The impact of self-selection based on HIV risk on the cost-effectiveness of preexposure prophylaxis in South Africa

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Objectives: We explored the impact and cost-effectiveness of preexposure prophylaxis (PrEP) provision to different populations in South Africa, with and without effective self-selection by individuals at highest risk of contracting HIV (through concurrent partnerships and/or commercial sex).

Design and methods: We used a previously developed HIV transmission model to analyse the epidemiological impact of PrEP provision to adolescents, young adults, pregnant women, female sex workers (FSWs) and (MSM), and data from South African PrEP programmes to estimate the cost and cost-effectiveness of PrEP (cost in 2019 USD per HIV infection averted over 20 years, 2019, 38). PrEP uptake followed data from early implementation sites, scaled-up linearly over 3 years, with target coverage set to 18% for adolescents, young adults and pregnant women, 30% for FSW and 54% for MSM.

Results: The annual cost of PrEP provision ranges between \$75 and \$134 per person. PrEP provision adolescents and young adults, regardless of risk behaviour, will each avert 3.2–4.8% of HIV infections over 20 years; provision to high-risk individuals only has similar impact at lower total cost. The incremental cost per HIV infection averted is lower in high-risk vs. all-risk sub-populations within female adolescents (\$507 vs. \$4537), male adolescents (\$2108 vs. \$5637), young women (\$1592 vs. \$10 323) and young men (\$2605 vs. \$7715), becoming cost saving within 20 years for high-risk adolescents, young women, MSM and FSWs.

Conclusion: PrEP is an expensive prevention intervention but uptake by those at the highest risk of HIV infection will make it more cost-effective, and cost-saving after 14–18 years.

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Introduction

In September 2015, the WHO released updated antiretroviral treatment guidelines, which included recommendations that preexposure prophylaxis (PrEP) be made available to people at substantial risk of acquiring HIV [1–3]. 'Substantial risk of acquiring HIV' was purposefully not defined in the guidelines, although an acceptable threshold for high risk was given as an annual HIV incidence of greater than 3% in a particular sub-population [1]. PrEP has been shown to be effective in preventing HIV infection through sexual transmission in different population groups, when used consistently [3–10].

Although previous studies focusing on sub-Saharan Africa have concluded that overall PrEP provision is cost-effective in a number of countries, in relation to a threshold of three times gross domestic product per capita [11–21], few have looked at how HIV, cost and cost-effectiveness are impacted when targeting PrEP to high-risk subpopulations relative to the general population [12,15,18,20,21]. None of these studies have included the detailed costs of PrEP provision based on observations of routine care.

Additionally, a recently published review of modelled economic analyses of PrEP provision by Case *et al.* [22] found that there was limited modelling of PrEP for men at high risk of HIV, and modelling of PrEP provision for female adolescents and young women did not incorporate uptake and adherence observed in current implementation projects. Case *et al.* identified that most modelling studies assumed that existing human resources would suffice to cover an increase in PrEP demand, and many excluded the cost of outreach and engagement, as well as the additional benefit of linkages of PrEP programmes to HIV testing and treatment.

The 2016 South African HIV Investment Case [23] estimated that PrEP provision was one of the least cost-effective interventions to implement and should only be implemented after scaling up more cost-effective interventions, such as condom provision, medical male circumcision (MMC), universal test and treat (UTT), HIV counselling and testing of different population groups, and a number of social and behaviour change mass media campaigns. However, the Investment Case did not consider a higher adoption by individuals at higher HIV risk and was based on preliminary cost estimates that have since been updated based on data from early implementation sites, where delivery is part of other public health services.

PrEP roll-out in South Africa commenced in June 2016 with the launch of a female sex worker (FSW)-targeted prevention campaign. More recently, PrEP has also become available to MSM, university students and young women, financed by international donors and by the government's conditional grant for HIV/AIDS [23]. To guide local PrEP guidelines [24] and planning of further PrEP scale-up under the conditional grant, we were tasked by the South African National Department of Health's (NDOH) PrEP technical working group (TWG) to estimate the average and total cost of PrEP provision to different populations, and to generate evidence on which distribution strategy would be most cost-effective and whether higher PrEP uptake by high-risk individuals would improve cost-effectiveness.

This study aims to determine the cost-effectiveness of provision of daily oral PrEP in South Africa, a setting with one of the highest HIV prevalence levels in the world, whereas considering the possibility that those at higher risk of contracting HIV may self-select into the PrEP programme. Our focus on self-selection over supply-side targeting was informed by the TWG's preference that a risk screening tool should not be used to determine whether an individual receives PrEP, to avoid stigmatizing PrEP as an intervention reserved for those with higher risk behaviour and to not exclude anybody who perceive themselves to be at HIV risk. Existing risk-scoring tools for HIV often have low sensitivity and/or specificity, leading to misclassification of those at risk of HIV [25–27].

Methods

Epidemiological model

The impact of PrEP on HIV incidence and HIV infections averted was estimated using the Thembisa model (version 4.2) [28,29], a compartmental HIV transmission model of the South African HIV epidemic. The population is stratified by age, sex, sexual experience, marital status, HIV testing history, male circumcision status and sexual behaviour. In addition, the sexually experienced population is divided into two broad sexual risk groups: 'high-risk' (people with a propensity for concurrent partnerships and/or commercial sex) and 'low-risk', with the high-risk group constituting 35% of men and 25% of women. For further details on the model calibration and sexual behaviour assumptions, see section 1 in the supplementary material, http://links.lww.com/QAD/B646.

PrEP is modelled by subdividing the sexually experienced risk groups into individuals who are receiving PrEP or not. PrEP uptake rates vary by age, sex and risk group. On the basis of a recent meta-analysis, PrEP effectiveness, which accounts for both efficacy and adherence, is assumed to be 65% for non-MSM and 85% for MSM [3,4]. The average duration on PrEP is assumed to be 2 years [29]. On the basis of data from open-label PrEP trials, it is assumed that PrEP users have a 10% lower rate of condom use than individuals of the same age and sex who are not using PrEP [30,31]. Individuals who acquire HIV while on PrEP are assumed to be less likely to transmit HIV than individuals who acquire HIV in the absence of regular HIV testing, as the latter would remain undiagnosed and untreated for longer periods.

Scenarios and target population

We separately modelled the epidemiological impact and the cost effectiveness of PrEP provision to adolescents aged 15–19 years, young adults aged 20–24 years, pregnant women, MSM and FSW of all ages. For the pregnant women, women remain on PrEP from the time of first antenatal visit until cessation of breastfeeding. In HIV-negative women, 87% are assumed to breastfeed, and of those who choose to breastfeed, the median duration of breastfeeding is assumed to be 18 months [32]. For adolescents and young adults, we evaluated additional subscenarios in which only the high-risk sub-population would adopt PrEP, to simulate scenarios in which individuals can assess their own HIV risk accurately and only those who correctly consider themselves to be at high-risk use PrEP.

For the main analysis, PrEP was assumed to be scaled-up linearly from 2019 onwards. On the basis of guidance from the NDOH's PrEP TWG and current uptake in demonstration projects, a target coverage of 18% for adolescents, young adults and pregnant women, 30% for FSWs and 54% for MSM by 2021, maintained up until 2038, was assumed. For additional information on model parameterisation and calibration see Appendix.

Cost and cost-effectiveness analysis

The average cost of PrEP provision was estimated using an ingredient approach, as complete cost data was unavailable because of PrEP being not yet implemented in the public sector beyond demonstration or early implementation sites. We worked closely with the NDOH's PrEP TWG and with experts from two demonstration projects of PrEP provision in South Africa: the Treatment And Prevention for FSW in South Africa (TAPS) demonstration project of PrEP provision to sex workers, for which data from a comprehensive economic analysis was available [33], and the Health4-Men demonstration projects of PrEP provision to MSM. On the basis of these and on the WHO and South African PrEP guidelines [24], we assumed PrEP would be provided in primary healthcare clinics alongside a package of HIV prevention interventions, including HIV testing and counselling, provision of condoms, screening for symptoms of sexually transmitted infections, laboratory monitoring, and adherence counselling. For additional details of cost analysis, see section 2 in Appendix, http://links.lww.com/QAD/B646; for a summary of the cost items included see Supplementary Table S1, http://links.lww.com/QAD/B646; a detailed break-down of the costs is available in Supplementary Table S2, http://links.lww.com/QAD/B646.

Costs were analysed from the provider perspective, the South African government, and separated into patient-level and health system-level costs. Patient-level costs included costs associated with provision at the facility, such as cost of staff, HIV testing (at screening, 3-monthly per year and at re-initiation), laboratory monitoring tests, and the PrEP drugs (daily oral PrEP), assuming a generic combination of tenofovir and emtricitabine. We differentiated between costs for the first year (which included an initiation visit) and follow-up years, and calculated costs separately for each population group capturing differences in the HIV and syphilis prevalence, and the need for pregnancy tests.

Health-system costs included staff training, outreach, mobilisation, monitoring and evaluation costs. These costs assumed a service volume of 160 PrEP clients per clinic per year, based on demonstration project experience. Additional building maintenance and utilities were accounted for by inflating the cost per visit by 7%, based on the TAPS cost analysis [33].

Cost inputs for staff and laboratory testing were sourced from the 2019 Government Salary Scales and the 2018 National Health Laboratory Service price list, respectively. Costs for the PrEP regimen and HIV testing consumables were sourced from recent National Department of Health tenders. Costs are presented in 2019 USD, using the January to September 2019 average exchange rate of 1 USD = 14.32 South African Rand [34]. To inform future budgets, both costs and outcomes are presented undiscounted and unadjusted for inflation.

To evaluate the long-term impact of PrEP in different populations, we analysed the cost-effectiveness of PrEP as cost per HIV infection averted over a 20-year time period (2019–2038) over a baseline of currently available HIV interventions in the South African public sector HIV programme. This allowed us to ascertain the impact of a reduction in incidence because of PrEP on the need for future ART, in addition to existing prevention interventions at high coverage, such as condom provision, counselling and testing, and medical male circumcision. The calculation of HIV programme costs followed the same approach as the South African HIV Investment Case [23,35], with target populations calculated by Thembisa and per-service costs updated to 2019 prices and salaries. An additional analysis compared the cost effectiveness of PrEP provision with that of scaling up existing HIV interventions, based on an update to the South African HIV Investment Case [23] as shown in Supplementary Table S3, http://links.lww.com/QAD/B646.

Sensitivity analysis and uncertainty analysis

We evaluated the impact of uncertainty around four main model parameters (PrEP effectiveness, reduction in condom use while on PrEP, relative rate of PrEP uptake by those at low risk of HIV, and average cost) by conducting a probabilistic sensitivity analysis (PSA) using Monte Carlo simulation. The epidemiological and cost impact of PrEP was recalculated 1000 times for each population group by randomly drawing parameter values from appropriate probability distributions (Supplementary Table S4, http://links.lww.com/QAD/B646). We report the cost-effectiveness over a 20-year period consisting of the average estimate and a 95% confidence interval using the 2.5th and 97.5th percentiles. The sensitivity of incremental cost and new HIV infections averted to the parameters included in the uncertainty analysis are quantified using partial rank correlation coefficients. One-way sensitivity analyses for PrEP coverage, and average duration on PrEP was performed (Supplementary Figs. S1 and S2, http://links.lww.com/QAD/B646).

Results

Annual total HIV incidence was projected to decline in all scenarios, including baseline (Fig. 1a and b), with PrEP reducing HIV incidence marginally over time. Over a 20-year period (2019–2038), PrEP given to 18% of female adolescents and young men from all risk groups had a larger impact on new HIV infections averted compared with PrEP provision to young women (4.3 and 4%, respectively, vs. 3%) (Table 1). Providing PrEP to high-risk sub-populations within these populations, also at 18% coverage by 2021 and maintained until 2038, had 80–95% of the impact of PrEP provision to all risk groups within the same population. The largest impact was from providing PrEP to 54% of MSM, reducing new HIV infections by 4.9%, due to both larger coverage and PrEP effectiveness within this population group. Providing PrEP to 30% of FSW and 18% of pregnant women reduced the number of new HIV infections by 1.4% and 1.7% over the 20-year period, respectively. Though FSW is a high-risk group, the overall impact on reducing new HIV infections is smaller due to the fact that the FSW population is relatively small. Impact on HIV incidence within the high-risk sub-populations only are shown in Supplementary Fig. S3, http://links.lww.com/QAD/B646).

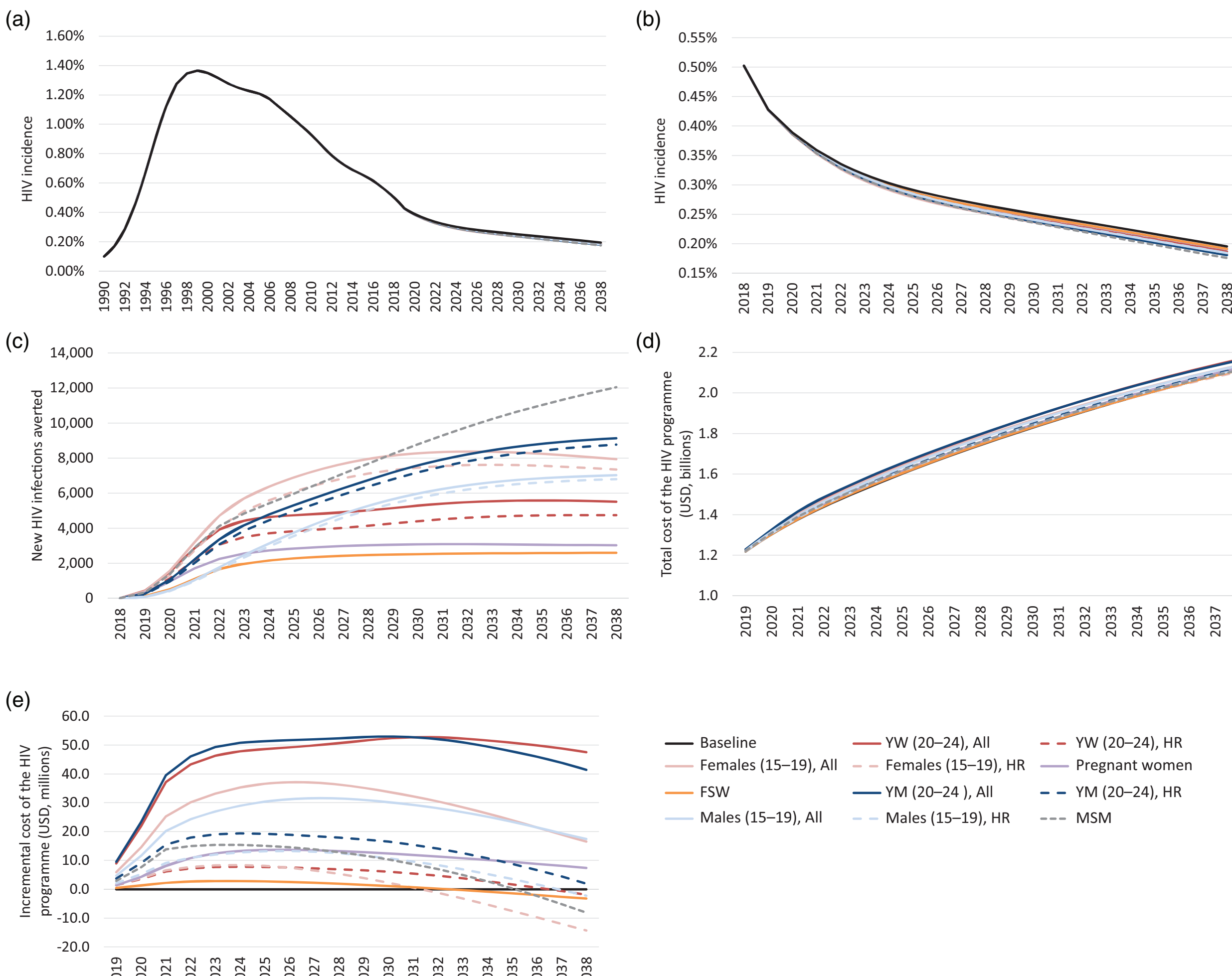

Fig. 1. Impact of preexposure prophylaxis provision to different populations on (a) total HIV incidence from 1990, (b) total HIV incidence from 2018 onwards, (c) new HIV infections averted annually, (d) total cost (2019 USD) of the HIV programme and (e) incremental cost (2019 USD) to the HIV programme.

Table 1. Cost-effectiveness of preexposure prophylaxis provision by population (2019–2038).

	Baseline	Female adolescents (15–19)		Young women (20–24)		Pregnant/ breastfeeding women	FSW	Male adolescents (15–19)		Young men (20–24)		MSM
PrEP coverage by 2021	0%	18%		18%		18%	30%	18%		18%		54%
Risk group		All	High-risk	All	High-risk	All	All	All	High-risk	All	High-risk	All
Number of person-years on PrEP (millions)	0.0	7.3	2.0	10.0	2.0	2.8	0.8	5.7	2.6	10.1	4.0	3.4
Total HIV programme cost (billions 2019 USD)	34.68	35.29	34.74	35.63	34.80	34.91	34.71	35.20	34.87	35.64	34.99	34.89
Incremental HIV programme cost (millions 2019 USD) (% change)		608 (1.8%)	61 (0.2%)	949 (2.7%)	121 (0.3%)	227 (0.7%)	31 (0.1%)	522 (1.5%)	187 (0.5%)	957 (2.8%)	306 (0.9%)	205 (0.6%)
Total new HIV infections (millions)	3.81	2.95	2.96	2.99	3.01	3.03	3.04	2.99	2.99	2.96	2.96	2.93
HIV infections averted (thousands) (% change)		134 (4.8%)	121 (4.2%)	92 (3.2%)	76 (2.6%)	53 (1.8%)	43 (1.4%)	93 (3.2%)	89 (3.1%)	124 (4.4%)	117 (4.1%)	150 (5.4%)
ICER (USD/HIV infection averted)		4537	507	10,323	1592	4,283	724	5637	2108	7715	2605	1370

FSW, female sex workers; ICER, incremental cost-effectiveness ratio; USD, United States dollar.

The average cost of PrEP provision per nonpregnant client was \$129–\$134 for the first year, and \$107–\$110 for every year thereafter (Table 2). PrEP for pregnant/breastfeeding women cost \$75 for coverage during their first year (as PrEP provision was assumed to be part of ANC services) and \$110 for every year thereafter. Across initiation and follow-up years, the drug cost only contributed 35% of the cost, whereas 13–28% was because of laboratory testing (Fig. 2). Laboratory costs are higher in the first year because of the higher number of monitoring tests required. Staff costs, not reported separately, made up ∼25% of the cost.

The annual cost of the HIV programme was expected to rise in the baseline scenario as a result of covering an increasing population with interventions including ART, costing \$34.7 billion over the 20-year period (2019–2038) (Table 1). Introducing PrEP increased the total cost of the HIV programme by 0.1–0.8% and by 1.2–2.3% when provided to high-risk sub-populations and all risk groups, respectively. The cost of the HIV programme increased by 1.2% over the 20-year period if 18% of pregnant/breastfeeding women were provided with PrEP. Successful self-selection by high-risk adolescents of both sexes and young women, as well as providing PrEP to FSW and MSM at our assumed target coverages, resulted in declines in the annual cost of the HIV programme, mostly because of the reduced need for ART, but only from 2033 at the earliest (Fig. 1e). The annual cost for each scenario for the first 5 years are shown in Table S4, http://links.lww.com/QAD/B646.

The differential impact of PrEP provision to the different population groups on cost and infections averted translated into stark differences in the cost-effectiveness of each scenario. PrEP provision to high-risk groups compared with all risk groups was more cost-effective across all populations: female adolescents (\$507 vs. \$4537) and male adolescents (\$2108 vs. \$5637), young women (\$1592 vs. \$10 323 per HIV infection averted) and young men (\$2605 vs. \$7715). Providing PrEP to 18% of pregnant women will cost \$7897 per HIV infection averted and providing PrEP to 30% of FSW and 54% of MSM costed \$724 and \$1370 per HIV infection averted, respectively (Table 1).

A one-way sensitivity analyses for PrEP coverage shows a linear relationship between coverage and impact, and as a result there is no optimal coverage target (Supplementary Fig. S1, http://links.lww.com/QAD/B646). One-way sensitivity analysis of average time on PrEP reaches similar conclusions (Supplementary Fig. S2, http://links.lww.com/QAD/B646).

Results from the PSA are shown in scatterplots depicting incremental cost and new HIV infections averted over the 20-year period (Supplementary Fig. S4 with varying average PrEP cost and Fig. S5 with constant cost, http://

Table 2. Preexposure prophylaxis average cost per population group for first and follow-up years on preexposure prophylaxis (2019 United States dollars).

Year of PrEP	Female adolescents (15–19)	Young women (20–24)	Pregnant/breastfeeding women	FSW	Male adolescents (15–19)	Young men (20–24)	MSM
First year	\$132	\$132	\$75	\$134	\$130	\$130	\$129
Follow-up year	\$110	\$110	\$110	\$109	\$108	\$108	\$107

FSW, female sex workers; USD, United States Dollar.

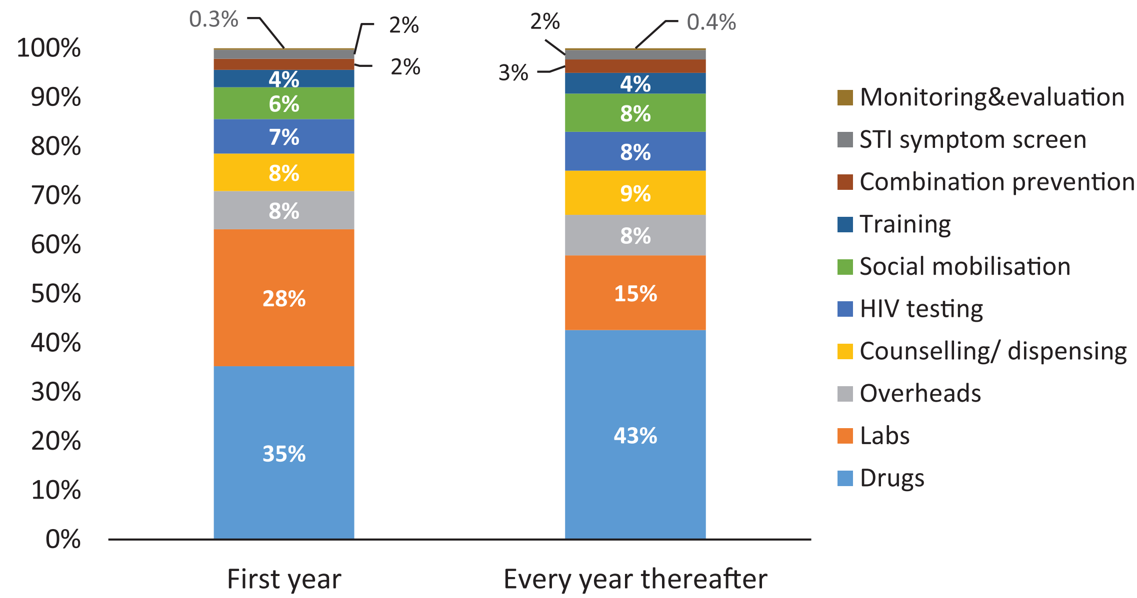

Fig. 2. Distribution of preexposure prophylaxis cost between different cost components for the average preexposure prophylaxis average cost across nonpregnant populations: (a) first year, and (b) every year thereafter.

links.lww.com/QAD/B646). The mean and the 95% confidence interval estimates are shown in Table 3. Varying the average cost of PrEP for FSW cost-saving in some scenarios, with around 22% of simulations having a negative incremental cost. Other populations with a potential for cost-savings, though with lower likelihood, were female adolescents, young women and MSM, with cost savings occurring in 0.3, 4.1 and 2% of simulations, respectively. The annual impact on new HIV infections averted and cost for each population are available in Supplementary Figs S6–S8, http://links.lww.com/QAD/B646. The 5-year budget impact is available in Supplementary Table S5 http://links.lww.com/QAD/B646).

In addition to PrEP average cost, incremental cost was most sensitive to the relative rate of PrEP uptake by those at low risk of HIV (Supplementary Table S6, http://links.lww.com/QAD/B646). New HIV infections averted were sensitive to all parameters we varied, with the exception of PrEP average cost and for PrEP uptake by those at low risk of HIV within pregnant women, FSW and MSM.

Discussion

We found that PrEP is a costly intervention at \$129–\$134 per user year for nonpregnant users, roughly half the annual cost per patient of ART, and more expensive per unit of service provided than other prevention interventions (for example, condom provision at \$0.05/condom and medical male circumcision at \$87/procedure) [36]. We found that PrEP provision to high-risk groups will have a very similar impact in terms of HIV infections averted but at a much reduced cost compared with providing PrEP to the larger sub-population at the same relative coverage level. Successful self-selection will thus allow for PrEP to be more affordable while still having a substantial impact in the general population.

Our results suggest that it may be more cost-effective to promote PrEP to adolescent girls (ages 15–19 years) than young women (ages 20–24 years). This is in part as the Thembisa model assumes a heightened biological risk of HIV transmission in younger girls, associated with the high prevalence of cervical ectopy in puberty [37], and in part because an individual who acquires HIV has more potential to transmit HIV the younger the age at which they become infected [38]. Thus, the benefits of PrEP in terms of reduced secondary transmission are greater in adolescent girls.

Our analysis echoes what existing PrEP cost-effectiveness studies have shown that targeting PrEP to high-risk populations is more cost-effective than targeting the general population [12,15,18,20,21]. We showed that targeting can make PrEP more cost effective than scaling up existing HIV interventions, such as MMC, HCT and UTT, depending on the target population.

Our analysis addresses some of the gaps identified by the PrEP modelling review by Case *et al.* [22]. Our model includes scenarios of PrEP provision for male adolescents and young men at high risk of HIV, and MSM. Our average cost includes additional staff time for all services at each visit, as we do not assume that the increase in PrEP

Table 3. Results of probabilistic sensitivity analysis; incremental impact on new HIV infections and cost (2019 USD) over 20 years (2019–2038).

			Varying PrEP average cost			Constant PrEP average cost		
PrEP target population	Number of new HIV infections averted (95% CI)	% of new HIV infections averted over baseline (95% CI)	Incremental cost of the HIV programme over baseline [millions] (95% CI)	% increase in cost of the HIV programme over baseline (95% CI)	Incremental cost effectiveness ratio [USD/HIV averted] (95% CI)	Incremental cost of the HIV programme over baseline [USD] (95% CI)	% increase in cost of the HIV programme over baseline (95% CI)	Incremental cost effectiveness ratio [USD/HIV averted] (95% CI)
Young women	82,044 (58,756;104,337)	2.7% (1.9%;3.4%)	444 (83;1,054)	1.28% (0.24%;3.04%)	5,480 (1,074;13,039)	424 (156;759)	1.22% (0.45%;2.19%)	5,220 (1,849;9,753)
Female adolescents	125,805 (92,345;154,922)	4.1% (3.0%;5.0%)	275 (5;709)	0.79% (0.02%;2.04%)	2,230 (45;5,880)	259 (75;488)	0.75% (0.22%;1.41%)	2,097 (538;4,214)
Pregnant/ breastfeeding women	53,136 (37,822;66,029)	1.7% (1.2%;2.1%)	237 (76;427)	0.68% (0.22%;1.23%)	4,592 (1,355;9,579)	226 (208;248)	0.65% (0.60%;0.72%)	4,375 (3,150;6,558)
FSW	42,813 (29,141;54,137)	1.4% (0.9%;1.8%)	34 (-17;93)	0.10% (-0.05%;0.27%)	858 (-347;2,794)	31 (15;49)	0.09% (0.04%;0.14%)	776 (282;1,691)
Young men	120,072 (100,649;136,227)	3.9% (3.3%;4.4%)	571 (183;1,163)	1.65% (0.53%;3.35%)	4,780 (1,519;9,786)	544 (334;809)	1.57% (0.96%;2.33%)	4,553 (2,655;6,970)
Male adolescents	90,352 (77,165;101,123)	2.9% (2.5%;3.3%)	324 (98;655)	0.93% (0.28%;1.89%)	3,602 (1,108;7,289)	308 (200;444)	0.89% (0.58%;1.28%)	3,425 (2,114;5,100)
MSM	149,638 (130,221;158,909)	4.9% (4.2%;5.2%)	219 (26;446)	0.63% (0.07%;1.29%)	1,473 (170;3,145)	205 (194;228)	0.59% (0.56%;0.66%)	1,378 (1,222;1,747)

demand can be covered by existing resources, and costs for outreach campaigns and mobilization. Lastly, modelling the impact of PrEP on the full range of HIV services using Thembisa allowed us to incorporate the additional uptake and benefits of increased HIV testing and subsequent treatment linkage due to PrEP uptake.

Our analysis has a number of limitations. Firstly, there is currently limited data available on the relative uptake of PrEP across different risk groups in routine care, the average duration that people will take PrEP once initiated, and on effective use. In the absence of such data, we assumed PrEP effectiveness for non-MSM populations to be 65%, reflecting the state of current evidence [3,4]. Our sensitivity analysis shows that PrEP effectiveness has a large impact on HIV incidence and a smaller but significant impact on incremental cost. Achieving better adherence to PrEP than in the clinical trial setting may be more likely if PrEP efficacy is known to the user. Regardless of the population, a strong focus on adherence, or effective use, will have to be part of any implementation strategy for the benefits from both an epidemiological and economic perspective to unfold.

Secondly, even though the three main cost drivers, drugs, HIV testing, and staff, were costed at high scales and at the lowest cadre levels possible, the estimated cost of PrEP might be an overestimate, and nonessential elements, such as demand creation and screening might become less prominent at higher levels of uptake as economies of scale might take hold. In contrast, it might be an underestimate, as additional interventions might have to be added to increase demand if self-selection is not successful.

A general limitation of frequency-dependent models, such as Thembisa is that they understate the importance of high-risk groups in sustaining HIV and STI incidence at a population level, when compared with more realistic network models [39]. This in turn implies that the cost-effectiveness of PrEP targeted to high-risk groups (especially FSWs and MSM) could be under-estimated. Another limitation is that we lack data on HIV prevalence in high-risk groups other than FSWs and MSM, and this makes it difficult to estimate with confidence the impact of higher PrEP uptake in these groups.

More work needs to be done on geospatial targeting of PrEP, as this will allow more effective targeting of those at highest risk of HIV. McGillen *et al.* [40] found that optimizing prevention interventions, including PrEP, to high-risk populations can have up to an 14% greater impact on reducing incidence compared with without PrEP. Preliminary studies have shown that the presence of sexually transmitted infections (STI) is a good surrogate marker for HIV risk; however, integrating this into a PrEP programme will increase the cost as additional laboratory testing, and possibly STI treatment, is required.

Currently discussions on integrating STI care into the PrEP programme are still underway within the NDOH. It remains to be seen whether self-selection based on individuals' own perception of risk will be successful, and what its effect on overall PrEP effectiveness will be. There has been evidence to show self-selection of those at highest risk of HIV within MSM and FSW populations [33,41,42]; however, there is uncertainty whether this would be the case in the general population as data on PrEP uptake in these populations are limited.

We found PrEP to be an expensive intervention, especially when compared with existing prevention interventions. However, if self-selection by high-risk groups is successful, it can be rendered much more cost effective and, especially if effectiveness in these populations is higher than current trial data suggest, possibly cost-saving in the long-term.

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Contributors: L.J., L.F.J. and G.M.R. drafted the manuscript. L.J. and G.M.R. developed the unit costs. L.F.J. developed the epidemiological model. L.J. and L.F.J. performed the epidemiological modelling, whereas L.J. performed the cost modelling and drafted all figures and tables. G.B.G., K.R. and B.B. provided data from South African PrEP implementation studies. H.S., S.J. and N.S. provided input from the South African government's early implementation sites. L.J., G.M.R., L.F.J., H.S., S.J., N.S. and L.G.B. conceptualized the analytical framework and scenarios and reviewed results critically. All authors critically reviewed and revised the manuscript, and approved the final manuscript.

Data sharing: A fully parameterized Microsoft Excel version of Thembisa is available on www.thembisa.org.

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Conflicts of interest

There are no conflicts of interest.

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