table A11: Summary table of results for variation in coverage scenarios (increasing coverage in at-high-risk GBM in 10% increments). Median and range for the 50 ensemble simulations. Incremental costs are calculated by subtracting the costs for the baseline scenario. Negative values correspond to the specified scenario have lower costs than the baseline scenario. All values rounded to the nearest 10.

Scenario	Infections averted (Undiscounted)	QALYs gained (Discounted)	Incremental PrEP costs (discounted)	Incremental ART costs (discounted)	Incremental cost (discounted)	Cost per QALY gained
Scenario10-0-0	1510 (800-2120)	670 (360-900)	$90,452,050 ($49,868,450-$137,976,420)	$-41,318,170 ($-54,132,760-$-20,781,690)	$48,972,640 ($21,333,470-$91,175,990)	78750 (24710-130360)
Scenario20-0-0	3240 (1730-4490)	1480 (780-1930)	$217,339,390 ($125,012,700-$323,633,330)	$-89,703,930 ($-117,289,240-$-46,110,910)	$124,251,730 ($63,662,600-$222,981,570)	91880 (33530-148250)
Scenario30-0-0	4720 (2510-6440)	2190 (1160-2840)	$344,458,170 ($200,179,720-$509,346,430)	$-133,361,830 ($-173,303,590-$-68,967,440)	$205,242,910 ($111,520,410-$360,722,570)	102440 (39490-162870)
Scenario40-0-0	5940 (3170-8080)	2820 (1500-3640)	$471,634,630 ($275,380,860-$695,143,790)	$-171,995,780 ($-222,881,930-$-89,592,950)	$291,395,410 ($164,481,630-$503,790,110)	113050 (45230-177270)
Scenario50-0-0	6950 (3710-9500)	3350 (1800-4360)	$598,888,050 ($350,627,520-$881,053,550)	$-206,241,170 ($-266,749,690-$-108,219,610)	$381,884,490 ($217,023,090-$651,602,890)	123860 (51120-191900)
Scenario60-0-0	7790 (4170-10670)	3830 (2060-4990)	$726,237,770 ($425,931,130-$1,067,103,970)	$-236,755,840 ($-305,605,710-$-125,064,360)	$476,225,550 ($271,550,470-$803,625,710)	134950 (57250-206840)
Scenario70-0-0	8500 (4550-11630)	4240 (2300-5540)	$853,703,230 ($501,303,190-$1,253,323,460)	$-264,002,300 ($-340,095,030-$-140,325,830)	$573,972,450 ($328,146,650-$959,378,530)	146330 (63630-222120)
Scenario80-0-0	9070 (4880-12430)	4610 (2510-6030)	$981,303,960 ($576,755,260-$1,439,740,550)	$-288,396,130 ($-370,796,070-$-154,183,200)	$674,725,810 ($386,602,190-$1,118,438,880)	158110 (70260-237710)
Scenario90-0-0	9540 (5160-13080)	4940 (2690-6450)	$1,109,059,640 ($652,298,970-$1,626,383,990)	$-310,304,340 ($-398,217,340-$-166,796,370)	$778,135,040 ($446,727,460-$1,280,440,160)	170160 (77110-253570)
Scenario100-0-0	9940 (5400-13630)	5230 (2860-6830)	$1,236,990,090 ($727,946,030-$1,813,282,740)	$-330,047,160 ($-422,799,960-$-178,306,980)	$883,896,740 ($508,353,510-$1,445,067,570)	182430 (84150-269690)

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