

Title: The cost-effectiveness of HIV pre-exposure prophylaxis among heterosexual men in South Africa: a cost-utility modelling analysis

Authors:

Michelle Vogelzang MSc¹, Fern Terris-Prestholt PhD¹, Peter Vickerman DPhil², Sinead Delany-Moretlwe PhD³, Danielle Travill MBChB³, Matthew Quaife PhD^{1,3}

1 Department of Global Health and Development, London School of Hygiene and Tropical Medicine, United Kingdom

2 School of Social and Community Medicine, University of Bristol, United Kingdom

3 Wits RHI, University of the Witwatersrand, South Africa

Corresponding Author:

Michelle Vogelzang

Email: mvogelzang1@gmail.com

Tel: +44747407538

Address: LSHTM, 15-17 Tavistock Place, London, WC1H 9SH, UK

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Running Head: PrEP Cost-utility for South African men

Ethical Statement: The study was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee (M140614) and the Research Ethics Committee at the London School of Hygiene and Tropical Medicine (8541-2). All participation in the DCE and supporting qualitative studies was voluntary and subject to completion of a written informed consent process.

ABSTRACT

Introduction: Heterosexual men are not considered a key population in the HIV response and are mostly absent from pre-exposure prophylaxis (PrEP) studies to-date. Yet South African men face considerable HIV risk. We estimate the incremental cost-effectiveness of providing oral PrEP, injectable PrEP, or a combination of both to heterosexual South African men to assess if providing PrEP would efficiently use resources.

Methods: Epidemiological and costing models estimated the one-year costs and outcomes associated with PrEP use in three scenarios. PrEP uptake was estimated for younger (aged 18-24) and older (aged 25-49) men using a discrete choice experiment. Scenarios were compared to a baseline scenario of male condom use, while a health system perspective was used to estimate discounted lifetime costs averted per HIV infection. PrEP benefit was estimated in disability-adjusted life years (DALYs) averted. Uncertainty around the estimated incremental cost-effectiveness ratios (ICERs) were assessed using deterministic and probabilistic sensitivity analyses.

Results: No PrEP intervention scenarios were cost-effective for both age-groups at a willingness-to-pay threshold of \$1,175/DALY averted. The lowest ICER (\$2,873/DALY averted) was for the provision of oral PrEP to older men, although probability of cost-effectiveness was just 26%. Results found that ICERs were sensitive to HIV incidence and antiretroviral coverage.

Conclusion: This study estimates that providing PrEP to heterosexual South African men is not cost-effective at current cost-effectiveness thresholds. Given the ICERs' sensitivity to several variables, alongside the heterogeneity of HIV infection among South African men, PrEP may be cost-effective for older men with high incidence and other subgroups based on locality and race. We recommend further investigation to better identify and target these groups.

Keywords: HIV prevention; pre-exposure prophylaxis (PrEP); South Africa; heterosexual men; cost-effectiveness

MANUSCRIPT

INTRODUCTION

The HIV/AIDS response in South Africa is likely the largest and most costly in the world at around USD\$2 billion in 2018 with almost 80% of all spending from domestic public funds[1]. The epidemic is generalised and although incidence is decreasing overall[1], prevalence and incidence vary geographically and within population subgroups. Consequently, investment in preventative interventions has focused on certain key populations, yet men have been described as a “blind-spot” in the HIV response[2]. South African men have been identified as one of the key drivers of the country’s HIV epidemic due to comparatively low levels of health-seeking behaviour and age disparate relationships, alongside gender norms and inequalities that contribute to the cycle of transmission[3]. Yet, unless in a serodiscordant relationship, men have been largely absent from studies on new preventative technologies.

The South African government’s combination prevention strategy was recently updated to include daily oral PrEP at select facilities to female sex workers (FSW), men who have sex with men (MSM), serodiscordant couples, and adolescent girls and young women (AGYW)[4], [5]. A second PrEP formulation, cabotegravir, a long-acting injectable, is in phase III trials[6]–[9] to test its efficacy at preventing HIV acquisition, as an alternative to oral PrEP[6]. The effectiveness of PrEP is dependent on both biological determinants of drug concentration and adherence to the product. Oral PrEP, which is required to be taken daily under current South African guidelines, has poor adherence in some studies[10]–[12]. Good adherence may be partly attributable to convenience of use; consequently, injectable PrEP administered every few weeks may result in better adherence than a daily oral pill[13].

Although the country’s HIV response is comparatively well funded, existing programmes are not effectively reaching heterosexual men in the general population. Shisana et al.[14] argue for an expanded definition of key populations that recognises the varied risks faced by members of the general South African population. Although overall incidence in South Africa is decreasing[1], the 2012 survey identified urban informal areas as having the highest HIV prevalence (20%) by locality type, and Black African men as having the highest prevalence by race (15%) [15]. Non-biomedical HIV prevention activities have had varying success at effectively reaching men, with only 34% of men aged 15-64 years medically circumcised [16].

Only providing PrEP for heterosexual men who are in serodiscordant relationships may miss others at high risk of HIV acquisition. Additionally, the considerable size and potential impact of the male heterosexual population on HIV transmission in South Africa makes this population group worth investigating. To-date, there has been no study assessing the potential cost-effectiveness of PrEP introduction among heterosexual men in generalised epidemics. This study addresses this gap by conducting a cost-utility analysis for the provision of oral and injectable PrEP to South African men.

METHODS

Model design

Static epidemiological and costing models were developed to estimate the health system costs and impact (DALYs averted) associated with use of oral and injectable PrEP by heterosexual South African men under three intervention scenarios : 1) Provision of oral PrEP, 2) provision of injectable PrEP, and 3) provision of dual PrEP (both oral and injectable PrEP) where men’s preference for one modality over the other was considered using a discrete choice experiment (DCE) (Model structure in Supplement A). Results for each scenario were compared to a counterfactual of current practice (no PrEP). We take a simple, transparent modelling approach and focus on the impact of PrEP modalities

in one year, and do not model temporal reductions in the overall level of HIV transmission due to long-term product use, which may be sensitive to assumptions around adherence and retention. We model the one-year impact of introducing each product among heterosexual men in South Africa and compare the total and incremental costs and benefits of each of the three introduction scenarios over the life course. Summary model inputs are listed in Table 1 with full details available in Supplement B.

Product uptake and study cohorts

A DCE, conducted in South Africa in 2015, assessed the preferences of a random sample of peri-urban men for three HIV prevention products (condoms, oral and injectable PrEP)[17]. We used DCE data[17] for the 95% of men reporting sexual attraction to women to estimate uptake of daily oral PrEP and 3-monthly injectable PrEP for two cohorts: younger men aged 18-24 and older men 25-49. These age cohorts were selected due to the availability of epidemiological incidence data for South African men in similar age groups.

Epidemiology

Central prevalence and incidence for each cohort were taken from the 2017 HSRC survey and weighted by population[16], [18], [19]. Prevalence and incidence for men 15-24 years was assumed to be equal to the incidence for the 18-24 year-old cohort (Table 1)[16].

Estimating costs

Data from a demonstration project on the provision of PrEP among South African FSW was used to establish costs associated with the provision of PrEP[10]. Costing calculations and assumptions are detailed in supplement B. In brief, we use primary cost data from a PrEP demonstration project among FSW in South Africa, take a health system perspective to include all relevant treatment and hospitalisation costs, and account for variation between first- and second-line ART. All cost parameters were adjusted for inflation and adjusted to 2018 USD. Lifetime costs were applied after the first year modelled and discounted at 3% based on life expectancy and adjusted for anticipated inflation using the January 2018 inflation rate.

The incremental cost-effectiveness ratios (ICERs) from each scenario were compared to a conservative cost-effectiveness threshold of USD\$1,175/DALY averted. This threshold was taken from the lowest estimates of Woods et al.[20] following critiques of cost-effectiveness thresholds based on Gross Domestic Product (GDP)[21]–[23].

ART coverage

ART coverage was assumed to be unchanged from the current national coverage of 61% of HIV-positive individuals[1]; however, the effect of variable coverage rates on the incremental cost-effectiveness ratio (ICER) was explored in a sensitivity analysis.

Prevention product efficacy

The effectiveness of any HIV prevention product was estimated as the product of efficacy, correct use and adherence (Table 1. More details in Supplement C). Published evidence on product effectiveness was used to calculate central, best case, and worse case effectiveness estimates. As injectable PrEP was still in the trial stage, efficacy per dose was assumed to be similar to oral PrEP.

Calculating protective effect

As condoms act as a physical barrier and PrEP is pharmacological, the model assumes that protective effect of multiple products is additive. The final protective effect (P) of a PrEP product (denoted $i=1\dots m$) under each intervention scenario (s) was determined using formula (1) adapted from Quaipe et al.[17]. E_0U_0 represents base case protection from existing condom use (U_0) at current efficacy (E_0), α is the estimated proportional decrease in condom use among previous condom users who now use

PrEP, and PrEP efficacy ($E_{i,c}$) and uptake ($U_{i,c}$) varies between PrEP products and among condom users ($c=1$) and non-condom users ($c=0$). The formula is below, with further details in Supplement C.

$$P_m^s = \frac{\sum_{i=1\dots m} [U_{i,0}^s E_i^s (1 - U_0) + E_0 U_0 U_{i,1}^s E_i^s (1 - \alpha) + E_0 U_0 U_{i,1}^s E_i^s \alpha] + (1 - U_{i,1}^s) - E_0 U_0}{1 - E_0 U_0} \quad (1)$$

The protective effect is equivalent to the reduction in incidence resulting from the use of PrEP and any change in condom use. This protective effect was applied to the baseline incidence to determine the new incidence rate associated with each PrEP scenario compared to the counterfactual. The new incidence was calculated as:

$$Incidence_{new} = Incidence_{baseline} * (1 - P_m^s)$$

DALYs

Disability weightings associated with HIV and ART take-up were taken from the 2013 Global Burden of Disease Report (Supplement B). Years lived with disability were calculated for both cohorts, accounting for ART coverage and discounted at 3%. It was assumed that those not on treatment progressed to symptomatic HIV after the first model year while those on treatment were initiated immediately. All those with HIV were assumed to experience an AIDS health state for two years before death. Age-specific weighting was not used in the DALY calculation. Total DALYs averted were calculated by multiplying the number of infections averted by the intervention by the average discounted lifetime DALYs averted accounting for age and ART coverage rate.

Uncertainty analyses

The ICER of providing PrEP in each of the three intervention scenarios given a counterfactual of current practice was calculated as net costs divided by the DALYs averted per scenario. ICERs were calculated for varying incidence levels (central and bounds), and further one-way deterministic sensitivity analyses (DSA) were conducted using upper and lower bound model parameters. Two-way deterministic sensitivity analyses simultaneously varied two parameters that caused the most variation in ICERs in order to determine further uncertainty (Supplement H). Additionally, a threshold analysis was conducted on the ICER for each intervention scenario and each male sub-group to identify the minimum incidence required to produce a cost-effective result (Supplement G). Finally, a probabilistic sensitivity analysis (PSA) sampled parameter values 1000 times with results presented as cost-effectiveness acceptability curves (CEACs).

Ethical approvals

The DCE study was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee (M140614) and the Research Ethics Committee at the London School of Hygiene and Tropical Medicine (8541-2).

Table 1: Summary of model parameters used in epidemiological and costing model. Parameters to determine the cost-effectiveness of the use of oral, injectable (inj.) or dual pre-exposure prophylaxis (PrEP) among South African (RSA) heterosexual men for one year.

ZAR = South African Rand; USD = United States Dollars, Dist. = Distribution

Type	Variable Description	Central Value	Lower – Upper Bounds	Dist.	Reference
Epidemiology	HIV prevalence (Men, 15-24)	4.7%	(3.8% - 5.7%)	Beta	[16]
	HIV prevalence (Men, 25-49)	19.4%	(15.5% - 23.3%)	Beta	[16]
	HIV incidence (Men, <25)	0.49%	(0.27% - 0.71%)	Beta	[16]
	HIV incidence (Men, 25+)	0.97%	(0.85% - 1.09%)	Beta	[16]
Costs	Oral PrEP (30 pills) (ZAR, 2018)	15.21	-		[24]
	Inj. PrEP (ZAR, 2018)	15.21	(10 - 70.69)	Gamma	Central: Assumption [24], Low bound -33%, High bound [25]
	VCT session (USD, 2015)	18.10	(15.1 - 21.2)	Gamma	[10]
	PrEP enrolment visit (USD, 2015)	29.90	(24.2 - 35.6)	Gamma	
	PrEP monitoring visit (USD, 2015)	30.40	(28.2 - 32.6)	Gamma	
	PrEP refill visit (USD, 2015)	2.00	(1.4 - 2.6)	Gamma	
	Early ART enrolment visit (USD, 2015)	57.20	(55.7 - 58.8)	Gamma	
	Early ART monitoring visit (USD, 2015)	59.40	(54.6 - 64.2)	Gamma	
	Early ART refill visit (USD, 2015)	3.30	(1.5 - 5.1)	Gamma	
	HIV+ population annual hospital admission	7%	(6% - 8%)	Uniform	[26] range assumed
	Annual HIV+ hospitalisation cost to health system (USD, 2009)	72	(56 – 89)	Gamma	[26]
	Annual supply 1L ART (DTG/TDF/EFV) (USD, 2017)	75.00	(56.25 - 93.75)	Uniform	[25], Bounds +/-25%
	Annual supply 2L ART (USD, 2018)	463.98	(350 - 577.95)	Gamma	[27], [28]
	Exchange rate, 2018 ZAR:USD	0.07426			[29]
	Historical inflation (2015-18 ave.)	5.3%			[30]
	Future RSA inflation	4.4%	(4% - 6%)		[31], CI assumed
	Discount rate ART costs	3%			[32]
ART coverage	0.61	(0.48 - 0.81)	Beta	[1], upper bound at UNAIDS target	
Proportion of time spent on 1L	0.8			Assumption based on probability of switching [28]	
Proportion of time spent on 2L	0.2			Assumption	
Population	Median age at death (average male)	52.7			[33]
	Average age at infection (<25)	24	22 - 24		Assumption
	Average age at infection (25+)	29	26 - 33		Assumption
	Life expectancy with ART	50			[34]
	Additional years of life after HIV infection (HIV+, no ART treatment)	10			[17]
HIV Prevention Products	Efficacy Oral PrEP with correct use	0.85	(0.75 - 0.95)	Uniform	[12], [35], [36]
	Efficacy Inj. PrEP with correct use	0.75	(0.55 - 0.95)	Uniform	[17]
	Daily Adherence to Oral PrEP	0.9	(0.8 - 1)	Uniform	Assumption based on adherence in [35], [36]
	Average time on Oral PrEP over year	0.8	(0.75 - 1)	Uniform	Assumption based on data from [35], [36]
	Average time on Inj. PrEP over year	0.8	(0.75 - 1)	Uniform	Assumption based on data from [35], [36]
	Consistent condom user (<25)	0.55	(0.43 - 0.68)	Uniform	[37] ¹
	Consistent condom user (25+)	0.46	(0.38 - 0.54)	Uniform	[37] ¹
	% decrease in condom use	0.1	(0.2 - 0.05)	Uniform	[38]
	Probability of correct condom use	0.96	(0.94 - 0.98)	Beta	Assumption
Condom efficacy with correct use	0.9			[38], [39]	

RESULTS

Uptake

The DCE indicates that PrEP uptake may be higher among non-condom users (90% in younger men and 89% in older men) than condom users (59% in younger men and 59% in older men), and that oral PrEP is more preferred than injectable PrEP.

Averted infections, DALYs and costs

Based on a potential susceptible nationwide population of 4 million younger men and 9 million older men, an estimated 3,668 infections in younger men could be averted in one year through the introduction of dual PrEP while more than 4 times as many infections (16,786) could be averted with the same intervention in older men. Introducing oral PrEP could avert 24,511 DALYs in younger men and 99,548 DALYs in older men. In contrast, less DALYs were averted if only injectable PrEP was introduced (Supplement F).

ICERs

The analysis found that, at a central incidence estimate, all calculated ICERs were not cost-effective as a threshold of \$1,175/ DALY averted (Fig. 1). However, for all intervention scenarios, the incremental cost-effectiveness ratio of providing PrEP to older men was better than providing PrEP to younger men, with introducing oral PrEP to older men having the lowest ICER (\$2,873 per DALY averted) (Fig. 1). Interestingly, the mean ICERs did not vary much across the different intervention scenario for each age sub-group (Fig. 1).

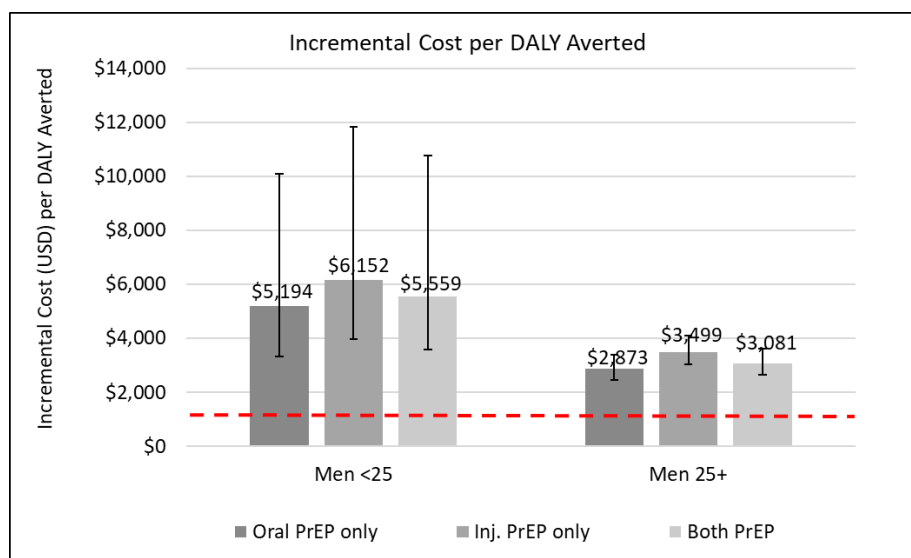


Fig. 1: Incremental Cost per DALY averted for three PrEP interventions in two South African cohorts. Results following a one-year cost-utility analysis of the use of oral, injectable, or dual PrEP for two cohorts in South Africa (men 18-24 and men 25-49). Error bars indicate variance in results using 95% confidence intervals for HIV incidence. - - - = Willingness to pay US\$1,175/ DALY averted

Deterministic sensitivity analyses

A one-way deterministic sensitivity analysis found the model results were robust to most parameter variations, but highly sensitive to a few. The ICER for each scenario was most sensitive to HIV incidence, varying the ICER by as much as 150% for younger men and 211% for older men (Fig. 2 and Supplement G). The ICER for interventions among younger men was also sensitive to ART coverage, adherence to PrEP products, and the efficacy of PrEP products although none of the sensitivity analyses resulted in the ICER going below the cost-effectiveness threshold i.e. making products cost-effective (Fig. 2). However, when HIV incidence was increased in older men, the ICER fell below the cost-effectiveness threshold for oral and dual PrEP intervention scenarios. The model was also highly sensitive to uncertainty around ART coverage, product efficacy, and adherence. Among older men, the model was also sensitive to age at infection. Additional two-way sensitivity analyses are presented in Supplement H.

We note that the sensitivity analysis for increases in incidence is mathematically equivalent to including a multiplier for onward infections in a static model. In this case, the 45% (12%) increase in incidence assumed among younger (older) men is the same as assuming that every HIV infection averted by PrEP will also avert 0.45 (0.12) onward infections. PrEP tends towards marginal cost effectiveness at these upper bounds for older men, though not for younger men.

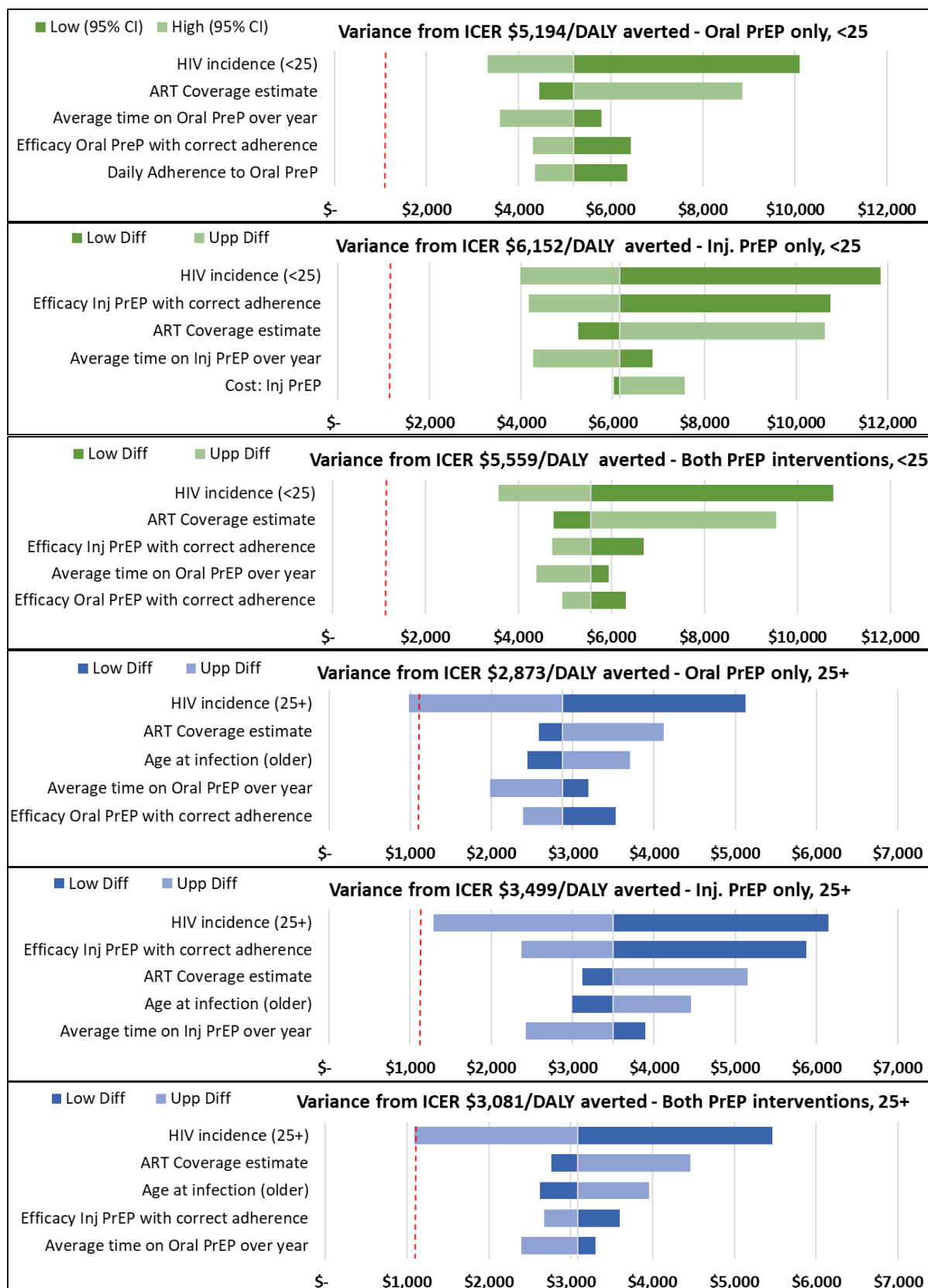


Fig. 2: One-way sensitivity analysis on the ICER for South African men 18-24 and 25-49 years. Upper and lower bound parameters (Table 1) from a one-year cost-utility analysis of the use of oral, injectable, or dual PrEP (both oral and injectable) were varied to estimate uncertainty in the calculated incremental cost-effectiveness ratio (ICER). A cost-effectiveness threshold of USD\$1,175/ DALYs averted was used. - - - = WTP

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis results are displayed in the CEACs in Figure 3 and demonstrate that oral PrEP is more likely to be cost-effective under assumptions of high incidence, but only for those over 25 years.

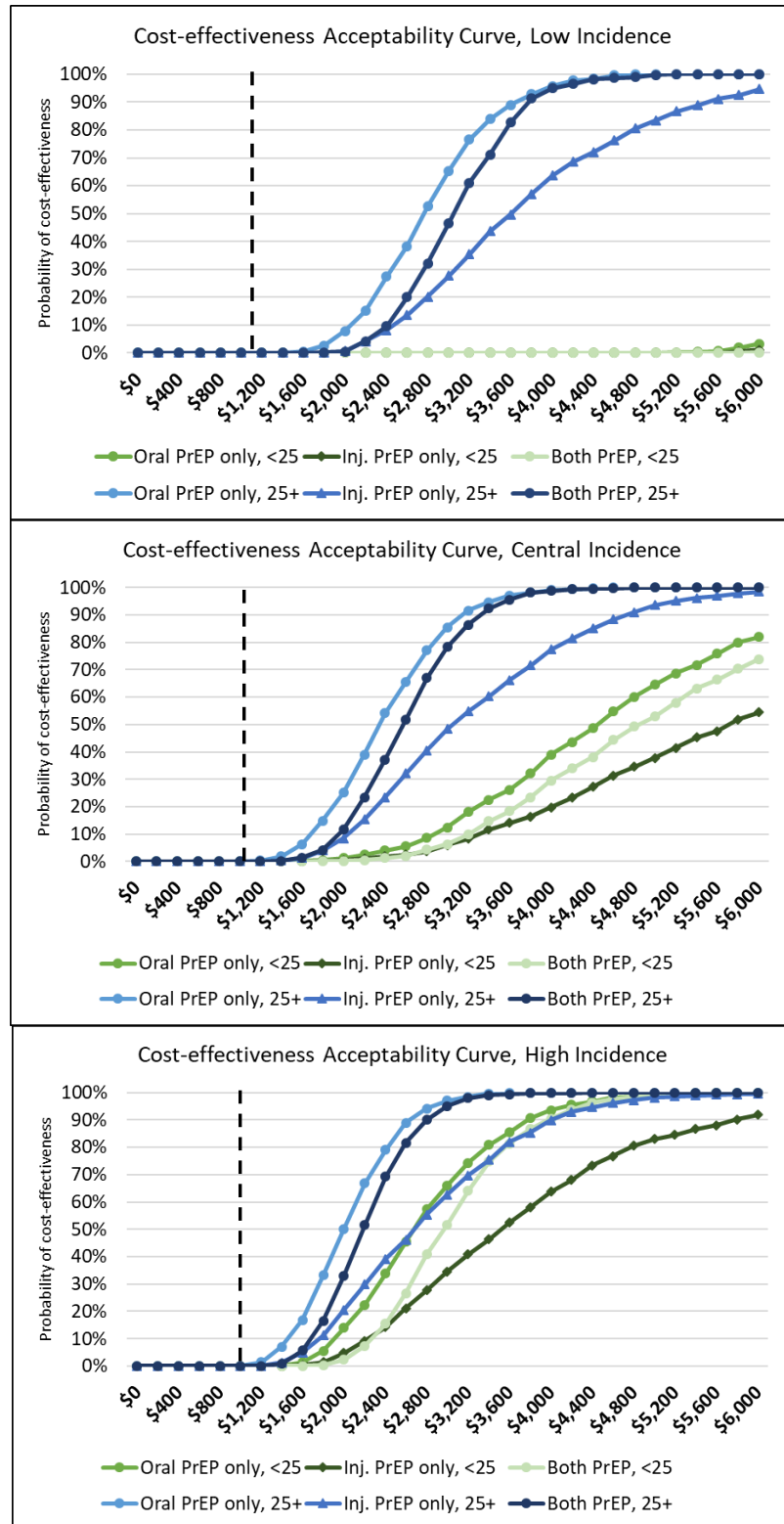


Fig. 3: Cost-effectiveness Acceptability Curve. The cost-effectiveness of PrEP availability under three intervention scenarios (oral, injectable, or dual PrEP (both oral and injectable)) for two cohorts (South African men 18-24 and men 25-49 years) at varying incidence was assessed through a Monte Carlo simulation. -- = Willingness to pay (WTP) – US\$1,175/ DALY averted

DISCUSSION

Overall, results indicate that expanding PrEP to all South African men is unlikely to be cost-effective at a willingness-to-pay threshold of USD \$1,175/DALY averted. In contrast, PrEP was found elsewhere to be highly cost effective for South African FSW and women 15-24 years at the same threshold[17]. Moreover, as ART coverage increases with the national push towards the 90% coverage target, PrEP is likely to become even less cost-effective if current incidence remains constant (Supplement H) This mirrors the analysis in South Africa's investment case for HIV and tuberculosis which found that the expansion of PrEP to AGYW, FSW, and serodiscordant couples was less cost-effective than alternative spending options[40].

This analysis found that considerably more DALYs could be averted by extending PrEP to older men than younger men; however, this may be explained by older men having a larger population cohort, a higher incidence rate, or higher predicted PrEP uptake than younger men. In particular, incidence was an important determinant of cost-effectiveness. According to the WHO, "PrEP should be a priority for populations with an HIV incidence of about 3 per 100 person-years or higher"[41]. However, this study demonstrated that a <2% incidence in the target population could result in a cost-effective intervention (shown in sensitivity analyses of Supplement G). Incidence is substantially harder to measure than prevalence, and data are not currently publicly available at granular levels, such as by age group, sex and race for men. A study in 2017 suggests that black men in informal urban areas have higher incidence rates than their rural or white counterparts[16] but exact data for our cohorts is not available.. Ideally, further studies would build more heterogeneity into the population cohort to determine if PrEP is cost-effective to specific male population subsets which could be effectively targeted by PrEP programmes, for example age or geographical heterogeneity.

Without the DCE, uptake parameters across cohorts and products would be assumptions or based on expert opinions, which are uncertain. Inclusion of men's stated preferences considers patterns of heterogeneity in use (e.g. among condom users) within the targeted population[37], [42] and can aid in determining the true cost implications of introducing PrEP[43]. Although, using stated preference data may introduce hypothetical bias since users are not observed [43]. However, systematic review evidence shows that DCEs can predict health choices with imperfect but substantive accuracy[43].

Furthermore, the DCE found condom use likely to decrease with the uptake of PrEP making it important that programmes continue to emphasise co-use, particularly if users cannot fully adhere to PrEP. This analysis assumed high levels of adherence compared to observational studies in other populations. A study among FSW found adherence has been observed to be low (70%) and loss to follow up high (77%) after 12 months[10]. In studies with serodiscordant couples (including heterosexual men), adherence was higher at 89%[35], and in a recent study on MSM in Australia, adherence was 85%[36]. This analysis assumed retention on both injectable and oral PrEP was equal, although comparatively high.

At a willingness-to-pay threshold of USD\$1,175, this study does not support a policy where PrEP is expanded to heterosexual South African men; however, we acknowledge several limitations to this study. Firstly, the choice of threshold greatly impacts recommendations. South Africa does not yet have a standard cost per DALY averted threshold, so we used the lower bound threshold from Woods et al.[20]. However, this threshold was calculated with a number of assumptions and sources of uncertainty, and at Wood's upper bound estimate \$4,714 per DALY averted[20], all PrEP scenarios for older men were cost-effective. Alternatively, the South African HIV investment case considers interventions cost-effective based on life-year saved (LYS) as benchmarked against costs of expanding UTT (~\$1,000 per LYS)[40]. Meyer-Rath calculated that actual spending on HIV interventions in South Africa used a threshold of \$547-\$872 per LYS[44]. There is therefore substantial uncertainty in South

Africa's true willingness to pay for new health investments, which would help inform analyses such as this.

Secondly, this model has structural limitations as future DALYs and costs averted from preventing HIV infections by having fewer infectious people (especially younger women) in the population is not considered. This understates PrEP's cost-effectiveness. Furthermore, South African men are known to test for HIV less regularly and initiate treatment later than women[3] but this model does not consider the downstream benefits of men's PrEP-associated access to health services such as initial HIV testing, regular HIV testing and STI screening, and earlier ART initiation[34]. We do not model how improved treatment regimens and adherence could reduce the proportion of infectious HIV positive persons. Similarly, we do not model changes in other preventative interventions such as male circumcision, and further research is needed to estimate HIV incidence among circumcised and non-circumcised men. This model also does not use age-weighted DALYs which would have made cost-estimates for infection averted in younger men more favourable.

As in a similar model[17], although our simple epidemiological model omits future costs and benefits of PrEP expansion, it is effective at providing transparent estimates of the individual benefits of PrEP for men, likely similar to short-term results should this intervention have been trialled[17]. A dynamic transmission model would have provided better insight into the long-term implications of PrEP expansion; however, projections would be strongly reliant on uncertain assumptions around disease transmission. Furthermore, Eaton et al's.[45] analysis of twelve dynamic models of ART uptake in South Africa found considerable variability in predictions and inaccurate predictions of future infections, suggesting that increased complexity is not necessarily a guarantee of accuracy.

There is uncertainty in the costs associated with the roll out of PrEP. Costs used in this study were drawn from cost estimates for the provision of PrEP to FSW in select government clinics. If PrEP was made available to men, it is not known where it would be distributed, or how potentially lower utilisation may affect costs. Older men in particular may need extra encouragement to attend services if PrEP is provided from government facilities that traditionally cater for women. Additionally, injectable PrEP (cabotegravir) is still under trial[46] and as a result the efficacy and market price of the product is yet to be determined. Even if approved, cabotegravir will remain subject to patent law and originator prices unless price negotiations are agreed upon. This may prevent the product from being available in South Africa. Lastly, PrEP has known side effects[47], [48]; however, the DALYs and associated care costs due to taking PrEP are unknown and not factored into this model. To understand the true cost implications of expanded PrEP, additional data needs to be collected to value these.

Finally, there are ethical considerations around expanding PrEP to those who may benefit. Some may argue that there is a human rights imperative to making PrEP available to anyone who wants it. This could even possibly result in the most at-risk men self-selecting to take PrEP or being more adherent to the product, which would make PrEP more cost-effective than estimated here.

CONCLUSION

This is the first study known to evaluate the cost-effectiveness of expanding PrEP to heterosexual men not in serodiscordant couples in a setting when HIV is a generalised epidemic. While our findings indicate neither oral nor injectable PrEP is cost-effective at a threshold of USD1,175/DALY averted, there may still be potential for select subpopulations such as those with high HIV incidence or low ART coverage to benefit. Future studies should explore the impact of variation in HIV risk and uptake on cost-effectiveness, particularly the role of geographical and age-related heterogeneities.

ACKNOWLEDGMENTS

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