A Cost-effectiveness Analysis of HIV Preexposure Prophylaxis for Men Who Have Sex With Men in Australia

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Background. Antiretroviral therapy (ART) used as preexposure prophylaxis (PrEP) by human immunodeficiency virus (HIV)–seronegative individuals reduces the risk of acquiring HIV. However, the population-level impact and cost-effectiveness of using PrEP as a public health intervention remains debated.

Methods. We used a stochastic agent-based model of HIV transmission and progression to simulate the clinical and cost outcomes of different strategies of providing PrEP to men who have sex with men (MSM) in New South Wales (NSW), Australia. Model outcomes were reported as incremental cost-effectiveness ratios (ICERs) in 2013 Australian dollars per quality-adjusted life-year gained (QALYG).

Results. The use of PrEP in 10%–30% of the entire NSW MSM population was projected to cost an additional $316–$952 million over the course of 10 years, and cost >$400 000 per QALYG compared with the status quo. Targeting MSM with sexual partners ranging between >10 to >50 partners within 6 months cost an additional $31–$331 million dollars, and cost >$110 000 per QALYG compared with the status quo. We found that preexposure prophylaxis is most cost-effective when targeted for HIV-negative MSM in a discordant regular partnership. The ICERs ranged between $8399 and $11 575, for coverage ranging between 15% and 30%, respectively.

Conclusions. Targeting HIV-negative MSM in a discordant regular partnership is a cost-effective intervention. However, this highly targeted strategy would not have large population-level impact. Other scenarios are unlikely to be cost-effective.

Keywords. cost-effectiveness; preexposure prophylaxis; HIV prevention; men who have sex with men.

There is increasing interest in the use of preexposure prophylaxis (PrEP) with antiretroviral medications to prevent the acquisition of human immunodeficiency virus (HIV). The efficacy of PrEP has been demonstrated in 4 randomized controlled trials: the iPrEx trial [1], the Partners PrEP study [2], the TDF2 Study [3], and the Bangkok Tenofovir Study [4]. The iPrEx trial randomly assigned 2499 HIV-seronegative men and transgender women who have sex with men to receive a combination of 2 oral antiretroviral drugs, emtricitabine and tenofovir disoproxil fumarate (FTC-TDF), or placebo once daily. This study reported a 44% reduction in HIV incidence among the FTC-TDF group [1]. The Partners PrEP study randomized 4758 serodiscordant heterosexual couples to TDF, FTC-TDF, or placebo once daily. Baeten and colleagues reported a 75% reduction in HIV incidence among the FTC-TDF group—with medication in use 92.1% of the total follow-up time [2]. The TDF2 Study randomly assigned 1219 HIV-seronegative sexually active heterosexual men and women to receive either FTC-TDF or a matching placebo once daily. In this study, FTC-TDF, taken orally once daily, decreased the rate of HIV infection by 62% [3]. The Bangkok Tenofovir Study randomized 2413 injecting drug users to receive TDF or placebo once daily, with the TDF arm having a 48.9% reduced risk of HIV infection [4].

On the basis of these findings, PrEP with FTC-TDF or TDF is being recommended for wider use for the
prevention of HIV infection [5, 6]. However, the cost-effectiveness of PrEP in a real-world setting remains undecided. The incremental cost-effectiveness ratio (ICER) for PrEP among high-risk men who have sex with men (MSM) in the United States has ranged between $31,970 per quality-adjusted life year gained (QALYG) (2007 US dollars) [7] and $298,000 per QALYG (2006 US dollars) [8]. Such modeled analyses remain highly sensitive to several real-world variables. These include the level of uptake and adherence among high-risk groups, the risk of resistance and toxicity, behavioral disinhibition, and drug costs. The objective of this study was to weigh the uncertainties surrounding PrEP in a real-world setting and determine in what clinical, epidemiologic, and economic circumstances PrEP is likely to be most cost-effective.

Methodology
We studied HIV transmission in New South Wales (NSW), Australia. New South Wales has approximately 350 annual HIV notifications with 80% of newly acquired HIV infections attributed to MSM [9, 10]. The HIV epidemic in NSW is thus similar to epidemics in other high-income settings, for example in the United States, the United Kingdom, and the Netherlands. The epidemic in NSW also broadly reflects the characteristics of HIV transmission in Australia generally. The Australian surveillance system does not report prevalence; however, studies estimate that approximately 10% of MSM in NSW are infected with HIV [11]. Periodic surveys report high levels of HIV testing and treatment, with 60%–80% of men surveyed currently taking antiretroviral treatment [12]. Men who have sex with men in NSW are highly knowledgeable about HIV and practice a number of risk-reduction behaviors based on the disclosure of HIV serostatus to partners [12]. Further population and epidemiologic details are provided in the Supplementary Data and in our previous studies [13–15].

Model Summary
We used a stochastic agent-based model of HIV transmission and progression to assess the effectiveness and cost-effectiveness of PrEP for HIV prevention among MSM living in NSW, Australia. We projected estimates of incidence, prevalence, health outcomes, and healthcare costs according to various PrEP-based interventions over a 10-year time horizon. We assumed a health provider perspective and discounted costs and health outcomes at 3.0% annually.

The model tracks HIV transmission within 60,000 men and is informed by extensive epidemiological, behavioral, and clinical data. It simulates the formation of, sexual activity within, and breakup of regular, casual, and group partnerships in the population. The model updates variables describing infection and disease status of HIV, disease progression, treatment status, sexual activity level, partnership availability, and current sexual partners of each individual in daily time-steps. Within the model, the characteristics associated with the type of sexual encounter determine the probability of HIV transmission.

We used this model previously to investigate other HIV interventions such as vaccination and increases in HIV diagnostic testing [13–15]. These studies provide extensive technical details of the model, including model parameter values and the calibration of the model to the HIV epidemic in NSW. We modified the model to incorporate PrEP interventions, the development of drug-resistant HIV due to PrEP, and the use of antiretroviral therapy (ART) regimens incorporating PrEP drugs. These modifications do not change the calibration of the model or the associated parameter values for 1996–2010 or the status quo simulation for projections over 2011–2020 in our previous work [13–15]. Table 1 presents the key model parameters for PrEP and the development of drug resistance. We provide further technical details of the model as Supplementary Data (Section 1).

Modeling PrEP-Based Interventions
We investigated the impact of PrEP interventions by assigning a proportion of HIV-negative or undiagnosed MSM to be taking PrEP in a number of theoretical simulated scenarios. These scenarios were based on available trial data and plausible assumptions. The scenarios we investigated include prioritizing PrEP for 10%–30% of the general MSM population, 15%–30% of MSM with >10–50 sexual partners per 6 months, and 15%–30% of HIV-negative MSM in discordant regular partnerships. Although Australia is a high-income country and could potentially afford PrEP for the entire HIV-negative MSM population, we assumed a maximum coverage of 30% based on studies of willingness to use PrEP and informal PrEP use among MSM [34, 35].

Overall, the iPrEX trial observed a 44% reduction in the probability of acquiring HIV (73% among fully adherent participants and >90% for those with detectable drug) [1]. Among individuals in the model who are adherent and therefore have detectable drug, we assumed a PrEP efficacy of 95% against wild-type virus and 40% against PrEP-drug-resistant virus (based on the iPrEX trial results for those with detectable drug and the efficacy overall [1]). We assumed PrEP provided no protection for those with poor adherence and therefore undetectable drug. The base case analysis assumes that 75% of MSM taking PrEP have detectable drug in each scenario, representing a 75% probability of adherence among MSM taking PrEP. We carried out sensitivity analyses varying the probability of adherence between 40% and 90%.

To date, PrEP studies have not identified any significant safety concerns associated with daily use of FTC-TDF and so we have not considered toxicity and drug-related adverse events in our model [1, 2, 36]. Behavioral disinhibition is an additional
Table 1. Summary of Model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Case Value (Range Used in Sensitivity Analysis)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PrEP and drug resistance parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of those on ART taking PrEP drugs</td>
<td>Increases from 1996 to 2010</td>
<td>[16]a</td>
</tr>
<tr>
<td><strong>Efficacy of PrEP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For PrEP users with detectable drug level against wild-type virus</td>
<td>0.95</td>
<td>[1]b</td>
</tr>
<tr>
<td>For PrEP users with detectable drug level against drug-resistant virus</td>
<td>0.4</td>
<td>Assumption</td>
</tr>
<tr>
<td>For PrEP users with undetectable drug level</td>
<td>0</td>
<td>Assumption</td>
</tr>
<tr>
<td><strong>Probability of developing drug resistance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People taking PrEP who have detectable drug level and who become infected with HIV</td>
<td>2% per day</td>
<td>Assumptionc</td>
</tr>
<tr>
<td>People with wild-type virus who begin ART</td>
<td>5% per year</td>
<td>[17–20]d</td>
</tr>
<tr>
<td>People with reservoirs of drug resistance who begin ART</td>
<td>0.27% per day</td>
<td>[17, 21, 22]e</td>
</tr>
<tr>
<td>Probability of those with PrEP-induced drug resistance reverting back to wild type</td>
<td>0.27% per day</td>
<td>[17, 23, 24]e</td>
</tr>
<tr>
<td>Per-act transmissibility of drug-resistant virus relative to wild type</td>
<td>0.4—0.85</td>
<td>[17, 25–27]f</td>
</tr>
<tr>
<td>Infection progression time for people with drug-resistant virus relative to those with wild type</td>
<td>1–1.25</td>
<td>Assumptiong</td>
</tr>
<tr>
<td>Probability of men with detectable drug level (adherence)</td>
<td>75% (40%–90%)</td>
<td>Assumption</td>
</tr>
<tr>
<td>Reduction in condom use with male partners due to PrEP</td>
<td>0% (25%–75%)</td>
<td>Assumption</td>
</tr>
<tr>
<td><strong>Utility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninfected</td>
<td>1.0</td>
<td>Assumption</td>
</tr>
<tr>
<td>CD4+ ≥500 cells/μL</td>
<td>0.935 (0.88–0.97)</td>
<td>[28–32]</td>
</tr>
<tr>
<td>CD4+ 350–499 cells/μL</td>
<td>0.935 (0.78–0.97)</td>
<td></td>
</tr>
<tr>
<td>CD4+ 200–349 cells/μL</td>
<td>0.818 (0.78–0.94)</td>
<td></td>
</tr>
<tr>
<td>CD4+ &lt;200 cells/μL</td>
<td>0.702 (0.70–0.87)</td>
<td></td>
</tr>
<tr>
<td><strong>Costs, annual</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative or HIV-positive and undiagnosed men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PrEP drug cost</td>
<td>$3,596.97 ($3,000–$12,000)</td>
<td>PBS item: 6468K</td>
</tr>
<tr>
<td>Monitoring cost</td>
<td>$765.00</td>
<td>h</td>
</tr>
<tr>
<td>HIV-positive men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug cost: first-line</td>
<td>$10,685 ($6,945–$14,424)</td>
<td>h</td>
</tr>
<tr>
<td>Drug cost: second-line</td>
<td>$19,364 ($12,587–$26,142)</td>
<td>h</td>
</tr>
<tr>
<td>Drug cost: third-line</td>
<td>$31,411 ($20,417–$42,405)</td>
<td>h</td>
</tr>
<tr>
<td>Drug cost: fourth-line</td>
<td>$28,162 ($18,305–$38,019)</td>
<td>h</td>
</tr>
<tr>
<td>Medical at CD4+ ≥500 cells/μL</td>
<td>$3,097 ($12,724–$7,642)</td>
<td>h</td>
</tr>
<tr>
<td>Medical at CD4+ 350–499 cells/μL</td>
<td>$4,402 ($14,73–11,672)</td>
<td>h</td>
</tr>
<tr>
<td>Medical at CD4+ 200–349 cells/μL</td>
<td>$4,762 ($18,333–12,032)</td>
<td>h</td>
</tr>
<tr>
<td>Medical at CD4+ &lt;200 cells/μL</td>
<td>$7,883 ($24,645–42,400)</td>
<td>h</td>
</tr>
<tr>
<td><strong>Discounting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs, outcomes, %</td>
<td>3%, 3% (0%, 0%); 5%, 5%; 5%, 0%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; PBS, Pharmaceutical Benefits Scheme; PrEP, preexposure prophylaxis.

- a The proportion of treated men on PrEP is based on data from the Australian HIV Observational Database [16]. The probability of taking PrEP increased from 10% in 2002 to 56% in 2010. From 1996 to 2002, we assumed a probability of 10% (equal to the probability on 2002). See Supplementary Data, Section 1, for further details.
- b This value is based on the estimated efficacy in the iPrEX trial for men who have sex with men (MSM) with detectable drug levels [1].
- c We assume a high probability of development of resistance in MSM who become infected while having detectable PrEP drug levels. This assumption is based on (1) the rate that nucleoside reverse transcriptase inhibitor (NRTI, particularly zidovudine)–resistant strains developed during the era of monotherapy (1987–1991) [27, 33]; (2) the high viral load during acute HIV infection; and (3) the high level of selection pressure due to the presence of detectable drug level.
- d This value is based on clinical trial data for the proportion of people on first-line ART who select for drug-resistant mutations each year and acquire drug-resistant strains [17–20]. We assume the same rate for all regimen lines/classes.
- e This proportion is equivalent to a 1 in 365 probability per day of developing drug resistance.
- f Based on single-class resistance to NRTIs [17, 25–27].
- g We assume a slower progression for people with majority-resistant viral strains.
- h See Supplementary Data, Section 2, for further detail on cost breakdown.
RESULTS

Preexposure Prophylaxis for the General MSM Population

In the absence of PrEP, we estimate 2388 new infections to occur among MSM in NSW during the next 10 years (Table 2). As illustrated in Figure 1, the results from our analysis demonstrate the use of PrEP to have potential for reducing the incidence of HIV in the general MSM population (Figure 1). PrEP in 30% of the MSM population reduced the number of new infections to 1670, accounting for a 30.1% reduction in incidence, and accumulated 2142 additional QALYs.

Although PrEP has potential for averting a considerable proportion of new infections among the MSM population, it is expensive. As the percentage of MSM taking PrEP increased, the costs associated with medical treatment and care rose. The use of PrEP in 10%–30% of the entire NSW MSM population was projected to cost an additional $316–$952 million over the next 10 years, resulting in ICERs of >$400 000 per QALYG compared with the status quo.

Preexposure Prophylaxis for Groups at Higher Risk of Infection

Targeting MSM at higher risk of infection improved the cost-effectiveness of PrEP (Figure 2). We found that targeting MSM with sexual partnerships ranging between >10 to >50 partners within 6 months reduced the cost considerably compared to targeting the entire MSM population. The incremental cost of these strategies ranged between approximately $31 and $331 million. However, these strategies were also associated with lower effectiveness. The QALY ranged between 228 and 1503 and averted between 82 and 535 infections over the course of 10 years. Consequently, the ICERs for these strategies remained >$110 000 per QALYG—above what is considered to be cost-effective for Australian settings.

We found that targeting HIV-negative men in a discordant regular partnership was the most cost-effective of all the strategies analyzed (Figure 2). The incremental cost of providing PrEP to 15%–30% of HIV-negative men in discordant partnerships ranged between approximately $4.4 million and $12.3 million over 10 years. The infections averted and QALY from 30% coverage of men in discordant partnerships is similar to that gained when targeting 10%–20% of the MSM population (Table 2). As a result, these strategies have extremely cost-effective ICERs, ranging between $8399 and $11 575, for 15% and 30%, respectively, of HIV-negative men in discordant regular partnerships taking PrEP.

Sensitivity Analysis

In sensitivity analysis, we found the cost of PrEP had a large influence on the cost-effectiveness of PrEP (Supplementary Data, Section 3). For the Australian setting, we estimate the cost of TDF/FTC-based PrEP to be $9597 per person-year. With this
cost, we projected the use of PrEP in 10%–30% of the entire NSW MSM population (adherence 75%) would cost an additional $316–$952 million over the next 10 years and resulted in ICERS of >$400 000 per QALYG compared with the status quo. If the cost of TDF/FTC-based PrEP falls to prices similar to those of commonly used first-line antiretroviral therapies (approximately $3000 per person-year), the budget impact dropped to $112–$338 million over the next 10 years and resulted in ICERS ranging between $157 911 and 185 851 per QALYG for coverage of 30% and 10%, respectively. Furthermore, at this lowered PrEP price, targeting 15% of MSM in discordant regular partnerships became a cost-saving strategy.

Other than the expense associated with PrEP, adherence and behavioral disinhibition are the primary concerns with the introduction of PrEP [43, 44]. In 1-way sensitivity analysis, a reduction of condom use of 75% in partnerships where 1 partner is taking PrEP increased the ICER of the most cost-effective strategy (15% coverage in discordant regular partnerships) from $8399 to $18 382. Reducing adherence from 75% to 40% reduced the ICER from $8399 to $7078.

DISCUSSION

This study suggests that PrEP could reduce the incidence of HIV among MSM living in Australia. Preexposure prophylaxis targeted for 30% of the MSM population reduced the number of new infections from 2388 to 1670, accounting for a 30.1% reduction in incidence over 10 years. However, based on the current treatment and monitoring cost of TDF-FTC–based PrEP and HIV-related medical care and treatment after infection, we estimated that PrEP for 10%–30% of the entire NSW MSM population to cost >$400 000 per QALYG. Therefore, from the Australian cost-effectiveness perspective, providing PrEP to the general MSM population is not cost-effective. Targeting a smaller group of MSM at higher risk of infection improves the cost-effectiveness of PrEP. The most cost-effective strategies targeted HIV-negative
men in a discordant regular partnership; ICERS ranged between $8399 and $11 575 per QALYG for coverage ranging between 15% and 30%, respectively.

The findings in this study are dependent on several unknown assumptions. At present, real-world data on changed safe-sex behaviors and adherence among people taking PrEP is lacking. These data are critical for accurately assessing the cost-effectiveness of PrEP. Our base case analysis assumed 75% adherence, and no change to safe sex practices. Whether or not this reflects reality remains unknown. Condom use reductions did not have a substantial impact on the model. A reduction of condom use of 75% in partnerships where 1 partner is taking PrEP increased the ICER of the most cost-effective strategy (15% coverage in discordant regular partnerships) from $8399 to $18 382. Although proportionally this is a considerable increase, the ICER remains cost-effective. This is primarily due to the high level of PrEP effectiveness assumed in men with detectable drug levels and the high level of adherence to PrEP in our model population. For example, if we had 75% adherence, but 100% reduction in condom use, there would be little change in new infections as we assumed PrEP has 95% efficacy against wild-type virus. However, it is important to note that whereas our model appears to be insensitive to a reduction in condom use, the model does not take into account a reduction in condom use among the wider MSM population not taking PrEP or the cost and utility associated with the transmission of other sexually transmitted infections. In addition, poor adherence in combination with a reduction of condom use would have a significant impact on incidence. Therefore, we emphasize that ongoing risk-reduction counseling during visits to healthcare professions during PrEP monitoring remains important.

Previous cost-effectiveness studies and the current study demonstrate that PrEP is most cost-effective when targeting MSM at high risk of infection and PrEP is least cost-effective when targeting the general MSM population. Our study suggests it is not cost-effective to target MSM based solely on the number of sexual partnerships they have. We found that targeting MSM with sexual partnerships ranging between >10 and >50 partners within 6 months reduced the overall cost compared to targeting the entire MSM population but still generated ICERS >$110 000 per QALYG. We suggest reaching higher-risk MSM through targeting of HIV-negative men in discordant regular partnerships.

Our modeling analysis has limitations. Although there is a large amount of data describing the sexual behavior of MSM in NSW, translating these data into appropriate parameter values is difficult, particularly for those describing group sex, serosorting, strategic positioning, and sexual behavior within regular partnerships. However, we were able to represent these behaviors while also accurately reflecting the trends in HIV epidemiology up to 2010. We do not capture variations in PrEP use over time. Men with undetectable drug levels may increase their adherence at times of higher risk and receive some protection from PrEP, making it more cost-effective.
Parameters describing the development of drug resistance are also highly uncertain, particularly the efficacy of PrEP against majoritysi-resistant viral strains. We saw only minimal levels of resistance develop. However, due to the reduced viral fitness and the high testing rate in the model population, our results will be robust to variations in the level of drug resistance in the population. Data describing the exact proportion of MSM on each ART regimen are difficult to obtain, and demarcating regimen lines or class stages is complex. This could affect our overall annual cost estimates for ART provision due to the variation in cost of different regimens. However, we used a simple model based on the only data available in Australia, and it provides a reasonable estimate for the number of MSM taking each line of ART. Changes to the proportion of MSM on each line have a similar effect on the cost of each scenario. Therefore, our rankings of PrEP interventions in terms of cost-effectiveness and our overall conclusions are maintained.

In conclusion, our modeled analysis demonstrates that PrEP provided to the wider MSM population would not be cost-effective. Use among HIV-negative men in a discordant regular partnership would provide substantial health gain at a lower cost. We hope the findings from this study will provide insight to Australian policymakers and healthcare professionals as to whom to provide PrEP.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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**References**


