AIDS

Modelling the impact and cost-effectiveness of combination prevention amongst HIV serodiscordant couples in Nigeria
--Manuscript Draft--

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Abstract:	Objective: To estimate the impact and cost-effectiveness of treatment as prevention (TasP), pre-exposure prophylaxis (PrEP) and condom promotion for discordant couples in Nigeria. Design: Mathematical and cost modelling. Methods: A deterministic model of HIV-1 transmission within a cohort of discordant couples and to/from external partners was parameterised using data from Nigeria and other African settings. The impact and cost-effectiveness were estimated for condom promotion, PrEP and/or TasP, compared with a baseline where ART was offered according to 2010 national guidelines (CD4<350 cells/l) to all HIV-positive partners. The impact was additionally compared with a baseline of current ART coverage (35% of those with CD4<350 cells/l). Full costs (in US$2012) of programme introduction and implementation were estimated from a provider perspective. Results: Substantial benefits came from scaling up ART to all HIV-positive partners according to 2010 national guidelines, with additional smaller benefits of providing

TasP, PrEP or condom promotion. Compared with a baseline of offering ART to all HIV-positive partners at 2010 national guidelines, condom promotion was the most cost-effective strategy (US$1206/DALY), the next most cost-effective intervention was to additionally give TasP to HIV-positives (incremental cost-effectiveness ratio US$1607/DALY), followed by additionally giving PrEP to HIV-negatives until partners initiate ART (US$7870/DALY). When impact was measured in terms of infections averted, PrEP with condom promotion prevented double the number of infections as condom promotion alone.

Conclusions: The first priority intervention for discordant couples in Nigeria should be scaled-up ART access for HIV-positives. Subsequent incremental benefits are greatest with condom promotion and TasP, followed by PrEP.

Dear Editor,

Thank you very much for your consideration of our manuscript, and for the opportunity to submit a revised version.

Please find below responses to each of the referees comments, including details of the changes which have been made to the manuscript. Page numbers refer to the revised manuscript.

Reviewers' comments:

Reviewer #3:

Methods

-- p.5: "Those refusing or dropping out of ART enter the post-ART group and may only initiate ART with CD4<200 cells/mL" : I am not sure I understand the authors' rationale since ART priority eligibility criteria are >350 cells/mL and the new WHO guidelines require initiating ART early.

We assumed that those refusing or dropping out of ART were dropping out of care and would only re-initiate ART once they became symptomatic (which generally only happens with CD4<200 cells/µl). We have now made this clear in the text (p6): "Those refusing or dropping out of ART enter the post-ART group and, assuming they only seek treatment upon becoming symptomatic, only (re-) initiate ART with CD4<200 cells/µl."

We relaxed this assumption in a sensitivity analysis to see what effect it would have if people in discordant couples dropping out of ART were to re-initiate ART at higher CD4 counts, at either the same rate or half the rate as ART naïve individuals. This has been added to the methods (p9): "In sensitivity analyses…higher rates of ART re-initiation for HIV positive members of serodiscordant couples (same treatment CD4 criteria and 50%,100% rate of ART naïve)… were also investigated".

In contrast to our main analysis - where the most cost-effective initial intervention (in terms of cost per DALY) was usually condom promotion, followed by condom promotion+TasP, and then condom promotion+TasP+short-term PrEP - as rates of ART-recruitment of ART dropouts increased, the most cost-effective intervention (in terms of cost per DALY) became more likely to be TasP, followed by the addition of condom promotion, and then adding short-term PrEP. The ICERs for all interventions became worse (i.e. greater cost per DALY). The results are now given in the sensitivity analysis section of the results (p13): "Higher rates of ART re-initiation gave increased impact for TasP, but decreased impact for PrEP and condom promotion, and all interventions cost more per DALY averted. With increasing ART re-initiation, TasP was more likely to be the most cost-effective initial intervention, followed by condom promotion, and the addition of PrEP was less likely to be cost-effective."

-- p.6: "with additional data from Europe informing estimates for those on ART": Why using estimates from Europe for Nigeria?

For CD4 transition rates on ART, we used data from two separate studies in South Africa as well as estimates from a previous cost-effectiveness analysis for ART in Nigeria (Schneider et al 2013), which was based upon European data. This only affects our estimate of the probability of moving from CD4 200-350 up to CD4>350, where the European data gives a lesser lower-bound than the South African studies (the upper bound reflects the higher rates seen in South Africa). We have retained this lower European estimate, as it comes from a larger cohort who were followed for a longer period of time

than the South African cohorts, and it captures the slower rates of CD4 increase observed after a longer period on ART. Slower rates of CD4 increase over time on ART have also been seen in studies from low-income countries (e.g. Nash et al 2008, now added as a reference in Table S1). We have not seen any studies directly comparing rates of CD4 reconstitution in African vs European settings so it is not clear whether this is likely to vary substantially between settings.

-- p.7: "Cost model": it would be good to give more detail in the main text; for example on whether increasing marginal costs were taken into account, especially as it is quite costly to find HIV-positive individuals in need of treatment.

We have added more detail about the cost model in the methods (p7). We now explicitly state that the costs do not include the costs of identifying serodiscordant couples (p7:"The costs of identifying serodiscordant couples are not included."), and we have made it clear at the start of the methods section (p5) that we are modelling interventions amongst discordant couples who have already been identified through testing in ANC (p5:"This model was … used to estimate the impact and cost-effectiveness of the interventions among serodiscordant couples already identified through ANC.") We agree that the costs of identification of serodiscordant couples will be large, however they will not affect our incremental cost-effectiveness ratios since identification of couples – with all of its associated benefits and costs - is assumed to happen in all of the intervention scenarios, including the baseline scenario.

-- p.8: Why keep ART coverage at 35% if the model is run for 20 years? It seems odd not to increase ART coverage over time using recent trends.

We agree that ART coverage is very likely to increase in the future, although it is difficult to predict this trend precisely. Our main aim with this model was to reflect the current situation and to provide predictions for different treatment scenarios that can then be used to guide future decision making on how interventions should be scaled up. Our modelled scenarios include increased ART coverage of HIV positives at current guidelines, as well as higher coverage regardless of CD4 count, both of which are predicted to be highly effective, and are recommended by this analysis.

-- p.8: it would be good to have results with a 3% discount rate as the baseline as this is commonly implemented in CEA.

To enable direct comparison with other studies using a 3% discount rate, we have given the ICERs using the 3% discount rate for the four interventions which fall on the efficiency frontier in the sensitivity analysis results (p12: "…ICERs were improved (condom promotion: US$590/DALY, adding TasP: US$1054/DALY, adding short-term PrEP: US$3536/DALY, switching to long-term PrEP: US$9259/DALY)"). However, we have kept the 10% discount rate for the main results, as we believe this more accurately represents the preference for the present in Nigeria, as discussed in detail in the Discussion section (p15).

-- Table 1 is very difficult to read.

We have reduced the number of columns in table 1 (only one range – used in sensitivity analysis – is given, units are now given with the parameter description, and sources/references have been moved to the supplementary material – table S1). We have also reduced the amount of text in table 1 and moved the description of some parameters –probability of starting ART due to being symptomatic,

probability of death from non-HIV related causes, HIV prevalence in the general population, and proportion with an external partner – to the supplementary material, as they did not fit the table format well. We have also reduced the spacing and font size and hope that this makes the table easier to read.

Discussion

-- It would be good if the authors could compare their ICER results with other results for HIV prevention and treatment interventions, in addition to PrEP interventions.

We have now included a comparison of our results with two other studies – in South Africa and Kenya – which looked at the cost-effectiveness of combination prevention, including PrEP, early ART, and in one study, behaviour change. (p15: "In agreement with our findings that condom promotion and TasP were more cost-effective than PrEP, a modelling study of a hyperendemic southern African setting found that it was more cost-effective to first give early ART before introducing PrEP [12]. Another study of combination prevention in Kenya found that it was usually most cost-effective to first implement behaviour change interventions, followed by early ART, and then PrEP[33].")

-- It would be good if the authors could discuss the feasibility and acceptability of theses combined interventions in the context of Nigeria and its rather weak health system.

We have now included an additional paragraph mentioning recently published results of formative research into attitudes towards PrEP use in Nigeria, and discussing the further information we will obtain on all of the interventions from ongoing PrEP demonstration projects among discordant couples in Nigeria (p16: "Formative research looking at perceptions of PrEP use in Nigeria found broad acceptability, although concerns were raised about the impact of stigma and sustainability of PrEP interventions[39]. The current PrEP demonstration project occurring among Nigerian serodiscordant couples will give a clearer picture of PrEP feasibility, as well as levels of condom use and ART uptake among serodiscordant couples.")

Reviewer #5: Video and Audio content comments:
The study objective is to estimate the impact and cost-effectiveness of PrEP, TasP and condom promotion for serodiscordant couples in Nigeria. Authors used an interesting, quite complicate, deterministic, compartmental cohort model.
Methods are very well detailed and well referenced. Results are are clearly reported. Authors recognized some limitations of the study (i.e most of the data used to inform this analysis came from outside Nigeria) In any case this is a very interesting manuscript with important information for public health interventions/policies in developing countries

We thank the reviewer for their supportive comments.

Editor Comment: Please limit the number of references to about 40.

We have reduced the number of references in the main text to 40. In order to do this, we have reduced the mention of references used to parameterise the model in the main text and table 1, and reproduced table 1 with all of the references in the supplementary material, as table S1. In the Methods we have retained only the references containing Nigerian data, others are given in the supplementary material.

Other changes made:

- *Short title changed to meet character limit (p2; new short title: HIV prevention in discordant couples)*
- *Sentence removed from the Discussion to reduce the word count to the specified limit: (sentence removed from p14: "Some studies suggest that the initial counselling visit accounts for most of the increase in condom use[9, 10], so less intensive condom promotion than was modelled here may suffice, further reducing costs.")*
- *Throughout the manuscript we have rephrased sentences while retaining the original meaning, in order to reduce the word count following the additions made in response to the reviewers' comments.*
- *We have added acknowledgements to Simon Cartier, Edward Oladele and Ignatius Mogaba for help with providing the data on discordant couples in Nigeria*
- *In the supplementary material, reference Gupta et al 2006 has been removed, this was cited in error; for the mass media costs, we now reference Bollinger et al 2006.*

Justification for having 12 authors:

This analysis involved the separate development of two different models – transmission dynamics and cost models – both of which required large amounts of data from diverse sources. We made every effort in this analysis to acquire as much data from Nigeria as possible, some of it unpublished, and a number of people were involved in obtaining this data. Kate Mitchell and Peter Vickerman conceived and carried out the transmission modelling, and Aurelia Lepine and Fern Terris-Prestholt designed and built the cost model. All of the other authors provided input and help with acquiring data from early on in this project. In particular, Kwasi Torpey and Hadiza Khamofu from FHI 360 provided unpublished data on discordant couples in Nigeria, Atiene Sagay provided data from Jos University hospital on HIV testing in ANC and cost data associated with ART, Jonah Musa provided costs data, James Anenih and Emmanuel Alhassan co-ordinated data requests and collection from different sites, Morenike Folayan and John Idoko co-ordinated the study and advised on the overall direction and John Idoko provided oversight. Kate Mitchell and Aurelia Lepine wrote different sections of the original manuscript, Peter Vickerman and Fern Terris-Prestholt critically revised the manuscript, Morenike Folayan and Kwasi Torpey made additions to the manuscript, and all authors approved the final version. Without the input of all 12 authors, it would not have been possible to bring together so much Nigerian data and carry out both analyses.

Abstract

Objective: To estimate the impact and cost-effectiveness of treatment as prevention (TasP), pre-exposure prophylaxis (PrEP) and condom promotion for discordant couples in Nigeria.

Design: Mathematical and cost modelling.

Methods: A deterministic model of HIV-1 transmission within a cohort of discordant couples and to/from external partners was parameterised using data from Nigeria and other African settings. The impact and cost-effectiveness were estimated for condom promotion, PrEP and/or TasP, compared with a baseline where ART was offered according to 2010 national guidelines (CD4<350 cells/μl) to all HIV-positive partners. The impact was additionally compared with a baseline of current ART coverage (35% of those with CD4<350 cells/μl). Full costs (in US$2012) of programme introduction and implementation were estimated from a provider perspective.

Results: Substantial benefits came from scaling up ART to all HIV-positive partners according to 2010 national guidelines, with additional smaller benefits of providing TasP, PrEP or condom promotion. Compared with a baseline of offering ART to all HIV-positive partners at 2010 national guidelines, condom promotion was the most cost-effective strategy (US$1206/DALY), the next most cost-effective intervention was to additionally give TasP to HIV-positives (incremental cost-effectiveness ratio US$1607/DALY), followed by additionally giving PrEP to HIV-negatives until partners initiate ART (US$7870/DALY). When impact was measured in terms of infections averted, PrEP with condom promotion prevented double the number of infections as condom promotion alone.

Conclusions: The first priority intervention for discordant couples in Nigeria should be scaled-up ART access for HIV-positives. Subsequent incremental benefits are greatest with condom promotion and TasP, followed by PrEP.

Full Title: Modelling the impact and cost-effectiveness of combination prevention amongst HIV serodiscordant couples in Nigeria

Short title: HIV prevention in discordant couples

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Conflicts of interest: The authors have no conflicts of interest to declare

Abstract

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Design: Mathematical and cost modelling.

Methods: A deterministic model of HIV-1 transmission within a cohort of serodiscordant couples and to/from external partners was parameterised using data from Nigeria and other African settings. The impact and cost-effectiveness were estimated for condom promotion, PrEP and/or TasP, compared with a baseline where ART was offered according to 2010 national guidelines (CD4<350 cells/μl) to all HIV-positive partners. The impact was additionally compared with a baseline of current ART coverage (35% of those with CD4<350 cells/μl). Full costs (in US$2012) of programme introduction and implementation were estimated from a provider perspective.

Results: Substantial benefits came from scaling up ART to all HIV-positive partners according to 2010 national guidelines, with additional smaller benefits of providing TasP, PrEP or condom promotion. Compared with a baseline of offering ART to all HIV-positive partners at 2010 national guidelines, condom promotion was the most cost-effective strategy (US$1206/DALY), the next most cost-effective intervention was to additionally give TasP to HIV-positives (incremental cost-effectiveness ratio US$1607/DALY), followed by additionally giving PrEP to HIV-negatives until partners initiate ART (US$7870/DALY). When impact was measured in terms of infections averted, PrEP with condom promotion prevented double the number of infections as condom promotion alone.

Conclusions: The first priority intervention for serodiscordant couples in Nigeria should be scaled-up ART access for HIV-positives. Subsequent incremental benefits are greatest with condom promotion and TasP, followed by PrEP.

Key words

Antiretroviral therapy; mathematical models; disability-adjusted life years; pre-exposure

prophylaxis; treatment as prevention; condom

Introduction

Although HIV incidence in Nigeria declined by more than 50% between 2001 and 2012, it remains the second-largest epidemic in the world, with 3.4 million people infected[1]. Only an estimated 35% of those eligible for antiretroviral therapy (ART) in Nigeria currently receive it[1].

Previous modelling for Nigeria using the UNAIDS modes of transmission model estimated that a large proportion (26-46%) of new HIV infections occur among couples in stable relationships [2]. Efforts are being stepped up to identify those in serodiscordant partnerships, by testing the male partners as well as the women attending antenatal care (ANC) for HIV[3].

Trials have demonstrated that pre-exposure prophylaxis (PrEP)[4] and treatment as prevention (TasP)[5] can substantially reduce transmission within serodiscordant partnerships. The Partners PrEP trial found that daily PrEP for HIV-negative partners in heterosexual serodiscordant couples reduced incidence by 67-75%[4]. Other studies giving PrEP to HIV-negative heterosexuals (not restricted to those in serodiscordant partnerships) have had mixed results, with PrEP effectiveness driven by medication adherence[6]. The HPTN 052 trial found that TasP – giving ART immediately to the HIV-positive partner, rather than waiting until they reached the recommended CD4 threshold to initiate ART – reduced transmission within serodiscordant partnerships by 96%[5]. Prospective studies have found lower protection levels in real-world settings[7].

Several studies have found that people increase condom use once they discover they are in an HIV-serodiscordant relationship[8-10], with this increase happening soon after diagnosis[8, 9]. Additional increases in condom use by serodiscordant couples have been reported following

couples[9] and male-focussed[10] HIV testing and counselling, with very high condom use reported by serodiscordant couples in HIV-prevention trials[4, 5, 11].

There is increasing interest in measuring the impact of combinations of prevention tools on HIV incidence, with mathematical modelling playing a key role in guiding policy makers by providing estimates of the combined impact of different interventions. Several models have been used to estimate the impact and cost-effectiveness of combination HIV prevention in South Africa[12, 13], but these findings cannot easily be extrapolated to Nigeria, which has higher male circumcision rates, lower HIV prevalence, and lower per-capita wealth than South Africa.

This study aimed to estimate the impact and cost-effectiveness of PrEP, TasP and condom promotion for serodiscordant couples in Nigeria.

Methods

We developed a mathematical model describing HIV-1 transmission within serodiscordant heterosexual partnerships and to/from external sexual partners. This model was parameterised with behavioural, biological and cost data from Nigeria and elsewhere, and used to estimate the impact and cost-effectiveness of the interventions among serodiscordant couples already identified through ANC.

Transmission model

The model is a deterministic, compartmental cohort model, dividing HIV-negatives by PrEP status, HIV-positives by CD4 count (>350 cells/μl, 200-350 cells/μl, <200 cells/μl) and ART status (naïve, on ART, post-ART), and couples by whether they are receiving condom promotion. PrEP

and condom promotion are assumed to be initiated at the beginning, whereas ART can also be initiated later, at a rate reflecting eligibility, CD4-testing frequency and ART acceptance. Those refusing or dropping out of ART enter the post-ART group and, assuming they only seek treatment upon becoming symptomatic, only (re-) initiate ART with CD4<200 cells/µl. HIV-negatives are assumed to stop taking PrEP due to dropout, acquiring infection, or (for some interventions) their partner starting ART. Couples receiving condom promotion have higher within-partnership condom use, but the same rates of condom use with external partners, as couples not receiving it. Conservatively, within-partnership condom use falls to non-intervention levels when couples drop out of condom promotion. HIV-negative partners acquire HIV either from their HIV-positive partner or from external partners, at a rate dependent upon frequency of sex, condom, ART and PrEP use, and CD4 count. All newly infected individuals have an initial CD4 count >350 cells/µl. CD4 counts decline amongst HIV-positives off ART, and increase on ART. Further details and equations are in supplement 1.

Transmission model parameters

All of the parameters are defined in Table 1, with data sources in Table S1.

Death rates and CD4 transition probabilities by CD4 count and ART status were estimated from data from other African countries, with additional data from Europe informing on-ART estimates. Age- and gender-specific non-HIV-related death rates were estimated from World Health Organisation (WHO) life-tables. All rates were converted to monthly probabilities. Data on sexual behaviour, CD4 counts at diagnosis, discordant couple characteristics and HIV testing came from Nigerian studies[14, 15].

Condom use by serodiscordant couples, with and without condom promotion, and ART acceptance rates were estimated from studies conducted elsewhere in Africa. Rates of ART

dropout were taken from Nigerian studies[16, 17], dropout rates from condom promotion and pre-ART care were informed by data from elsewhere in Africa, and PrEP dropout was informed by dropout rates in PrEP trials. The efficacy of PrEP, ART, male circumcision and condoms in reducing HIV transmission came from published trials and meta-analyses.

Cost model

Full costs (in US$2012) of programme introduction and implementation were estimated from a provider perspective and computed from costing studies conducted in Nigeria[18, 19] and elsewhere. For PrEP and ART, total costs include start-up costs (training and mass media campaigns), drug, laboratory tests and logistics, and facility delivery costs. Facility delivery costs take into account the number of visits patients make to health care facilities (including additional visits early on), and the duration and staff salary costs for each visit. ART costs include the costs of treating opportunistic infections. The costs of identifying serodiscordant couples are not included. Costs were calculated per person per year for PrEP and ART, and per couple per year for condom promotion. For further details see supplement 1.

Intervention scenarios

The main baseline scenario was offering ART at 2010 national guidelines (CD4<350 cells/μl) to all HIV-positive partners in serodiscordant couples. An additional baseline used for the impact analysis only assumed current ART coverage levels (35%) amongst eligible HIV-positive partners.

The intervention scenarios considered (in addition to the baseline offering ART at CD4<350 cells/μl to all HIV-positive partners) were: TasP (offering ART to all HIV-positives); short-term PrEP (offering PrEP to HIV-negatives whose partner is not on ART, ceasing when their partner

initiates ART or they contract HIV); long-term PrEP (offering PrEP to all HIV-negatives, ceasing

when they contract HIV); condom promotion; and all combinations of these. For PrEP

scenarios, we assumed 60% of HIV-negative partners accept and start using PrEP. We assumed

80% of couples begin the condom promotion program when offered.

Model calibration and analysis

Latin Hypercube Sampling[20] was used to sample all biological, behavioural and cost

parameters from their ranges (Table 1) 2000 times. All parameters were uniformly distributed

apart from ART efficacy (triangular distribution).

The model was run for two years without ART using each of these 2000 parameter

combinations in turn; those giving an average incidence among HIV-negative partners between

2-9 new infections per 100 person-years were retained for subsequent analyses. This range

reflects low HIV incidence in serodiscordant couples in clinical trials[5] up to higher rates seen

in cohorts in Zambia and Uganda[21, 22]. All retained parameter sets were run for 20 years, for

each baseline scenario and each combination of interventions.

The impact of each intervention scenario was estimated in comparison with each of the

baseline scenarios in terms of infections averted, percentage infections averted or disability-

adjusted-life-years (DALYs) averted, amongst members of both the serodiscordant couple

cohort and the pool of external partners, over 20 years. DALYs were calculated by summing up

person-years spent in different CD4 and ART categories, weighted with values from the 2010

Global Burden of Disease study. Incremental costs associated with each intervention were

estimated in comparison to the baseline scenario (with ART offered to all eligible HIV-positive

partners). Cost-effectiveness was calculated as the incremental cost per infection or DALY

averted over 20 years. Both impacts and costs were discounted into the future at a rate of 10%

per year in the main analysis, accounting for the high preference for the present observed in

Nigeria[23-26]. Uncertainty in predicted impacts were summarised using 95% credible

intervals (CrI), which bound the central 95% of impacts obtained across all parameter

combinations. ANCOVA was used to identify which parameters most influenced intervention

impact and cost.

The median incremental cost and impact of each intervention combination were plotted to

identify the efficiency frontier, which joins the incrementally most cost-effective interventions

as resources increase. The cost-effectiveness thresholds used were 1×GDP (US$2742)[27] and

3×GDP (US$8226) per DALY averted for highly cost-effective and cost-effective interventions

respectively.

In sensitivity analyses, alternative discount rates (3%, 15%), time horizons (10 years, full cohort

lifetime), acceptance rates for PrEP (40%, 80%) and condom promotion (40%, 60%), and higher

rates of ART re-initiation for HIV positive members of serodiscordant couples (same treatment

CD4 criteria and 50%,100% rate of ART naïve) were also investigated.

Results

Selected parameter sets

Of 2,000 parameter combinations investigated, 1,103 gave HIV incidence amongst HIV-

negative partners between 2 and 9 per 100 person-years over the first two years (median

incidence 5/100 person-years). These parameter combinations were used for all subsequent

analyses. A median 0.2% of infections came from external partners (range 0.02-2.4%).

Impact

Compared with current ART coverage

Compared with current ART coverage (35% of those eligible), offering ART to all eligible (CD4<350 cells/µl) HIV-positive partners in serodiscordant couples averted 15% of all infections over 20 years. This equated to 35% of the infections averted under the strategy with the greatest impact (TasP, long-term PrEP and condom promotion), and 73% of the DALYs (Fig. 1).

Compared with 2010 national treatment guidelines baseline

Compared with a baseline scenario where all HIV-positive partners in serodiscordant couples were offered ART once they reached a CD4 count<350 cells/µl, the relative impact of each intervention differed by impact measure (Fig. 2). Long-term PrEP averted the greatest proportion of remaining infections (15%), followed by condom promotion (11%), short-term PrEP (10%) and TasP (10%) (Fig. 2a). In terms of DALYs averted, TasP had the greatest impact, followed by long-term PrEP, short-term PrEP and condom promotion (Fig. 2b). The greatest impact using either measure was achieved with a combination of TasP, long-term PrEP and condom promotion, which averted 30% of infections (95% CrI 20-50%), and 356 DALYs (95% CrI 213-565).

Influential parameters

The parameters most influencing the impact were frequency of sex within serodiscordant partnerships, per-sex-act transmission probability, intervention efficacy and dropout rates (supplement 1). Cost estimates were most influenced by intervention dropout rates and yearly per-person intervention costs.

Cost-effectiveness

Cost-effectiveness was only estimated in comparison with a baseline scenario where all HIV-positive partners in serodiscordant couples were offered ART at CD4 <350 cells/µl. For impact on infections averted, Fig. 3a suggests that as more resources become available, after giving ART to HIV-positives with CD4<350 cells/µl, the most cost-effective interventions were: condom promotion, then additionally giving short-term PrEP to HIV-negatives (almost doubling the number of infections averted compared with condom promotion alone), then switching to long-term PrEP alongside condom promotion, and finally, additionally giving TasP to HIV-positives. This order was well conserved across the different parameter combinations; 61%(668/1103) gave this same sequence. All parameter combinations suggested condom promotion as the initial intervention, and 90%(997/1103) suggested adding short-term PrEP next.

For impact on DALYs, the most cost-effective initial intervention was condom promotion, but as more resources become available the next most cost-effective intervention was additionally giving TasP to HIV-positives, followed by additionally giving short-term PrEP (Fig. 3b). For the median values, condom promotion and the addition of TasP were incrementally highly cost-effective at a threshold of 1×GDP (incremental cost-effectiveness ratio (ICER) US$1206/DALY and US$1607/DALY, respectively). The median incremental benefit of adding short-term PrEP to the condom promotion and TasP interventions was cost-effective at a threshold of 3×GDP (ICER US$7870/DALY), but not at 1×GDP. With more resources, a slight additional benefit came from switching to long-term PrEP, but this was not cost-effective (ICER US$19054/DALY). There was substantial agreement across parameter sets: 57% gave this same order for prioritising interventions, with a further 32% suggesting TasP as the most cost-effective initial intervention, followed by condom promotion with TasP; 99% of parameter combinations had

condom promotion with TasP on the efficiency frontier as the second or third intervention .

Using a cost-effectiveness threshold of 1×GDP, when condom promotion was the first

indicated strategy, this was cost-effective for 741/742(99%) of these parameter sets, and

progressing to an intervention with TasP and condom promotion was incrementally cost-

effective for 96%(712/742) of parameter combinations. When TasP was the first indicated

strategy, this was cost-effective (at 1×GDP) for 356/361(99%) of parameter sets, and adding

condom promotion to TasP was cost-effective for 151/352(43%). Adding short-term PrEP to a

condom use with TasP strategy was only cost-effective for 1% of parameter combinations

using a 1×GDP threshold. Using a cost-effectiveness threshold of 3×GDP, condoms with TasP

(via TasP or condoms alone) was incrementally cost-effective for 99% of parameter

combinations, the addition of short-term PrEP was cost-effective for 73%, and the subsequent

switch to long-term PrEP for 6%.

At higher incidence, more infections and DALYs were averted by each intervention (p<0.001

for all), and the cost per infection or DALY averted decreased (p<0.001 for all). With higher

incidence, condom promotion (rather than TasP) was more likely to be the initial intervention

on the DALY efficiency frontier, but no difference was seen in the order of the efficiency

frontier for infections averted.

Sensitivity analyses

Higher discount rates reduced cost-effectiveness (Fig. S2). With the more standard 3% annual

discount rate (vs.10%), the order of incrementally cost-effective interventions remained the

same, but ICERs were improved (condom promotion: US$590/DALY, adding TasP:

US$1054/DALY, adding short-term PrEP: US$3536/DALY, switching to long-term PrEP:

US$9259/DALY).

Increased impact and cost-effectiveness were seen over longer timescales (Fig. S3). Assessing the impact over 10 rather than 20 years changed the order of incrementally cost-effective interventions, with TasP becoming the most cost-effective initial intervention, followed by condom promotion with TasP (Fig. S3).

Assuming different initial PrEP coverage (40% or 80% rather than 60%) made little difference to the number of DALYs averted, but higher coverage increased total costs (results not shown). Lower initial condom promotion coverage (40% or 60% rather than 80%) slightly reduced both costs and DALYs averted, and slightly reduced the cost per DALY (results not shown). The order of incrementally cost-effective interventions remained the same.

Higher rates of ART re-initiation gave increased impact for TasP, but decreased impact for PrEP and condom promotion, and all interventions cost more per DALY averted. With increasing ART re-initiation, TasP was more likely to be the most cost-effective initial intervention, followed by condom promotion, and the addition of PrEP was less likely to be cost-effective.

Discussion

We found that offering ART to all HIV-positive partners in serodiscordant couples in line with national treatment guidelines would have a large effect on survival and HIV transmission. Condom promotion for serodiscordant couples was predicted to be highly cost-effective and effective in reducing transmission within partnerships. In addition, treatment as prevention - already recommended by WHO for serodiscordant partnerships[28] - was predicted to bring about substantial and highly cost-effective additional gains in DALYS averted. Additionally offering HIV-negative partners PrEP until their HIV-positive partner initiated ART was also predicted to be cost-effective (US$7870/DALY). After offering ART to HIV-positive partners at

CD4 count<350 cells/µl, offering HIV-negative partners PrEP until their HIV-positive partner began ART was predicted to avert 10% of remaining new HIV infections.

Despite considerable uncertainty in several model parameters, we found consistent results for the efficiency frontier, with condom promotion and TasP for HIV-positives almost always recommended as the first two interventions to initiate to avert DALYs, followed by short-term PrEP for HIV-negatives, and condom promotion with short-term PrEP for HIV-negatives recommended to prevent new infections efficiently.

This analysis highlights the importance of condom promotion as part of combination prevention for serodiscordant couples – this costs the healthcare provider relatively little, but can substantially increase condom use, reducing the likelihood of within-couple transmission.

We allowed transmission rates amongst serodiscordant couples to vary between 2 and 9 new infections per 100 person-years, in the absence of Nigeria-specific incidence estimates. We expect transmission rates amongst serodiscordant couples in Nigeria to be somewhat lower than the higher transmission estimates (up to 9 per 100 person-years) from studies in Zambia and Uganda, since Nigeria has higher circumcision rates[29], and these studies were conducted in populations with very low condom use[21], or amongst couples unaware of their HIV status[22]. We predicted that PrEP, TasP and condom promotion would be more cost-effective at higher incidence, and so data on behaviour and incidence from demonstration projects will be crucial for improving the accuracy of cost-effectiveness estimates for Nigeria.

We predicted that very few infections (<3%) amongst HIV-negative people in serodiscordant partnerships would come from external partners, lower than the estimated 20-30% in clinical trials[5, 30]. This is in agreement with previous modelling for sub-Saharan Africa which predicted that less than 3% of HIV infections among serodiscordant couples would come from external partners in countries with low (≤3%) HIV prevalence[31].

In comparison with previous African cost-effectiveness studies[12, 13, 32], there is less difference in our study between the estimated annual costs of PrEP and ART; this is likely to be because our cost estimates for PrEP and ART include all of the same components, whereas previous studies often took into account more components for ART than for PrEP. A previous modelling study of serodiscordant couples in South Africa[13] suggested that PrEP may be more cost-effective than early ART for the relative ratio of PrEP to ART costs and PrEP efficacy used in our study, in couples with 'typical' levels of risk. This was not found in our study, perhaps because we assumed lower levels of unprotected sex with external partners and a lower ratio of risk of infection from external relative to stable partners, leading to fewer infections coming from external partners. In agreement with our findings that condom promotion and TasP were more cost-effective than PrEP, a modelling study of a hyperendemic southern African setting found that it was more cost-effective to first give early ART before introducing PrEP[12]. Another study of combination prevention in Kenya found that it was usually most cost-effective to first implement behaviour change interventions, followed by early ART, and then PrEP[33].

We assumed a discount rate of 10% for both impacts and costs in our baseline analysis, which led to lower estimated cost-effectiveness than for the more standard 3% discount rate. While the 3% discount rate is usually recommended[34], it may not reflect the willingness to trade-off future for present consumption in Nigeria. Although the preference for present is in theory well captured by the interest rate, the presence of market imperfections as well as the inability of the interest rate to account for the interest of future generations[35] justifies our decision not to use the interest rate as a proxy for the societal discount rate. Instead, we found evidence that preference for present is particularly high in Nigeria since discount rates used in Nigeria project reports varied between 8.0% and 13.7%[23-26].

We permitted a wide range of ART efficacy in our analysis, with a preference for higher efficacies, reflecting the fact that some observational studies have found lower levels of transmission reduction than clinical trials[7, 36]. High rates of viral suppression, between 77-90%[17, 37] have been reported for ART patients in Nigeria, which compares well with the levels of viral suppression (70%[38], 89%[5]) measured in transmission studies which found high levels of reduction in transmission (92%,96% respectively). Therefore assuming a large effect in this setting seems reasonable.

Formative research looking at perceptions of PrEP use in Nigeria found broad acceptability, although concerns were raised about the impact of stigma and sustainability of PrEP interventions[39]. The current PrEP demonstration project occurring among Nigerian serodiscordant couples will give a clearer picture of PrEP feasibility, as well as levels of condom use and ART uptake among serodiscordant couples.

Limitations

Much of the data used to inform this analysis came from outside Nigeria, and while HIV progression and mortality estimates are not expected to differ greatly between countries, there could be strain-related differences in survival and progression[40]. Most of the behavioural data came from married people of unknown HIV status, which may underestimate the risk behaviour of serodiscordant couples. We did not consider second-line ART which may have affected our ART cost estimates. We assumed that the infectiousness of HIV-positive individuals decreased to low levels as soon as they started ART, with partners immediately stopping short-term PrEP. We therefore did not evaluate the cost-effectiveness of the more realistic scenario where HIV-negative partners continue to take PrEP for several months after ART initiation, while viral loads decline. Previous modelling suggests only a small impact is achieved over this period[13].

In conclusion, these results suggest that the best first intervention strategy for serodiscordant couples in Nigeria would be ensuring that all HIV-positives are offered ART at current national guidelines. Additional reduction in new infections could be achieved by promoting condom use amongst serodiscordant couples, and offering PrEP to HIV-negatives until their partner initiates ART. Additional DALYs could be averted through condom promotion for couples and TasP for HIV-positive partners, which would both be incrementally highly cost-effective, followed by offering PrEP to HIV-negatives until their partner initiates ART.

Acknowledgements

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Tables

Table 1. Parameters used in the model, with definitions, estimated values and ranges. All sources and references are given in the supplementary material.

Parameter (symbol used in equations)	Estimate	Range	Country/study for estimate
Number of discordant couples	1000	fixed	-
% of couples with HIV-positive woman	93	85-100	Nigeria
% CD4 at ANC testing 200-350 cells/µl	29	28-29	Nigeria ANC data
% CD4 at ANC testing <200 cells/µl	13	13-21	Nigeria ANC data
% PrEP effectiveness (efficacy × adherence θ)	70	44-90	Partners PrEP trial in Kenya and Uganda
% condom efficacy (e)	80	58-95	East and southern Africa; Cochrane review
% of sex acts in which condom used (f)	66	64-80	Rwanda; Uganda; South Africa
% reduction in non-condom protected acts following condom promotion	62	50-62	Rwanda; Uganda; South Africa
Frequency of CD4 testing for HIV-positives in care but not yet on ART (ρ), per year	2	1-2	Nigeria
% of treatment naïve accept ART (ϕ)	68	65-83	sub-Saharan Africa; Africa, Thailand
Relative prob. death per month off ART, CD4>350 vs 200-350 cells/µl ($\alpha_{1,1} : \alpha_{2,1}$)	0.206	0.206-0.258	Cote d'Ivoire; Zimbabwe; South Africa
Monthly probability of death off ART, CD4 200-350 cells/µl ($\alpha_{2,1}$)	0.00272	0.00156 – 0.00397	Cote d'Ivoire
Relative prob. death per month off ART, CD4>350 vs 200-350 cells/µl ($\alpha_{3,1} : \alpha_{2,1}$)	9.08	3.45-9.08	Cote d'Ivoire; Zimbabwe; South Africa
Relative prob. death on vs. off ART for the same CD4 count ($\alpha_{i,2} : \alpha_{i,1}$)	0.19	0.14-0.25	South Africa
Off ART, monthly probability of moving from CD4>350 to 200-350 cells/µl ($\delta_{1,1}$)	0.0257	0.0119-0.0289	eART-linc cohorts in Uganda and Cote d'Ivoire; South Africa; Ethiopia
Off ART, monthly probability of moving from CD4 200-350 to <200 cells/µl ($\delta_{2,1}$)	0.0188	0.0186-0.0274	eART-linc cohorts in Uganda and Cote d'Ivoire; South Africa; Ethiopia
On ART, monthly probability of moving from CD4 200-350 to >350 cells/µl ($\delta_{2,2}$)	0.0569	0.0247-0.0888	South Africa; Europe
On ART, monthly probability of moving from CD4<200 to CD4 200-350 cells/µl ($\delta_{3,2}$)	0.0293	0.0274-0.0863	South Africa; Europe
Yearly % of people who drop out of ART(σ)	10	5-30	Nigeria (multiple sites); Kenya

Parameter (symbol used in equations)	Estimate	Range	Country/study for estimate
Ratio of dropout from PrEP relative to ART dropout ($\omega:\sigma$)	-	1-1.5	PrEP trials multiple sites; allowing for higher dropout expected outside trial
Ratio of dropout from condom promotion relative to ART dropout ($\kappa:\sigma$)	-	0.3-1	DR Congo, Uganda
Ratio of dropout from pre-ART care relative to ART dropout ($\nu:\sigma$)	-	1-2	South Africa, Malawi
Per vaginal sex act probability of HIV transmission HIV from man to woman (β_f)	0.0019	0.0010-0.0037	Partners HIV/HSV study, multiple sites in east and southern Africa
% efficacy of medical male circumcision in reducing female to male HIV transmission (υ)	0.66	0.4-0.77	South Africa, Kenya and Uganda
% of men circumcised (τ)	98	fixed	Nigeria
% efficacy of ART in reducing HIV transmission (χ)	92	26-99 (triangular)	Meta-analysis; east/southern Africa; HPTN052 trial (multiple countries); China
Relative transmission risk from HIV-positive person with CD4<200 vs >200 cells/µl (ξ)	4.18	2-8	Partners in Prevention cohort, east/southern Africa
DALY weight HIV-positive on ART or CD4>350 cells/µl	0.947	0.921-0.966	Global Burden of Disease study 2010
DALY weight HIV-positive CD4 200-350 cells/µl	0.779	0.690-0.854	Global Burden of Disease study 2010
DALY weight HIV-positive CD4<200 cells/µl	0.453	0.285-0.618	Global Burden of Disease study 2010
Sex acts per month with external partners	3.4	1.3-6.4	Nigeria
Sex acts per month with regular partner (c)	5.6	1.4-15.3	Nigeria
% sex acts condom used with external partners (men)	49.0	44.9-53.1	Nigeria
% of sex acts condom used with external partners (women)	11.8	6.4-17.2	Nigeria
ART coverage external partners (%)	35	fixed	Nigeria
Yearly % testing for HIV, general population	6.5	6.5-11.7	Nigeria
Relative infectiousness of external vs asymptomatic regular infected partner	2	1-2.5	Uganda
Provider unit cost PrEP initiation (2012$)	118	82.6-153.4	Nigeria, South Africa (drug costs)
Provider unit cost PrEP per year (2012$)	233	163.1-302.9	Nigeria, South Africa (drug costs)
Provider unit cost ART initiation (2012$)	150	105.0-195.0	Nigeria costing studies
Provider unit cost ART per year (2012$)	365	255.5-474.5	Nigeria costing studies
Provider costs of condom promotion per couple per year (2012$)	19	13.3-24.7	Nigeria costs for counselling, international prices for condoms

Figure captions

**Figure 1. Impact compared to current ART coverage (35%) of those with CD4 <350 cells/µl),
for all intervention combinations considered.** Impact is measured in terms of (a) infections
averted, (b) DALYs averted. Error bars are 95% credible intervals from 1103 simulations.

**Figure 2. Impact compared to baseline scenario (ART offered to all HIV-positive partners
within discordant couples once their CD4 <350 cells/µl), for all intervention combinations
considered.** Impact is measured in terms of (a) infections averted, (b) DALYs averted. Error
bars are 95% credible intervals from 1103 simulations.

**Figure 3. Incremental impact and cost compared to baseline scenario (ART offered to all HIV-
positive partners within discordant couples once their CD4 <350 cells/µl), for all intervention
combinations.** Impact is measured in terms of (a) infections averted and (b) DALYs averted.
Plotted points are medians for each intervention from 1103 parameter sets. Intervention
combinations are shown by letters and symbols combining individual intervention elements
shown in the key (e.g. open circle with a cross through it, labelled "c,sp", indicates condom
promotion plus short-term PrEP). Interventions appearing on the efficiency frontier are shown
in black, with those interventions not appearing on the frontier in grey. The solid straight lines
join the medians for the incrementally most cost-effective interventions as budget increases.
In (b) incremental additions which are highly cost-effective (incremental cost per DALY averted
< 1×GDP) are shown by solid lines, additions which are cost-effective (incremental cost per
DALY averted <3×GDP) are shown by dashed lines, and additions which are not cost-effective
(incremental cost per DALY averted >3×GDP) are shown with a dotted line.

List of supplemental digital content
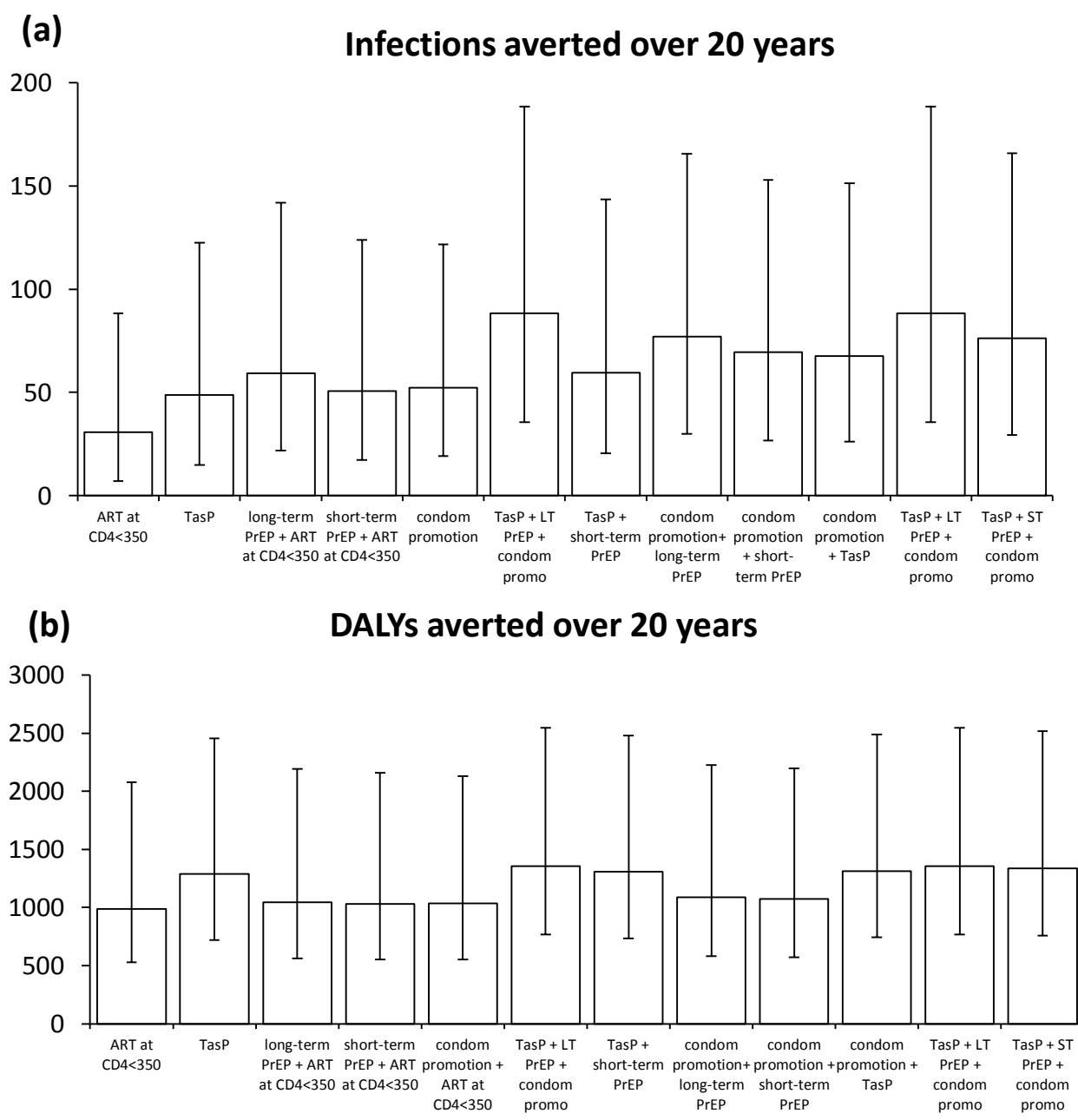
Supplement_1.docx

Figure 1

(a)
Infections averted over 20 years

(b)
DALYs averted over 20 years

Figure 2

(a) Infections averted over 20 years

(b) DALYs averted over 20 years
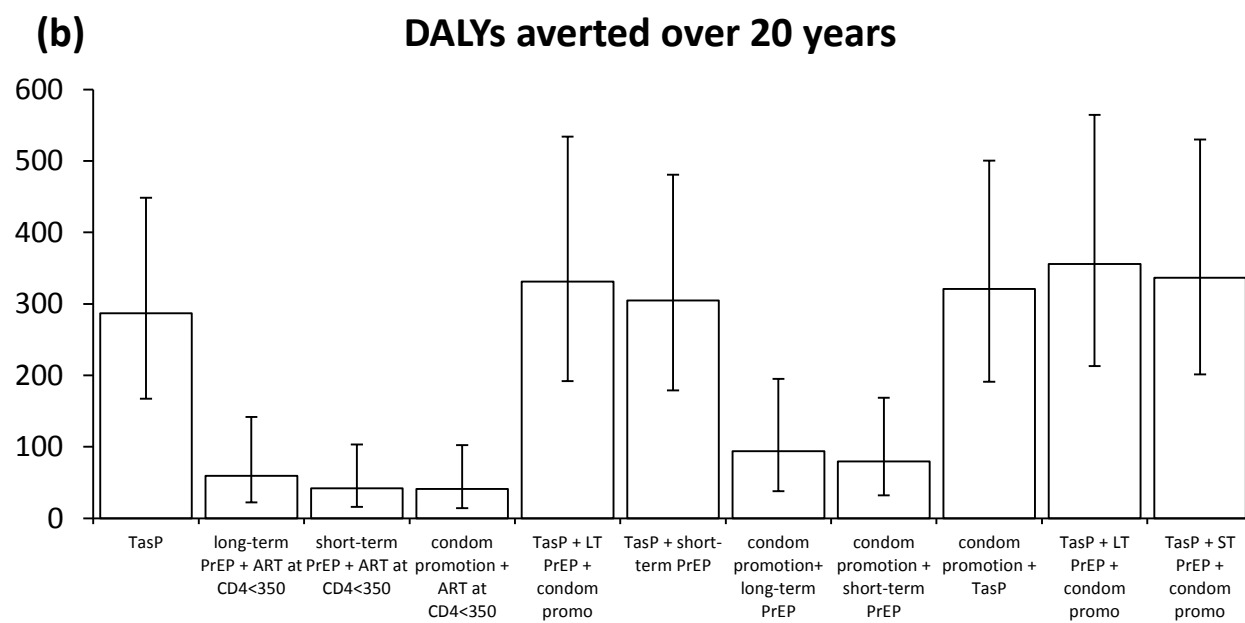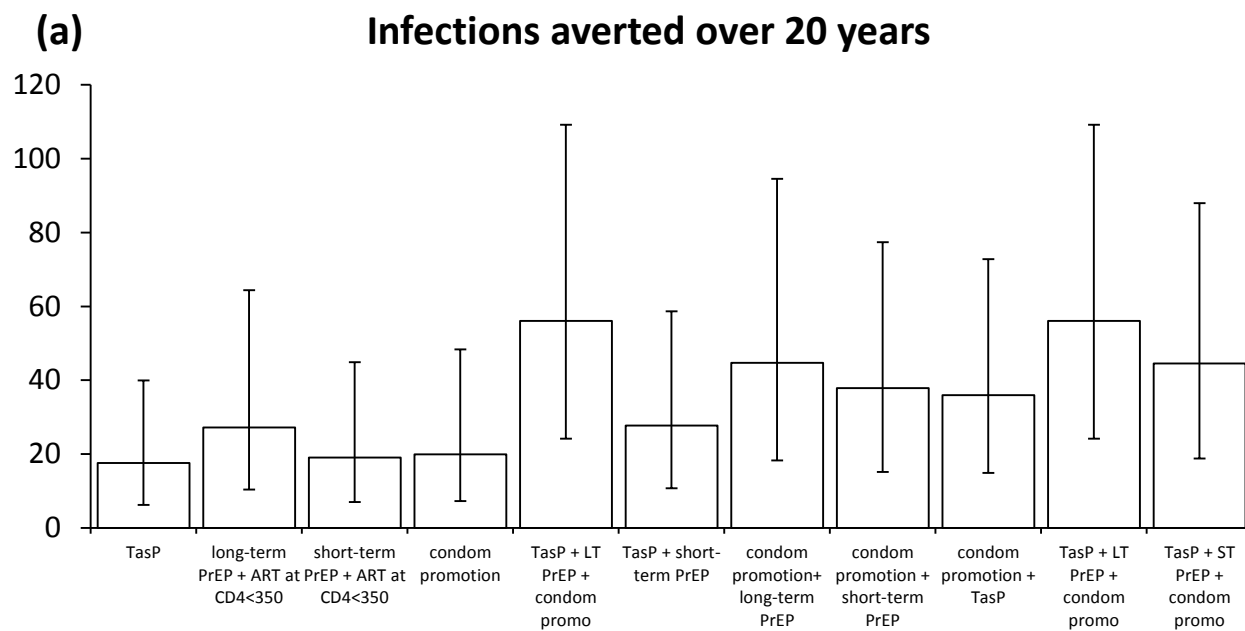
Figure3
Click here to download Figure: Figure 3.tiff

(a)

Infections averted over 20 years

Incremental cost (x 10,000 US$2012)

+ c   condoms
o sp short-term PrEP
● lp long-term PrEP
× t   TasP

(b)

DALYs averted over 20 years

Incremental cost (x 10,000 US$2012)

+ c   condoms
o sp short-term PrEP
● lp long-term PrEP
× t   TasP
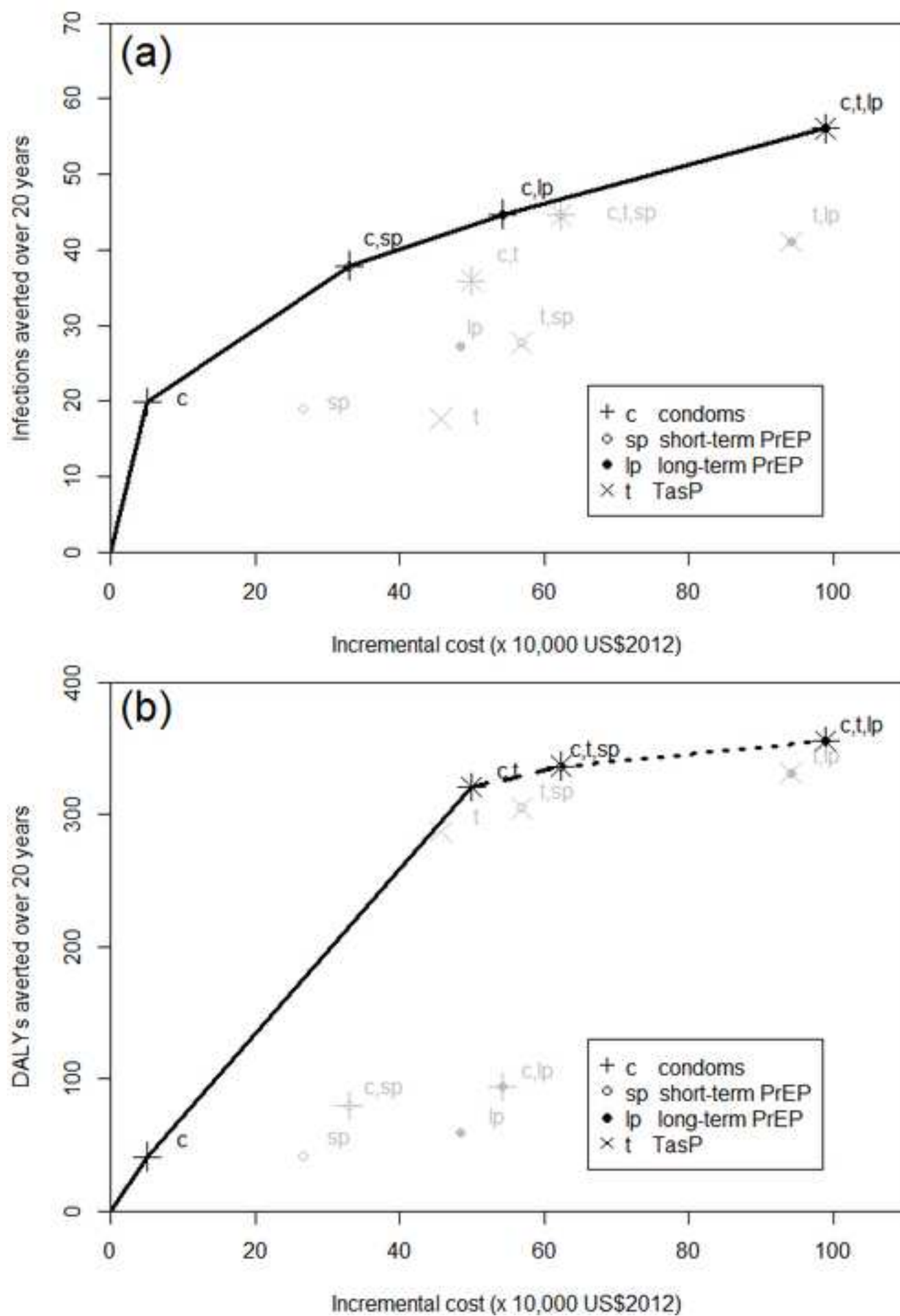
Supplementary material

Supplementary methods

Transmission model

The model is a deterministic, compartmental cohort model, which describes HIV transmission from HIV-positive to HIV-negative partners in serodiscordant relationships, as well as transmission from and to external partners. The model divides HIV-negative people into those who are on or off PrEP (S^P and S^0, respectively), and HIV-positive people into nine groups ($I^{i,j}$) according to CD4 count (i) and ART status (j), where CD4 count is >350 cells/μl (i = 1), 200-350 cells/μl (i = 2), or <200 cells/μl (i = 3), and ART status is either ART naïve (j = 1), currently on ART (j = 2), or post- ART (j = 3). No separate compartment is included for CD4>500 cells/μl, as this is not yet the threshold for ART treatment in Nigeria. The model also tracks the number of people who have died, D (from both HIV-related and other causes). All of the possible model states for individuals are shown in figure S1. The model follows a cohort of 1,000 already identified discordant couples, from the point of initial identification and over their full subsequent lifespan. Within the couples, each partner is in one of the twelve states mentioned above and shown in figure S1 (giving a total of 143 different couples states) Additionally, couples where both partners are still alive may be engaged in a condom promotion program (giving an additional 121 couple states). External partners are modelled as a pool of individuals in one of the 12 states shown in figure S1. At the start, when the couples have just been identified, one partner in each couple is positive, and the distribution of CD4 counts for the HIV-positive partner (either male or female) is assumed to be the same as that for women testing positive for HIV in ANC in Nigeria [1]. At the start, some HIV-positive partners may be put onto ART and some HIV-negative partners put onto PrEP, depending upon the intervention scenario (see 'intervention scenarios' section). Both at the start and subsequently, ART naïve HIV-positive partners are offered ART if their CD4 count is below the assumed threshold, at a rate, $\rho_{i,j}$, reflecting rates of CD4 testing. Once offered ART, a certain percentage, ϕ, are assumed to accept and initiate ART, entering the 'on ART' category; those not accepting ART are transferred to the post-ART category. People may drop out of ART (at a rate σ) and enter the post-ART category. Additionally, those in the ART naïve category are assumed to drop out of pre-ART care at a certain rate ν and also enter the post-ART category. Those in the post-ART category may (re-)initiate ART if their CD4 count falls below 200 cells/μl – this assumes that they only seek treatment once they become symptomatic. Those on PrEP can come off PrEP, either due to becoming HIV-positive (entering the first infection compartment, $I^{1,1}$), drop-out from the PrEP program (at a rate ω, entering the 'no PrEP' category, S^0), or because their partner has initiated ART (HIV-negative partner enters S^0). At the start, some

couples may receive condom promotion, and are assumed to have higher condom use with their couple partner (but the same condom use with external partners) than couples not participating in the condom promotion program. Couples drop out of the condom promotion program, at a rate κ, and return to their equivalent disease and treatment states without condom promotion, returning to the levels of condom use assumed for those not receiving condom promotion. HIV-negative individuals can become infected with HIV through contracting HIV from their HIV-positive partner (with the probability of infection, Λ_t, which is calibrated to incidence rates measured in other African countries, calculated from the frequency of sex acts between married/cohabiting couples, c_l, and the probability of HIV transmission per sex act, β_k, taking into account the level of condom use within the partnership, f, the CD4 count of the HIV-positive partner, whether or not the HIV-negative partner is taking PrEP and whether or not the HIV-positive partner is on ART). HIV-negative individuals can also contract HIV from an external partner (with the probability of infection calculated from the (age-related) proportion who have external partners, the frequency of sex acts and levels of condom use with external partners, probability of infection per sex act with an HIV-positive individual, age-specific HIV prevalence in the general population and overall ART coverage in the general population, adjusting for the probability that external partners may be in the highly infectious acute or late stages of HIV infection). When HIV-negative individuals become infected with HIV, they enter the compartment of ART naïve individuals with a CD4 count >350 cells/µl ($I^{1,1}$). Those not on ART are assumed to have a declining CD4 count over time, moving into lower CD4 count categories (at the same rate ($\delta_{i,j}$) regardless of previous ART status), while those on ART are assumed to have an increasing CD4 count, moving into progressively higher CD4 count categories. Individuals die either due to HIV infection (at a rate, $\alpha_{i,j}$, which varies with CD4 count and ART status) or due to other non-HIV related factors, which vary with age (at a rate μ_t). The cohort ages over time, with the pool of external partners assumed to be the same age as couples in the cohort. External partners can become infected by the cohort members at a rate estimated from the proportion with external partners, levels of condom use and number of sex acts with external partners, probability of infection per sex act and the infection status, CD4 count and ART status of cohort members. External partners' HIV progression is modeled in the same way as cohort members, with lower rates of ART initiation (calculated to give similar levels of ART coverage to that currently achieved in the general population) assumed for external partners. All sex acts are assumed to be heterosexual, vaginal sex acts, and the probability of acquiring transmission is assumed to be lower for men, due to the high levels of male circumcision.

Dropout from ART, PrEP, pre-ART care and condom promotion were assumed to occur independently of one another.The equations were solved numerically in R (version 2.13.0), using an Euler algorithm and a time step of 1 month.

The equations for infection and progression of individuals in each of the 12 states are given below:

$$S_{t+1}^0 = S_t^0 + \omega S_t^P - \left(\Lambda_t + \mu_t \right) S_t^0$$

$$S_{t+1}^P = S_t^P - \left(\Lambda_t + \mu_t + \omega \right) S_t^P$$

$$I_{t+1}^{1,1} = I_t^{1,1} + \Lambda_t S_t^0 - \left(\mu_t + \alpha_{1,1} + \rho_{1,1} + \nu + \delta_{1,1} \right) I_t^{1,1}$$

$$I_{t+1}^{2,1} = I_t^{2,1} + \delta_{1,1} I_t^{1,1} - \left(\mu_t + \alpha_{2,1} + \rho_{2,1} + \nu + \delta_{2,1} \right) I_t^{2,1}$$

$$I_{t+1}^{3,1} = I_t^{3,1} + \delta_{2,1} I_t^{2,1} - \left(\mu_t + \alpha_{3,1} + \rho_{3,1} + \nu \right) I_t^{3,1}$$

$$I_{t+1}^{1,2} = I_t^{1,2} + \phi \rho_{1,1} I_t^{1,1} + \delta_{2,2} I_t^{2,2} - \left(\mu_t + \alpha_{1,2} + \sigma \right) I_t^{1,2}$$

$$I_{t+1}^{2,2} = I_t^{2,2} + \phi \rho_{2,1} I_t^{2,1} + \delta_{3,2} I_t^{3,2} - \left(\mu_t + \alpha_{2,2} + \sigma + \delta_{2,2} \right) I_t^{2,2}$$

$$I_{t+1}^{3,2} = I_t^{3,2} + \phi \rho_{3,1} I_t^{3,1} + \rho_{3,2} I_t^{3,3} - \left(\mu_t + \alpha_{3,2} + \sigma + \delta_{3,2} \right) I_t^{3,2}$$

$$I_{t+1}^{1,3} = I_t^{1,3} + (1-\phi) \rho_{1,1} I_t^{1,1} + \nu I_t^{1,1} + \sigma I_t^{1,2} - \left(\mu_t + \alpha_{1,3} + \delta_{1,3} \right) I_t^{1,3}$$

$$I_{t+1}^{2,3} = I_t^{2,3} + (1-\phi) \rho_{2,1} I_t^{2,1} + \nu I_t^{2,1} + \sigma I_t^{2,2} + \delta_{1,3} I_t^{1,3} - \left(\mu_t + \alpha_{2,3} + \delta_{2,3} \right) I_t^{2,3}$$

$$I_{t+1}^{3,3} = I_t^{3,3} + (1-\phi) \rho_{3,1} I_t^{3,1} + \nu I_t^{3,1} + \sigma I_t^{3,2} + \delta_{2,3} I_t^{2,3} - \left(\mu_t + \alpha_{3,3} + \rho_{3,2} \right) I_t^{3,3}$$

$$D_{t+1} = D_t + \mu_t \sum_{x=1}^{x=3} \sum_{y=1}^{y=3} I_t^{x,y} + \alpha_{1,1} I_t^{1,1} + \alpha_{2,1} I_t^{2,1} + \alpha_{3,1} I_t^{3,1} + \alpha_{1,2} I_t^{1,2} + \alpha_{2,2} I_t^{2,2} + \alpha_{3,2} I_t^{3,2} + \alpha_{1,3} I_t^{1,3} + \alpha_{2,3} I_t^{2,3} + \alpha_{3,3} I_t^{3,3}$$

The infection rate, Λ_t, is as follows for infection of HIV-negative cohort members by their HIV-positive regular partners, where the HIV-negative partner is not on PrEP, and the HIV-positive partner is not on ART and has a CD4 count >200 cells/μl:

$$\Lambda_t = \beta_k c_l (1 - ef)$$

where e is the efficacy of condoms is reducing HIV transmission. The probability of transmission from women to men, β_m, is calculated as $\beta_m = (1 - \tau \upsilon) \beta_f$, where τ is the proportion of men who are circumcised, υ is the efficacy of circumcision in reducing HIV transmission, and β_f is the probability of transmission from men to women. If the HIV-positive partner has a CD4 count <200 cells/μl and is not taking ART, the probability of transmission is increased by a factor ξ, and if the HIV-positive partner is on ART (at any CD4 count), the probability of transmission is multiplied by (1-χ), where χ is the efficacy of ART in reducing HIV transmission. If the HIV-negative partner is on

PrEP, the probability of transmission is multiplied by (1-θ), where θ is the efficacy of PrEP in reducing HIV transmission.

Estimation of number of external partners

Data from the Nigeria national DHS survey for 2008 [2], on the proportion of married men and women reporting an extramarital partner in the last year, were used to estimate the equation for the straight-line relationship between age and % of men with an extramarital partner as

Percent_extramarital_partner$_a$ = ϑ -(ψ *(a-37.5)

Where a is the current age of the man, ϑ is the estimated proportion of men aged 37.5 years old who have an external partner, and ψ is the estimated decrease in this proportion per extra year of life. ϑ is varied uniformly between 0.0389-0.0541, and ψ is varied uniformly between 0.00079-0.00209 as part of the Latin Hypercube sampling of parameter space.

The relative ratio of men: women with an external partner was estimated from comparing the age-specific ratios for men and women, and was uniformly sampled from a range of 1-13.

Estimation of rate of starting ART due to sypmtoms

The monthly probability that those with a CD4 count <200 cells/μl will start ART due to being symptomatic was estimated as a function of the ART dropout rate, to give 35% ART coverage [3]. The function used was:

Probability_start_ART_symptomatic = 47.61*ART_dropout^2+1.321*ART_dropout-0.0065.

Cost model and data

Our cost model takes into account the higher number of medical visits required during the initiation year. According to Nigerian national ART guidelines, patients are required to have thirteen visits during the initiation year while it is common to have one visit every two months for the follow-up years. For PrEP users, we assumed that those initiating PrEP would have one visit to confirm HIV testing and conduct laboratory tests, and that, similar to ART, they would have eight additional collection visits during the first year to monitor adherence and ensure that treatment is well tolerated, and another two visits to increase adherence and monitor side effects, giving a total eleven visits during the initiation year. In subsequent years, it was assumed that patients would have collection visits every two months, the same as for ART.

We followed Nigerian national guidelines on the treatment regimens prescribed for first line ART (Lamivudine/Zidovudine/Nevirapine), to estimate the drug cost ($146 per person per year) and used local estimates of the costs for the drugs used for PrEP (Tenofovir/Emtricitabine, $91 per person per year).

Laboratory test costs were estimated separately for ART and PrEP users. For HIV-positive patients on TasP or ART, we considered that one CD4 count ($3.16), one full blood count ($24.00), one creatinine test ($4.17), two viral loads ($27.80 each), one chest X-ray ($12.00), one TB sputum test ($10.00), one hepatitis B test ($12.00) and two pregnancy tests for female users ($5.00 each) were conducted during the initiation year. We then considered that during the following years, HIV-positive patients receive one CD4 count, one full blood count and two viral load assessments every year. This is in line with the national guidelines on ART and also seems realistic if we refer to the availability of those tests in ART clinics in Nigeria[4]. Quantities were obtained from national guidelines [5] and from Filler et al.[6]. For PrEP users, during the initiation year we considered one HIV test ($11.54) to confirm the eligibility for PrEP. To monitor liver and kidney function, we also assume one serum creatinine and one hepatitis B test. Additionally two pregnancy tests were considered for the initiation year [7]. For follow up years, we considered that PrEP users will receive one HIV test and one serum creatinine assessment per year. We also included logistics costs, obtained from [8], in the estimated laboratory costs.

Facility delivery costs were estimated using information on the wages of health staff as well as the duration of each visit. We obtained this information from health staff of two hospitals in FCT and Plateau states. We found that an initiation visit lasts 30 minutes on average and is carried out by a doctor who usually earns around 200,000 Naira per month ($US1274), giving an estimated human resources cost per initiation visit of $4.25. For the collection visits, we found that on average about 15 minutes are spent with a doctor and 15 minutes with a pharmacist, resulting in a cost of $3.72 for human resources. To these costs, we applied a facility and health system mark-up equal to 100% and 50% to account for facility delivery costs (staff recruitment, etc.) and health system costs above facility [9]. We multiplied the cost of each visit by the number of visits per year.

For the different scenarios, a training cost of $27 was used per person on ART/PrEP, estimated from the literature [10]. We also included a mass media campaign cost. Since we did not have any cost information for Nigeria we used the microbicide campaign conducted in South Africa, which gave a cost of $1 per person [11].

The cost of opportunistic infections for people on ART was found to be around $10 per year in the literature [12].

For condom promotion, we assumed 12 visits per couple per year. We considered that 8 condoms (at a unit price of $0.0362) would be distributed per visit. Human resources costs were estimated assuming that the condom promotion was conducted by a nurse and that each visit would last 15 minutes. We also considered a 20% wastage[13]. This gives a total of $1.62 per condom promotion visit.

Costs are summarised in Table S2.

The total costs of each intervention scenario in the transmission model were estimated by calculating, for each scenario, the number of people initiating PrEP or ART per month, the number of individuals on PrEP or ART each month and the number of couples engaged in condom promotion. The number of people initiating PrEP or ART was multiplied by the estimated initiation costs plus any additional costs incurred in the first year of treatment relative to subsequent years, and the number of individuals currently on each intervention was multiplied by the estimated yearly cost per person.

Supplementary results

Influential parameters

Estimated impact varied substantially across different parameter combinations. For PrEP and condom promotion interventions, ANCOVA showed that the most influential parameters upon both infections and DALYs averted were the frequency of sex within serodiscordant partnerships (accounting for 27-29% of all variation accounted for by the varied parameters), the probability of transmission per sex act (14-16%), circumcision efficacy (8-9%), condom efficacy (16-17% for condom promotion, 4% for PrEP) and ART dropout rate (8% for condom promotion, 20-23% for PrEP). PrEP impact was also influenced by PrEP efficacy (16%) and the impact of condom promotion by background condom use (7%) and condom dropout (8%). For TasP, the parameters influencing infections averted were frequency of sex (28%), ART efficacy (22%), per-sex-act transmission probability (16%), ART dropout (12%), circumcision efficacy (8%) and condom efficacy (4%). The parameters influencing DALYs averted by TasP were somewhat different: ART dropout (28%), dropout from pre-ART care (19%), HIV-related death rate (11%), frequency of sex acts (10%), percentage accepting ART (6%), per-sex-act transmission probability (6%) and CD4 testing frequency (4%). The total costs of each intervention were most strongly influenced by ART dropout (≥24%), rates of intervention dropout (PrEP 3-4%, condom promotion 14%) and the yearly per-person costs of each intervention (≥33%). The total costs of TasP were additionally influenced by rates of HIV progression (10%) and proportion accepting ART (8%).

Table S1: Parameter table with data sources and references

Parameter (symbol used in equations)	Estimate	Range	Country/study for estimate	Source/reference
Number of discordant couples	1000	fixed	-	Set
% of couples with HIV-positive woman	93	85-100	Nigeria	FHI 360 data
% CD4 at ANC testing 200-350 cells/μl	29	28-29	Nigeria ANC data	Jos University hospital;[1]
% CD4 at ANC testing <200 cells/μl	13	13-21	Nigeria ANC data	Jos University hospital;[1]
% PrEP effectiveness (efficacy × adherence θ)	70	44-90	Partners PrEP trial in Kenya and Uganda	[14]
% condom efficacy (e)	80	58-95	East and southern Africa; Cochrane review	[15, 16]
% of sex acts in which condom used (f)	66	64-80	Rwanda; Uganda; South Africa	[17-19]
% reduction in non-condom protected acts following condom promotion	62	50-62	Rwanda; Uganda; South Africa	[17-19]
Frequency of CD4 testing for HIV-positives in care but not yet on ART (ρ), per year	2	1-2	Nigeria national treatment guidelines	[5]; assume sometimes lower frequency achieved
% of treatment naïve accept ART (ϕ)	68	65-83	sub-Saharan Africa; Africa, Thailand	[20] [21]
Relative prob. death per month off ART, CD4>350 vs 200-350 cells/μl ($\alpha_{1,1} : \alpha_{2,1}$)	0.206	0.206-0.258	Cote d'Ivoire; Zimbabwe; South Africa	[22-24]; non-HIV death rates subtracted [25]
Monthly probability of death off ART, CD4 200-350 cells/μl ($\alpha_{2,1}$)	0.00272	0.00156 – 0.00397	Cote d'Ivoire	[22]; non-HIV death rates subtracted [25]
Relative prob. death per month off ART, CD4>350 vs 200-350 cells/μl ($\alpha_{3,1} : \alpha_{2,1}$)	9.08	3.45-9.08	Cote d'Ivoire; Zimbabwe; South Africa	[22-24] non-HIV death rates subtracted [25]
Relative prob. death on vs. off ART for those with the same CD4 count ($\alpha_{i,2} : \alpha_{i,1}$)	0.19	0.14-0.25	South Africa	[24, 26]
Off ART, monthly probability of moving from CD4>350 to 200-350 cells/μl ($\delta_{1,1}$)	0.0257	0.0119-0.0289	eART-linc cohorts in Uganda and Cote d'Ivoire; South Africa; Ethiopia	[24, 27, 28]
Off ART, monthly probability of moving from CD4 200-350 to <200 cells/μl ($\delta_{2,1}$)	0.0188	0.0186-0.0274	eART-linc cohorts in Uganda and Cote d'Ivoire; South Africa; Ethiopia	[24, 27, 28]
On ART, monthly probability of moving from CD4 200-350 to >350 cells/μl ($\delta_{2,2}$)	0.0569	0.0247-0.0888	South Africa; Europe	[24, 29-31]
On ART, monthly probability of moving from CD4<200 to CD4 200-350 cells/μl ($\delta_{3,2}$)	0.0293	0.0274-0.0863	South Africa; Europe	[24, 29-31]

Parameter	Value	Range	Location	Reference
Yearly % of people who drop out of ART (σ)	10	5-30	Nigeria (multiple sites); Kenya	[32-36][37]
Ratio of dropout from PrEP relative to ART dropout ($\omega : \sigma$)	-	1-1.5	PrEP trials multiple sites; allowing for higher dropout expected outside trial	PrEP trials reported 2-29% loss per year [14, 38, 39]
Ratio of dropout from condom promotion relative to ART dropout ($\kappa : \sigma$)	-	0.3-1	DR Congo, Uganda	Condom promotion dropout 2.8-3.3% [19, 40]
Ratio of dropout from pre-ART care relative to ART dropout ($\nu : \sigma$)	-	1-2	South Africa, Malawi	41-59% loss from pre-ART care [41]
Per vaginal sex act probability of HIV transmission HIV from man to woman (β_f)	0.0019	0.0010-0.0037	Partners HIV/HSV study, multiple sites in east and southern Africa	[15]
% efficacy of medical male circumcision in reducing female to male HIV transmission (υ)	0.66	0.4-0.77	South Africa, Kenya and Uganda	[42]
% of men circumcised (τ)	98	fixed	Nigeria	[2]
% efficacy of ART in reducing HIV transmission (χ)	92	26-99 (triangular)	Meta-analysis; east/southern Africa; HPTN052 trial (multiple countries); China	[43-46]
Relative transmission risk from HIV-positive person with CD4<200 vs >200 cells/µl (ξ)	4.18	2-8	Partners in Prevention cohort, east/southern Africa	[44, 47]; range is halved and doubled
DALY weight HIV-positive on ART or CD4>350 cells/µl	0.947	0.921-0.966	Global Burden of Disease study 2010	[48]
DALY weight HIV-positive CD4 200-350 cells/µl	0.779	0.690-0.854	Global Burden of Disease study 2010	[48]
DALY weight HIV-positive CD4<200 cells/µl	0.453	0.285-0.618	Global Burden of Disease study 2010	[48]
Sex acts per month with external partners	3.4	1.3-6.4	Nigeria	[2]
Sex acts per month with regular partner (c)	5.6	1.4-15.3	Nigeria	[2]
% sex acts condom used with external partners (men)	49.0	44.9-53.1	Nigeria	[2]
% of sex acts condom used with external partners (women)	11.8	6.4-17.2	Nigeria	[2]
ART coverage external partners (%)	35	fixed	Nigeria	[3]
Yearly % testing for HIV, general population	6.5	6.5-11.7	Nigeria	[2, 49]
Relative infectiousness of external vs asymptomatic regular infected partner	2	1-2.5	Uganda	[50, 51]
Provider unit cost PrEP initiation (2012$)	118	82.6-153.4	Nigeria, South Africa (drug costs)	[7, 10, 12, 52, 53] (range + 30%)
Provider unit cost PrEP per year (2012$)	233	163.1-302.9	Nigeria, South Africa (drug costs)	[7, 10, 12, 52, 53] (range + 30%)
Provider unit cost ART initiation (2012$)	150	105.0-195.0	Nigeria costing studies	[7, 10, 12, 52, 53] (range + 30%)
Provider unit cost ART per year (2012$)	365	255.5-474.5	Nigeria costing studies	[7, 10, 12, 52, 53] (range + 30%)
Provider costs of condom promotion per couple per year (2012$)	19	13.3-24.7	Nigeria costs for counselling, international prices for condoms	Jos university hospital, [13]

Other parameters used in the transmission model

- The monthly probability of death from non-HIV related causes varied with age and gender. The values used are given in table S3 and come from WHO life-tables for Nigeria [25]

- HIV prevalence in the general population varied with age and gender. The ranges used came from a 2007 national HIV survey [54], and are given in table S4.

Table S2: Cost components

Cost component		Unit cost (2012 $)	quantity per year	source
ART/TasP				
HIV testing	Voluntary counselling and testing	12	1	[8]
Drug costs	ART price 1st line Lamivudine/Zidovudine/Nevirapine	146	1	[53]
Laboratory costs	CD4 count	3	1	[55]
	Full blood count	24	1	[8]
	Serum creatinine test	4	1	[8]
	Viral load	28	2	[55]
	Pregnancy test for women	5	2	obtained from discussion with experts in Nigeria
	Chest X-ray	12	1	[56]
	Sputum	10	1	obtained from discussion with experts in Nigeria
	Hepatitis B test	12	1	obtained from discussion with experts in Nigeria
	Logistics costs	20	1	[8]
Facility delivery	Initiation costs	38	1	From Nigeria
	Collection costs 1st year	89	1	From Nigeria
	Collection costs subsequent years	67	1	From Nigeria
Training	Training costs per person	27	1	[6]
Mass Media	Mass media	1	1	[11]
Opportunistic infection	cost of opportunistic infections per year	28	1	[8]
PrEP				
Drug costs	PrEP regimen (TDF/FTC)	91	1	obtained from discussion with experts in Nigeria
Laboratory costs	HIV test	12	1	[8]
	Serum creatinine test	4	1	[7]
	Hepatitis B test	12	1	obtained from discussion with experts in Nigeria
	Pregnancy test for women	5	1	obtained from discussion with experts in Nigeria
	Logistics costs	20	1	[8]
Facility delivery	Initiation costs	28	1	From Nigeria (data on wages of HRH and time were collected at the Maitama facility in Abuja)
	Collection costs 1st year	89	1	From Nigeria
	Collection costs subsequent years	67	1	From Nigeria
Training	Training costs per person	27	1	[6]
Mass Media	Mass media	1	1	[11]
Condom promotion				
Condoms	condom unit price	0.04	96	[57]
	condom wastage	20%		Assumption
	counselling session	1.6	12	Estimated from Nigeria

Table S3: Monthly age and gender specific non-HIV related probabilities of death used in the model (taken from WHO life-tables[25])

Age group	Men	Women
18-19	0.00013	0.00034
20-24	0.000279	0.000403
25-29	0.000405	0.000562
30-34	0.000574	0.00074
35-39	0.000777	0.000894
40-44	0.000975	0.000927
45-49	0.001182	0.000989
50-54	0.001486	0.00119
55-59	0.002059	0.001619
60-64	0.002796	0.00215
65-69	0.00402	0.00331
70-74	0.006102	0.005202
75-79	0.009279	0.008081
80-84	0.014351	0.012526
85-89	0.022486	0.019556
90-94	0.029473	0.026124
95-99	0.034394	0.031501
100-104	0.040744	0.037381
105-109	0.047095	0.043261
110	0.053445	0.049141

Table S4: Age- and gender-specific HIV prevalence (%) amongst external partners assumed in the model (estimated from national HIV survey 2007 [54]). Note that, in the model, for each parameter set a single parameter is selected from a uniform distribution between 0 and 1, and this is used to determine where between the minimum and maximum values for each age- and gender specific range the HIV prevalence is assumed to be.

Age group	Men	Women
18-19	1.24-2.96	0.57-2.03
20-24	0.99-2.81	3.10-5.90
25-29	2.25-4.95	3.18-6.22
30-39	3.68-6.52	4.27-7.13
40-49	2.99-6.21	2.12-4.88
50-64	1.42-3.98	-

Figure S1. Schematic diagram showing different infection states for individuals within the model and transitions between the states.
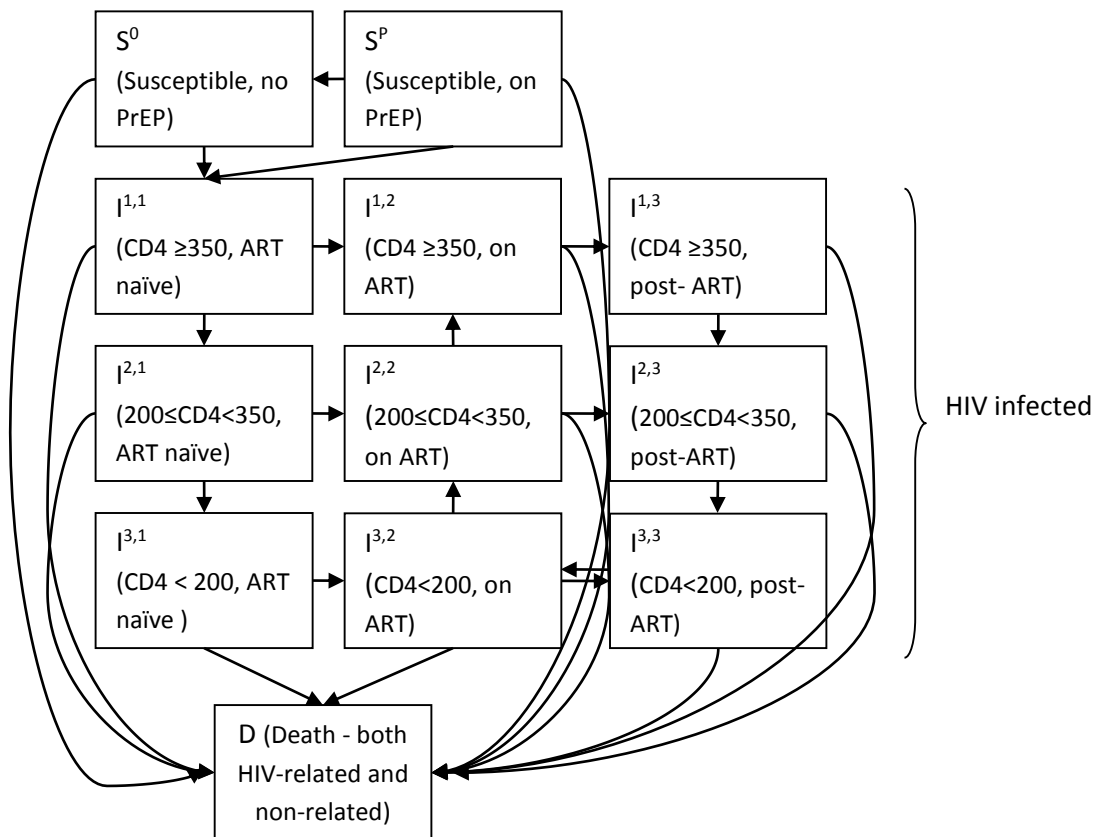
Figure S2. Sensitivity of results to assumed discount rate. Cost-effective frontiers for median values (from 1103 parameter sets) are plotted for different discount rates, applied to both impacts and costs (see figure key).
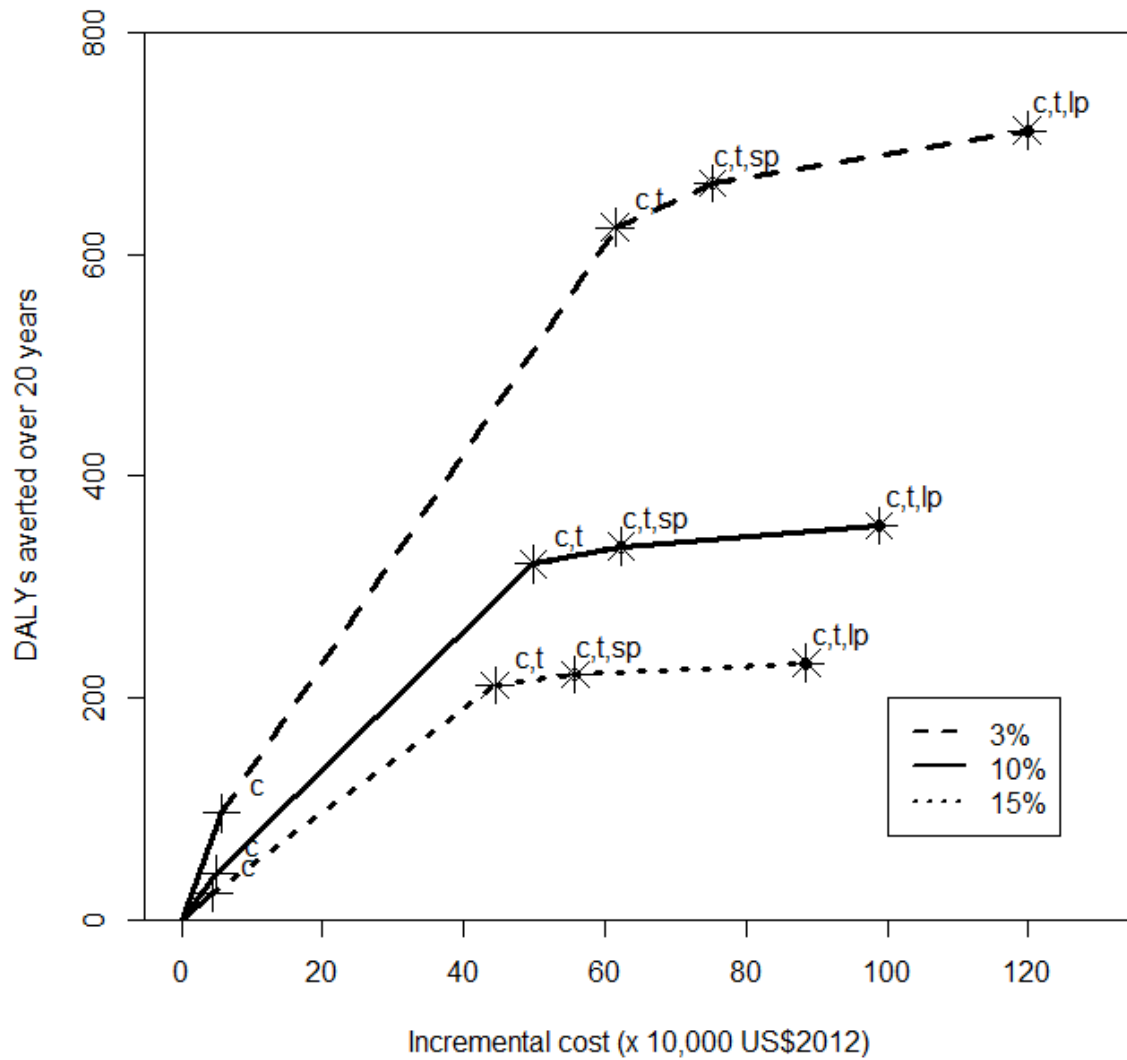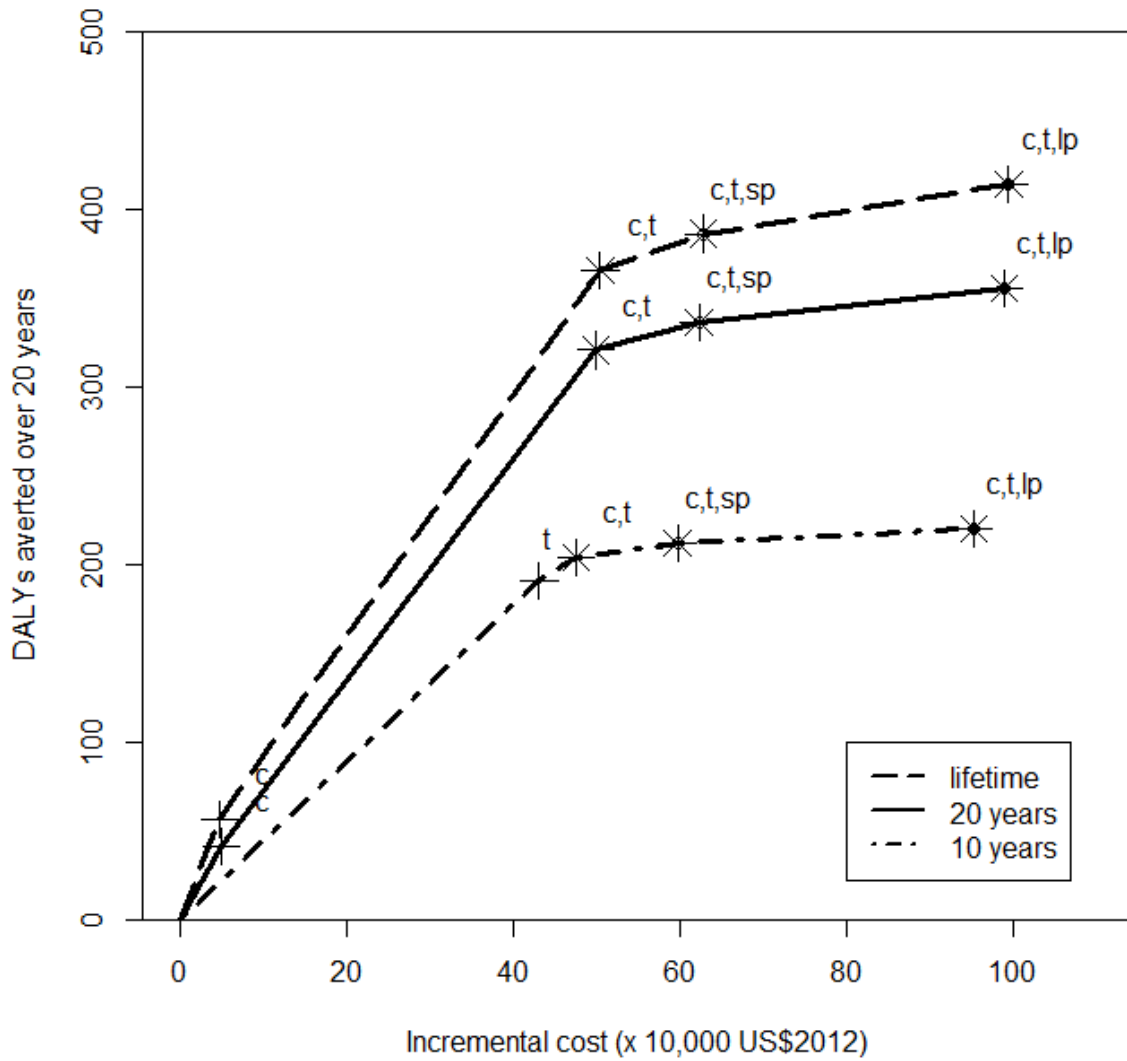
Figure S3. Sensitivity of results to time horizon used. Cost-effective frontiers for median values (from 1103 parameter sets) are plotted for time horizons of 10 years, 20 years and full life time (see figure key).

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