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Phillips, Andrew, Cambiano, Valentina, Johnson, Leigh et al. (16 more authors) (2019) Potential impact and cost-effectiveness of condomless-sex-concentrated PrEP in KwaZulu-Natal accounting for drug resistance. The Journal of Infectious Diseases. jiz667. ISSN 0022-1899

https://doi.org/10.1093/infdis/jiz667

Potential impact and cost-effectiveness of condomless-sex-concentrated PrEP in KwaZulu-Natal accounting for drug resistance

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Key words: HIV; model; individual-based; PrEP; cost-effectiveness analysis; cost; South Africa; drug resistance

Short summary

PrEP use concentrated during time periods of condomless sex has the potential to substantively impact HIV incidence and to be cost-effective in the example setting of KwaZulu-Natal, South Africa.

Abstract (200 words)

Introduction: Oral pre-exposure prophylaxis (PrEP) in the form of tenofovir-disoproxil-fumarate/emtricitabine is being implemented in selected sites in South Africa. Addressing outstanding questions on PrEP cost-effectiveness can inform further implementation.

Methods: We calibrated an individual-based model to KwaZulu-Natal to predict the impact and cost-effectiveness of PrEP, with use concentrated in periods of condomless sex, accounting for effects on drug resistance. We consider (i) PrEP availability for adolescent-girls-and-young-women (aged 15-24; AGYW) and female sex workers (FSW), and (ii) availability for everyone aged 15-64. Our primary analysis represents a level of PrEP use hypothesized to be attainable by future PrEP programmes.

Results: In the context of PrEP use in adults aged 15-64 there was a predicted 33% reduction in incidence, and 36% reduction in women aged 15-24. PrEP was cost effective, including in a range of sensitivity analyses, although with substantially reduced (cost) effectiveness under a policy of ART initiation with efavirenz- rather than dolutegravir-based regimens due to PrEP undermining ART effectiveness by increasing HIV drug resistance.

Conclusions: PrEP use concentrated during time periods of condomless sex has the potential to substantively impact HIV incidence and be cost-effective.

Introduction

Despite declining incidence, HIV remains a major public health challenge in South Africa. The roll-out of oral pre-exposure prophylaxis (PrEP) of tenofovir disoproxil fumerate (TDF) and emtricitabine (or lamivudine) to further reduce HIV incidence began with female sex workers (FSW), men who have sex with men (MSM) and adolescent girls and young women (AGYW). Model-based analyses are increasingly used to inform allocation of limited resources [1,2]. Cost-effectiveness studies of PrEP, mainly conducted before the current universal eligibility for antiretroviral therapy (ART), have cast doubt over its cost-effectiveness, in South Africa as well as elsewhere [3-12]. There has, however, been relatively little attention given to considering that people might in practice concentrate their PrEP use only during periods of condomless sex. In addition, there is a risk of taking PrEP while unknowingly having HIV, due to starting PrEP when already infected with HIV (caused by <100% HIV test sensitivity or due to being in the primary infection window period), or becoming infected while taking PrEP, due to sub-optimal adherence, less than 100% PrEP efficacy, or infection with PrEP drug resistant virus. Use of PrEP in people with HIV is associated with a risk of resistance to lamivudine or emtricitabine and TDF which are also used as part of 1st line ART [13]. Consequently, there is a risk that efficacy of ART is undermined, with further transmission of drug resistant virus [13]. While most cost-effectiveness evaluations have not explicitly taken this into account, modelling studies have suggested that resistance concerns should not preclude the use of PrEP [14-16]. The risk of resistance emerging is influenced by the length of time people with HIV stay on PrEP and hence by the frequency of HIV testing in people on PrEP. The WHO recommend three monthly testing for PrEP users [17]. Less frequent testing may improve retention on PrEP and reduce the cost of PrEP delivery but would have the disadvantage of extending the period in which people inadvertently take PrEP while having HIV.

With these considerations in mind we present an updated assessment of the cost-effectiveness of oral PrEP with tenofovir disoproxil fumarate and emtricitabine in the context of the KwaZulu-Natal

(KZN) province of South Africa, a province characterised by particularly high prevalence of HIV [18-22].

Methods

We updated a previously described individual-based model of HIV transmission, progression and the effect of ART[23,24] calibrating to the KZN epidemiological context, and undertook 500 model runs which are referred to as "scenarios". Each time the model is run it simulates data in 3-monthly time steps on whether the person has an on-going primary condomless sex partner, the number of other condomless sex partners, HIV acquisition and, in people with HIV, viral load, CD4 count, use of specific ART drugs (.e.g. use of TDF-lamivudine-efavirenz as 1st line regimen up to 2019), adherence, resistance and risk of HIV-related death. Details of the model and how it was calibrated to data from KZN are described in the Appendix. The model was programmed in SAS 9.4 (SAS Institute, North Carolina).

We considered scale up of PrEP implementation from 2017 in either (i) FSW having multiple condomless sex partners (women who had >5 short-term condomless sex partners in a 3 month period in the past year) and adolescent girls and young women (AGYW; defined as women aged 15-24; *PrEP-for-AGYW/FSW*), or (ii) all men and women aged 15-64 (*PrEP-for-all*). We refer to these as two alternative "policies", and we compare predicted outcomes of these two policies with no PrEP introduction.

Parameter values relating to many aspects of PrEP are uncertain and some will likely vary between populations and settings. We set out below our "primary analysis" assumptions; we explore variations in these assumptions in sensitivity analyses. Our primary analysis involves relatively high use of PrEP concentrated in periods of condomless sex which is hypothesized to be potentially attainable by future PrEP programmes that have learned from experiences, rather than the current

status of programmes. We assume PrEP is offered to people who have at least one condomless sex short-term partner in a 3 month period, or a condomless sex on-going primary partner who is diagnosed with HIV but not taking ART, and that individuals who initiated PrEP only take PrEP subsequently in 3 month periods in which they have at least one such condomless sex partner. We assume that the 1st-line ART regimen in use in new ART initiators will be dolutegravir-lamivudine-TDF in all adults from 2019 onwards, given the strong recommendation from WHO to use this regimen [26]. Results for intermediate outcomes such as HIV incidence are shown over the 20 years (2018-2037). The primary population health outcome measure was disability-adjusted life-years (DALYs), which is a generic measure that captures both premature mortality and morbidity. Our model allows direct calculation of DALYs for each individual which can then be summed. Disability weights are based on Salomon et al[25]. DALYs and costs are compared over up to 50 years, allowing the effects of HIV prevention to play out in terms of DALYs averted in those for whom infection in earlier life was averted.

The PrEP adherence level for an individual, quantified on a scale of 0-100% is the proportion of the drug target level that is attained for episodes of condomless sex in a given 3-month period. We assume an average adherence level per individual, but with within-person variability between 3 month periods. We further assume that 50% of adolescents and young people aged 15-24 years will be half as likely to adhere to PrEP compared to the rest of the population[27]. When providing *PrEP-for-AGYW/FSW* the assumptions result on average in 12% of people on PrEP with <50% adherence , 33% with 50-79% adherence and 55% with ≥80% adherence. The corresponding values for *PrEP-for-all* are 10%, 28% and 62%. PrEP efficacy, defined as the percent reduction in risk of HIV acquisition from a given HIV-positive condomless sex partner with non-resistant virus under 100% PrEP adherence is assumed to be 95%. PrEP effectiveness (what is measured in real life conditions) is assumed to be proportional (0.95-fold) to the PrEP adherence level, so in a person with current

PrEP adherence of 80% the current effectiveness would be 0.95x80% = 76%. Given the adherence distribution, average effectiveness as implemented was 70% for *PrEP-for-AGYW/FSW* (i.e. average 70% protection from each infected condomless partner in a 3 month period, 73% for *PrEP-for-all*), which compares with effectiveness estimates of 75% and 62%, respectively, in the Partners PrEP and TDF2 studies[28,29[. We also assume that 15% of 15-64 year olds who are not FSW (and 5% of FSW) will not consider starting PrEP even if eligible. Amongst those who would consider PrEP and for whom the condomless sex criteria are met, there is a 50% additional probability of being tested for HIV in each 3 month period (beyond background rates of testing); for those who test as HIV negative we assume an 80% chance that PrEP is initiated. After stopping PrEP due to having one or more 3 month periods with no condomless sex partners, PrEP can be restarted (with 95% probability) if the person tests HIV negative and again has condomless sex partners. Continuation of PrEP involves 3-monthly HIV testing. We consider that people may choose to stop PrEP despite condomless sex criteria being met (3% probability of discontinuation per 3 months, 20% chance of resumption per 3 month period of the condomless sex criteria being met). There is assumed to be no increases in condomless sex in the population as a result of PrEP being introduced. As mentioned, we recognise that in the early stages of PrEP roll-out in sub-Saharan Africa these levels of PrEP uptake and persistence of use have not been attained[30], but hypothesize that these are achievable as implementation lessons are learned[31], and we wished to explore the potential of PrEP, conditional on programmes being able to achieve our implementation conditions.

PrEP is assumed to have 50% efficacy against a virus containing both M184V and K65R mutations (conferring resistance to lamivudine/emtricitabine and TDF respectively) but fully efficacious (i.e. efficacy = 95%) otherwise. We explored other assumptions in sensitivity analysis, including that K65R mutation confers reduced efficacy regardless of presence of the M184V mutation. Our primary assumptions result in outputs of resistance emergence for persons who inadvertently take PrEP having been infected with HIV of mean 38% and 7% with M184V and K65R respectively by 3

months of infection[13,32]. We assume that voluntary medical male circumcision (VMMC), HIV-testing and ART initiation given HIV diagnosis all remain constant at the 2017 rate into the future.

Costs were estimated from the provider perspective, the South African government, on the basis of resource use due to PrEP (e.g. clinic visits, PrEP use and HIV tests) as well as subsequent healthcare interventions (ART and treatment of HIV-related diseases) and associated unit costs at relevant South African public-sector prices for 2017[33,34] and converted to in United States (US) dollars at an exchange rate of 13.6 ZAR/USD (Appendix page 7). The modelled cost per year for a person on PrEP is US$136 (US$36 for 4 3-monthly HIV tests as recommended, US$40 for 4 clinic visits and laboratory costs and demand generation, US$60 for PrEP drugs (regardless of PrEP adherence)) [30,33,34]. Our assumptions regarding unit costs result in a mean cost of clinical care (including ART costs) per year per person with HIV in care (in 2017) of US $367 in the South African setting.

In the cost-effectiveness analysis, both costs and health outcomes were discounted at 3% per annum, with a 7% local discount rate based on the South African Reserve Bank repurchase rate used in sensitivity analysis[35]. We assess cost-effectiveness using a measure called “net DALYs”, which account for the opportunity costs of health benefits foregone when an intervention is delivered as well as the health benefits, by use of the cost-effectiveness threshold, and are calculated as DALYs+costs/cost-effectiveness threshold. Incremental net DALYs show the difference between the health generated with the policy (compared with the no PrEP policy) and the health which would have been generated elsewhere in the healthcare system if the required resources were instead used for alternative purposes. The policy with the lowest net DALYs incurred is the one that would be selected as the cost-effective policy choice with the common approach using incremental cost-effectiveness ratios. We use a cost-effectiveness threshold of $750, as this is approximately the cost-per-life-year-averted of HIV interventions at the borderline for inclusion within the South African HIV Investment Case that prioritizes use of the national HIV budget on the basis of intervention cost-effectiveness[36]. We therefore adopt an opportunity-cost based assessment of

cost-effectiveness, rather than using GDP-per-capita-based thresholds that are now recognised as being too high, especially for middle-income countries like South Africa[36-38[.

Results

The HIV epidemic and programmatic characteristics estimated by the model for KZN in 2017 and comparable observed data are shown in Table 1. Table 2 shows, the predicted effect of the PrEP policies on a range of intermediate outputs relating to PrEP use over the next 20 years. On average, around 8% of 15-24 year old females are projected to be on PrEP at any one point in time (i.e. in a given three month interval) over the next 20 years, with 1.3% (with *PrEP-for-AGYW/FSW*) and 3.4% (*PrEP-for-all)* of all people aged 15-64 (and 25% and 29% of FSW, respectively) on PrEP . Of women age 15-24 who have one or more condomless sex partners in a 3 month period, the average proportion on PrEP at any one point in time over the next 20 years is 37%. In 20 years' time, under the *PrEP-for-AGYW/FSW* policy 0.4% of all people would have taken PrEP in their lifetimes for over 5 years, and 1.4% for the *PrEP-for-all* policy. In the *PrEP-for-all* policy, 2.1% of people on PrEP are expected to be (unknowingly) infected with HIV (2.7% under *PrEP-for-AGYW/FSW*).

PrEP policies lead to an increase in the proportion of ART initiators having resistance to at least one drug in their 1st-line regimen (7% for the no PrEP policy, 22% for the policy of *PrEP-for-all*), which translates into 84% and 81%, respectively, of ART initiators who remain on ART at 1 year having viral suppression.

There is predicted to be an average 25% decline in mean annual HIV incidence in women aged 15-24 over 20 years (23% over 5 years/26% over 50 years; Figure 1) with *PrEP-for-AGYW/FSW* and a 36% (31%/35%) decline in HIV incidence in women aged 15-24 with the policy of *PrEP-for-all,* and a 33% (27%/36%) lower overall incidence in people aged 15-64 with *PrEP-for-all*. In female sex workers

the predicted decline in incidence over 20 years is 33% (28%/35%) with *PrEP-for-AGYW/FSW* and 43% (39%/43%) with *PrEP-for-all*. The HIV prevalence for people age 15-49 in 20 (5 / 50) years time is predicted to be 23% (26%/22%) with no PrEP, 21% (26%/19%) with *PrEP-for-AGYW/FSW* and 17% (25%/14%) with *PrEP-for-all*. With the rate of scale-up as indicated, the annual cost of PrEP over the first 3 years is $7.4m ($20.7m) in year 1 (2017-18), $9.5m ($25.3m) in year 2 (2018-2019), $10.4m ($27.2m) in year 3 (2019-2020), $11.7m ($30.4m) in year 5 (2021-22) and $13.2m ($33.8m) in year 10 (2026-27) for *PrEP-for-AGYW/FSW* (*PrEP-for-all*).

Figure 2 shows that *PrEP-for-all*, while averting DALYs, is not expected to increase overall costs over the long term (50 years, at a 3% discount rate), suggesting that it is cost-effective. However, given the cost increases in the early years of introduction, especially with the *PrEP-for-all* approach, any cost savings would only be realized over an extended time horizon. We show the cumulative net DALYs averted over time expressed as a mean per year of the time horizon (Figure 2c) – there is a cumulative net health benefit by 2034 (17 years from PrEP introduction) with *PrEP-for-all*, and by 2039 (22 years after PrEP introduction) with *PrEP-for-AGYW/FSW.*

Table 3 (and Appendix Table S1, page 3) summarizes the impact and cost-effectiveness of PrEP for our primary analysis, and then shows the effect of variations in many of the model assumptions. As well as showing effects on DALYs, costs and net DALYs, we show effects on HIV incidence and, reflecting the impact of PrEP on acquisition and transmission of resistance, on virologic response to 1st-line ART. In the primary analysis (row 1), the *PrEP-for-all* policy is the cost-effective policy choice (most net DALYs averted) in 100% of scenarios. *PrEP-for-all* tended to remain cost-effective in most one-way sensitivity analyses, although quantitatively the net health benefit (net DALYs averted) was, as expected, lower with lower PrEP efficacy, adherence, uptake and less concentration of use around periods of condomless sex

PrEP was not cost-effective if it leads to substantial increases in condomless sex amongst people on PrEP. The continued use of efavirenz- rather than dolutegravir in ART initiators would be predicted

to lead to a substantial reduction in overall PrEP effectiveness, due to increased drug resistance. In this context of continuation of use of efavirenz in 1st line ART regimens, the response to first line ART would be predicted to be significantly reduced over the next 20 years with PrEP introduction. Six monthly HIV testing for people on PrEP is predicted to be of similar effectiveness and cost effectiveness compared with 3 monthly testing.

Discussion

This modelling study suggests that PrEP use concentrated amongst people and periods of condomless sex has the potential to be highly impactful on HIV incidence and cost-effective in KZN. The *PrEP-for-all* policy is predicted to have a substantially greater overall impact on incidence, and be more cost-effective than a policy of restricting PrEP availability to AGYW/FSW. There is also predicted to be a greater impact on incidence in women aged 15-24 with *PrEP-for-all* than when PrEP use is restricted to such women and FSW, due to the effects of a reduction in HIV prevalence in men. A policy of *PrEP-for-all* may have advantages over policies which restrict by demographics as it removes any issues with eligibility and helps to avoid PrEP programmes potentially spotlighting and stigmatising groups of people.

Cost-effectiveness of PrEP programmes remains subject to some uncertainty. If PrEP use leads to significant increases in condomless sex episodes that are not covered by PrEP it is unlikely to be cost-effective. Cost effectiveness of PrEP is also related to whether its use is concentrated in periods of condomless sex, but even with less concentrated use of PrEP, so that there is one 3 month period of use when there is no risk for each 3 month period in which there is risk through condomless sex, PrEP remained cost effective. However, if we assume that PrEP use is entirely unrelated to condomless sex (which perhaps seems unlikely but remains possible), it is not cost effective. A major challenge for programmes is to achieve and maintain high levels of PrEP use during periods of

condomless sex. The impact and cost-effectiveness of PrEP is substantially dependent on the avoidance of use of efavirenz in 1st-line regimens compared with use of dolutegravir. This is to avoid increases in NNRTI resistance, secondary to emergence of resistance to lamivudine/emtricitabine and TDF, which would be predicted to lead to effects of ART being undermined. In other work outside the context of PrEP we have considered the risks and benefits of this choice[47]. We found that PrEP with six monthly HIV testing has similar effectiveness and cost-effectiveness to three monthly testing but we see no compelling case to recommend less frequent testing than three-monthly. PrEP impact and cost-effectiveness is influenced by the extent to which PrEP has efficacy in preventing infection when the partner's virus has drug resistance to PrEP drugs. Continued monitoring of drug resistance is important.

In our primary analysis the time point at which a net health benefit is achieved is 2034 with the *PrEP-for-all* policy, and 2039 for the policy of *PrEP-for-AGYW/FSW.* Policymakers will need to trade short-term imposition of costs with longer-term health benefits and cost reductions as a result of HIV infections averted. Short term costs and longer-term benefits are expected to be greater with PrEP-for-all than PrEP-for-AGYW/FSW only. The use of discount rates facilitates the comparison of costs and health effects occurring at different points through time, but the appropriate discount rates are uncertain.

Programmes will need to innovate if they are to overcome the challenges of implementing PrEP as it has been modelled. Self-report of risk is unreliable. One approach would be to advise people to take daily PrEP for the next 3 months if they may have new sexual partners and are unsure about their ability to use condoms consistently with those new partners. We note our assumption that periods of PrEP use around condomless sex last at least 3 months, which may be conservative and PrEP use may be further concentrated in practice into shorter periods than we have assumed. We assume daily dosing during three month periods on PrEP, although dosing around sex acts may be feasible[48, 49]. A key challenge in the use of PrEP in Africa is the low reported levels of persistent

use [e.g. 50]. The reasons underlying this, and solutions to addressing those causes will need to be identified if effects of the magnitude we have modelled are to be realised.

Limitations of our analysis, as for any cost-effectiveness analysis, include that it involves projection of the HIV epidemic and HIV programme over several years - we assume rates of VMMC, HIV-testing and ART initiation given HIV diagnosis remain constant, which is associated with uncertainty which we explored in sensitivity analyses. We define a female sex worker as a woman who had over 5 short-term condomless sex partners in a 3 month period over the past year and this is a relatively simple characterization. We combined AGYW/FSW into one group although provision of PrEP to FSW is likely to be more cost-effective than provision to AGYW. We do not model sex between men, although we would note that an added benefit of the policy of PrEP-for-all is that MSM would be able to access PrEP without having to state their sexuality should they wish. We use a relatively long time step of 3 months which we consider should be adequate to accurately capture most effects but we cannot exclude the possibility that a shorter time step would reveal nuances that we missed. Lastly, we focussed on KZN province and further analyses of other provinces would be needed to assess how generalizable our findings are across South Africa.

Conclusions

PrEP use concentrated during time periods of condomless sex has the potential to substantively impact HIV incidence and to be cost-effective. Further research and monitoring are required to understand the effects of PrEP programmes, including on HIV drug resistance.

Funding

This article is made possible by the generous support of the American people through the United States Agency for International Development (USAID) and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). The contents are the responsibility of the authors and do not necessarily reflect the views of USAID, PEPFAR or the United States Government. Work towards this article was funded by USAID and PEPAFR under the terms of cooperative agreement AID-OAA-A-15-00031 to University of Pittsburgh, as well as Cooperative Agreements AID 674-A-12-00029 and 72067419CA00004 to HE2RO. F Tanser received funding from the Academy of Medical Sciences.

Potential competing Interests

JWM is a consultant for Gilead Sciences and Xi'an Yufan Biotechnologies, has received research grants to the University of Pittsburgh from Gilead Sciences and Janssen Pharmaceuticals, and owns share options in Co-Crystal Pharma, Inc., which are unrelated to the current study.

Author Contributions

Concept of the analysis, contributions to specific modelling aspects, interpretation of results, critical comments on manuscript drafts: all authors; drafting of the manuscript: AP; implementation of the modelling: AP, FN.

Additional files

Appendix

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Table 1. HIV epidemic and programmatic characteristics in 2017 (KZN, South Africa), based on 500 model runs.

Characteristic	**Model (Median, 90% range)**	**Examples of observed data (year)**
HIV prevalence: age 15- 49 (men and women combined)	27% (25% – 29%)	27% men and women (19.8% men, 33.0% women) (KZN, 2017) [22]
age 15-19 men / women	2.3% / 7.4%	2.2% / 8.5% [21] (KZN 2012) 3.6% / 5.3% (KZN 2017) [22]
age 20-24 men / women	8.7% / 24.4%	10.0% / 25.5% [21] (KZN 2012) 7.8% / 18.1% (KZN 2017) [22] age 15-24 7.6% / 22.3% (2014/2015) [20]
female sex workers**	72% (60% - 84%)	76% (2015) [39]
HIV incidence*: age 15- 49 (men and women combined)	2.6 (1.9 – 3.2)	3.3 (2012) [21]
age 15- 24 women	3.6 (2.1 – 5.4)	1.5 women age 15-24, 0.93 women aged 15-49 (South Africa as a whole, 2017) [22]
female sex workers**	60 (28 – 109)	
Proportion of new infections from new / short term partners	51% (38% - 66%)	no data identified
Proportion of HIV positive people diagnosed	83% (75% - 89%)	83% (2015) (South Africa [40]); 84.9% (South Africa [22]); 76% (2013) (within KZN [41]); 77% men age 15-49, 90% women age 15-49 [22] KZN (2017)
Proportion of diagnosed people who are on ART	76% (70% - 83%)	71% (South Africa [22]) 77% men age 15-49, 79% women age 15-49 [22] KZN (2017)
Proportion of all HIV positive people with viral load < 1000 copies/mL	50% (44% - 57%)	55% in women, 42% in men (2014/15) ([20] (< 400 copies/mL)) 52% of HIV+ people are on ART with VL < 1000 (South Africa [22]) 67.5% of all HIV+ people, including people with VL 1000 not on ART

		(KZN [22])
Number of adults on ART	1,144,000	1,222,000 (2017) (personal communication, authors)
Of people on ART, proportion with VL < 1000 cps/mL	82% (79% - 88%)	87% women, 84% men (2014/15) ([20] < 400 copies / mL)***); 85% (2015) (< 400 copies/mL[40]) ; 77% men age 15-49, 89% women age 15-49 [22] KZN (2017)
Of people who started ART 1 year ago and are still on ART, proportion with VL < 500 cps/mL	80% (70% - 89%)	no data identified
Of people on ART with VL > 1000 cps/mL proportion with K65R / M184V mutation in majority virus	64% (44% - 79%) / 92% (85% - 95%)	56%-60% (Africa) [42] 59%-71% (Africa) [42]
Proportion of all people with HIV who have viral load > 1000 copies/mL and carry M184V / K65R in majority virus.	11% (7% - 14%) / 7% (4% - 11%)	no data identified
Of people starting ART, proportion with NNRTI drug resistance	11% (5% - 17%)	14% [45,46]
Proportion of women who are FSW**	2.8% (0.9% - 4.7%)	0.4% - 4.3% urban areas in SSA 2006 [43] 0.9% [44]
Proportion of men age 15-64 (age 15-24) who are circumcised	35% (31% - 45%)	32% medically circumcised [22]
Cost of clinical care (including ART costs) per year per person with HIV in care (mean)	$367	$240 (excluding inpatient costs) [34]

People age 15- 64 unless stated. Population size 7.1 million, AGYW 1.1 million; * (/100 person years) ** Female sex workers defined as women having > 5 condomless sex partners in a 3 month period in past year; *** some people on ART with poor adherence do not report being on ART which affects comparison of model output with observed data.

Table 2. Predicted effects of PrEP policies on use and intermediate health outcomes over 20 years (2017 – 2036)

Outcome mean over 3 month periods 2017 - 2036 except where stated; (90% uncertainty range; 95% confidence interval*)	**No PrEP**	***PrEP-for-AGYW/FSW***	***PrEP-for-all***
Proportion of women age 15-24 on PrEP	0%	7.6% (3.4% - 12.4%; 7.3% - 7.9%)	7.9% (3.5% - 12.7%; 7.6% - 8.2%)
Proportion of people age 15-64 on PrEP	0%	1.3% (0.6% - 2.0%; 1.3% - 1.3%)	3.4% (1.9% - 5.4%; 3.4% - 3.4%)
In 2037, proportion of people age 15-64 ever taken PrEP	0%	13% (8% - 17%; 13% - 13%)	31% (23% - 39%; 31% - 32%)
Of women age 15-24 who have $\geq$ 1 new condomless sex partner in a 3 month period, proportion on PrEP	0%	37% (28% - 45%; 36% - 38%)	37% (30% - 46%; 36% - 38%)
Number of people on PrEP	0	103000 (49,000 – 159,000; 100,000 – 106,000)	275,000 (151,000 – 444,000; 266,000 – 284,000)
Of people on PrEP, percent with (undetected) HIV [&]	---	2.7% (1.0% - 5.1%; 2.6% - 2.8%)	2.1% (0.8% - 3.4%; 2.0% - 2.2%)
Of all people living with HIV, percent on ART	75% (68% - 80%; 75% - 75%)	76% (70% - 81%; 76% - 76%)	79% (73% - 84%; 79% - 79%)
Of people starting ART, proportion with NNRTI drug resistance	9% (4% - 14%;8% - 9%)	10% (5% - 16%; 10% - 10%)	14% (8% - 22%; 14% - 14%)
Proportion of all people with HIV who have viral load > 1000 cps/mL and carry M184V / K65R in majority virus.	6% (4% - 8%; 6% - 6%) / 4% (2% - 7%; 4% - 4%)	7% (4% - 9%; 7% - 7%) / 5% (2% - 7%; 5% - 5%)	8% (5% - 10%;8% - 8%) / 6% (3% - 9%; 6% - 6%)
Of people starting ART, proportion with resistance to at least one drug in their 1st-line regimen	7% (4% -10%; 7% - 7%)	11% (7% - 16%; 11% - 11%)	22% (15% - 29%; 22% - 22%)

Of people who started ART 1 year ago and are still on ART, proportion with VL < 500 cps/mL	84% (78% - 89%; 84% - 84%)	83% (77% - 89%; 82% - 83%)	81% (75% - 88%; 81% - 81%)
Of all people on ART, percent with viral load < 1000 copies/mL	91% (89% - 94%; 91% - 91%)	91% (89% - 94%; 91% - 92%)	91% (89% - 94%; 90% - 91%)
Of all people living with HIV, percent with viral load < 1000 copies/mL	67% (61% - 74%; 67% - 68%)	69% (62% - 75%; 69% - 69%)	71% (66% - 77%; 71% - 71%)
Of adult population, proportion with HIV and viral load > 1000 copies/mL	10% (8% - 13%; 10% - 10%)	10% (7% - 12%; 10% - 10%)	8% (6% - 10%; 8% - 8%)

*(90% uncertainty range represent variability across scenarios (n=500) that are consistent with observed data used in calibration (likely largely due to different sexual behaviour patterns in different scenarios - they do not include uncertainty over uptake and persistence of PrEP use)). 95% confidence interval represents uncertainty in the mean due to stochastic uncertainty (i.e. this tends to zero with increasing number of model runs).

& reasons for HIV infection in people on PrEP are (in order of importance): Infection on PrEP with drug resistant HIV, infection on PrEP with drug sensitive HIV due to fact that efficacy is 95% and not 100%, starting PrEP in primary infection, starting PrEP while HIV +ve due to < 100% sensitivity of HIV test.

Table 3. Reduction in incidence, difference in response to 1st line ART, DALYs averted and net DALYs averted with policies of PrEP-for-AGYW/FSW and PrEP-for-all. Variations in sensitivity analysis. Mean over 50 years (20 years for HIV incidence@ and difference in response to 1st line ART++) and 95% confidence interval.

Variation from primary analysis assumptions	**Reduction in Incidence (%)@**		**Difference in response to 1st line ART++**		**DALYs averted****		**Difference in cost** (US$ million; compared with no PrEP)		**Net DALYs averted**** (percent of scenarios in which PrEP policy is the cost-effective policy choice^.	
	PrEP for FSW/AGYW*	PrEP-for-all	PrEP for FSW/AGYW	PrEP-for-all	PrEP for FSW/AGYW	PrEP-for-all	PrEP for FSW/AGYW	PrEP for all	PrEP for FSW/AGYW	PrEP-for-all
No variation (primary analysis)	25% (25, 26)	33% (32, 33)	-1% (-1, -1)	-3% (-2, -3)	9.6 (9.0, 10.0)	34.7 (33.7, 35.7)	-$5.1 (-5.4,-4.8)	-$15.0 (-15.6, -14.4)	16.3 (0%) (15.3, 16.7)	54.7 (100%) (54.0, 56.4)
100% adherence when on PrEP **s1**	41% (39 42)	48% (45, 50)	-0% (0, 0)	-2% (-2, -2)	20.6 (18.1, 23.1)	58.0 (51.6, 64.4)	-$15.1 (-17.0, -13.2)	-$35.0 (-38.9 -31.1)	40.7 (0%) (36.1, 45.3)	105.6 (100%) (94.9, 116.3)
PrEP efficacy 80% (primary analysis: 95%) **s2**	20% (18, 22)	27% (24, 29)	-1% (-1, 0)	-2% (-2, -2)	6.3 (4.5, 8.1)	26.3 (21.4, 31.2)	-$1.2 (-2.8, +0.4)	-$5.2 (-8.5, -1.9)	7.8 (5%) (4.6, 11.0)	33.2 (95%) (25.2,

										41.2)
Probability of re-starting PrEP during a period with condomless sex partner(s)[+] having previously interrupted for a period with no new condomless sex partners 50% (primary analysis: 95%) [o] **s3**	24% (22, 26)	32% (29, 36)	-0% (-1, 0)	-2% (-2, -2)	8.9 (6.7, 11.1)	32.2 (27.0, 37.7)	-$4.0 (-5.9, -2.1)	-$13.7 (-17.9, -9.5)	14.3 (3%) (10.1, 18.5)	50.1 (97%) (40.6, 59.6)
Risk of stopping/interrupting PrEP per 3 months (despite continuing to have new condomless sex partner(s)) 10% (primary analysis: 3%) [o] **s4**	20% (17, 22)	27% (25, 29)	-2% (-1, -2)	-1% (0, -1)	6.5 (5.2, 7.8)	26.1 (22.8, 29.3)	-$3.2 (-4.4, +2.0)	-$11.2 (-13.4, -9.0)	10.8 (0%) (8.3, 13.3)	41.0 (100%) (35.9, 46.1)
50% of people will not consider starting PrEP despite having condomless sex partner(s)[+] (primary analysis: 15%) [o] **s23**	23% (21, 24)	19% (18, 22)	0% (-1, 0)	-1% (-1, -1)	6.9 (5.1, 8.8)	23.1 (20.2, 26.0)	-$4.8 (-5.9, -3.7)	-$11.4 (-13.4, -9.2)	13.3 (0%) (10.6, 16.0)	38.3 (100%) (33.6, 43.0)
Lower PrEP uptake and retention (as reflected by simultaneous variations above indicated by [o]) **s25**	17% (16, 18)	14% (13, 15)	0% (-1, 0)	-1% (-1, -1)	5.0 (3.6, 6.4)	16.6 (15.0, 18.2)	-$2.5 (-3.3, -1.7)	-$8.2 (-9.0, -7.4)	8.3 (0%) (6.3, 10.3)	27.5 (100%) (25.5, 29.5)
Efavirenz as 1st-line ART in all (primary analysis: dolutegravir as 1st line n all **s8**	21% (20, 22)	24% (22, 25)	-5% (-5, -5)	-14% (-14, -14)	-0.8~~ (-2.7, 1.1)	10.0 (6.4, 13.6)	+$1.6 (+0.4, +2.8)	+$0.9 (-1.3, +3.1)	-3.0~~ (6%)	8.9 (60%)

									(-7.2, 0.2)	(3.1, 14.7)
PrEP has 0.5 fold lower efficacy against virus with k65r (regardless of presence of m184v) **s28**	25% (24, 27)	33% (31, 35)	-1% (-1, 0)	-3% (-3, -2)	9.2 (7.9, 10.5)	31.6 (28.1, 35.1)	-$4.6 (-5.9,-3.3)	-$13.6 (-15.5, -11.7)	15.3 (1%) (13.4, 17.2)	49.6 (99%) (44.5, 55.0)
PrEP has zero efficacy against virus containing both M184V and K65R mutations **s22**	24% (23, 26)	29% (26, 30)	-1% (-1, -1)	-4% (-4, -3)	7.4 (5.9, 8.9)	25.4 (22.0, 28.8)	-$3.3 (-4.8, -1.8)	-$4.7 (-8.3, -1.1)	11.8 (6%) (8.8, 14.8)	31.7 (94%) (25.0, 38.4)
PrEP clinic visits and HIV testing 6 monthly (primary analysis: 3 monthly) **s9**	25% (24, 27)	34% (32, 35)	-1% (-1, 0)	-3% (-3, -2)	8.9 (7.9, 9.9)	32.9 (30.0, 35.5)	-$5.8 (-6.7, -4.9)	-$17.8 (-19.7, -15.9)	16.2 (0%) (14.4, 18,0)	56.6 (100%) (51.0, 61.2)
HIV testing uses antigen/antibody tests (primary analysis: antibody only)[&]	25% (23, 26)	33% (31, 35)	-1% (-1, 0)	-2% (-2, -2)	9.4 (8.1, 10.7)	35.9 (33.3, 38.5)	-$5.3 (-6.2, -4.4)	-$16.3 (-18.1, -14.5)	16.5 (0%) (14.3, 18.7)	57.6 (100%) (53.2, 62.0)
People on PrEP have 2 fold increased numbers of condomless sex partners due to taking PrEP (primary analysis: no increase)	16% (15, 17)	15% (14, 16)	-1% (-1, -1)	-4% (-4, -4)	-3.2~ -4.2, -2.2)	4.9 (2.9, 6.9)	+$6.3 (+5.5,+7.1)	+$12.2 (+10.8,+13.6)	-11.7~~ (5%) (-13.4, -10.0)	-11.3~~ (27%) (-14.7, -6.9)
One 3 month period of PrEP while no	as primary	as	as primary	as	as primary	as	+$0.7	+$0.8	8.6	33.7

condomless sex is experienced (not even with a primary partner) for each 3 month period of PrEP while having condomless sex partners[+] (primary analysis: PrEP not used in 3 month periods with no new condomless sex partners). **uses base runs**	analysis	primary analysis	analysis	primary analysis	analysis	primary analysis	(-0.2, +1.6)	(+0.4,+1.2)	(4%) (7.9, 9.3)	(95%) (31.9, 35.5)
7% discount rate (primary analysis: 3%) **uses base runs**	as primary analysis	as primary analysis	as primary analysis	as primary analysis	2.7 (2.5, 2.9)	10.6 (10.2, 11.0)	-$0.3 (-0.5, -0.1)	-$1.8 (+1.5, +2.1)	3.1 (2%) (2.8, 3.4)	13.0 (98%) (12.5, 13.5)
Plausible future reduced PrEP costs (four HIV tests per year $3 each, one annual PrEP clinic visit only, PrEP drug $35 = $57 per year) (primary analysis: $136 per year) **uses base runs**	as primary analysis	as primary analysis	as primary analysis	as primary analysis	as primary analysis	as primary analysis	-$8.5 (-8.8, -8.2)	-$24.5 (-25.1, -23.9)	20.9 (0%) (19.2, 22.6)	67.4 (100%) (66.7, 68/1)

[@] Reduction in incidence is shown over a shorter time period than 50 years as a mechanism of effect on DALYs is via reduction in new infections. [++] Difference in *of people who started ART 1 year ago and are still on ART, proportion with VL < 500 cps/mL* - differences are due to differences in drug resistance outcomes and this output is shown over a shorter time period than 50 years as drug resistance is a mechanism of effect on DALYs ; * Reduction in incidence relates to AGYW only in relation to PrEP for AGW and to all age 15-64 for PrEP-for-all; ** DALYS and net DALYs averted in whole population (in 1000s; net DALYs based on cost-effectiveness threshold of $750); ^ in remainder of scenarios no PrEP introduction is the most cost-effective policy; [+] or a period with a primary on-going condomless sex partner who is diagnosed with HIV but

off ART; [&] test cost assumed the same as antibody only test; ~ DALYs not averted, ~~ net DALYs not averted. # percentage of scenarios in which policy is cost-effective choice considering only no PrEP and PrEP for FSW

Legends for Figures

Figure 1. Percent reduction in HIV incidence compared with no PrEP introduction (mean over 20 years), with 95% confidence interval ▬ and 90% uncertainty range ——— *. (a) in women aged 15-24; (b) in people aged 15-64

*90% uncertainty range represent variability across scenarios (n=500) that are consistent with observed data used in calibration (likely largely due to different sexual behaviour patterns in different scenarios they do not include uncertainty over uptake and persistence of use). 95% confidence interval represents uncertainty in the mean due to stochastic uncertainty (i.e. this tends to zero with increasing number of model runs).

Figure 2. Cost, DALY and net DALY outcomes over 50 year time horizon, 3% per annum discount rate. (a) Breakdown of costs according to policy (b) DALYs averted and increment in cost for alternative PrEP targeting policies; PrEP-for-all is cost saving compared with no PrEP and compared with PrEP in FSW/AGYW (c) Cumulative net DALYs averted per annum according to length of time horizon. 3% discount rate. See appendix for similar figure but with 7% discount rate.

Figure 1

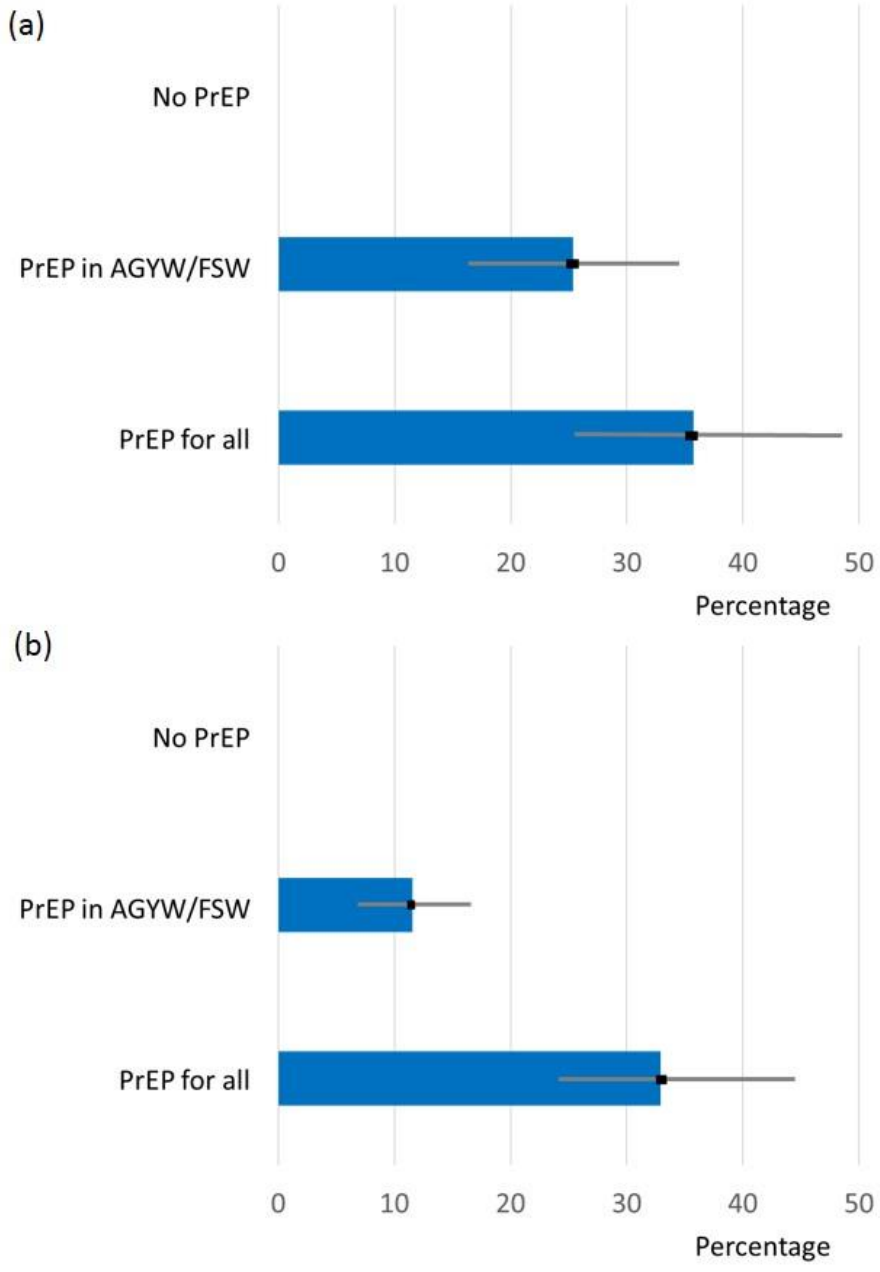

Figure 2