Economics of antiretroviral treatment vs. circumcision for HIV prevention

Till Bärnighausen[a,b], David E. Bloom[a], and Salal Humair[a,c,1]

[a]Department of Global Health and Population, Harvard School of Public Health, Boston, MA 02115; [b]Africa Centre for Health and Population Studies, University of KwaZulu Natal, 3935 Mtubatuba, KwaZulu Natal, South Africa; and [c]School of Science and Engineering, Lahore University of Management Sciences, DHA Lahore 54792, Pakistan

Edited by John Bongaarts, Population Council, New York, NY, and approved November 6, 2012 (received for review June 20, 2012)

The HIV Prevention Trials Network (HPTN) 052 study, which showed the effectiveness of antiretroviral treatment in reducing HIV transmission, has been hailed as a "game changer" in the fight against HIV, prompting calls for scaling up treatment as prevention (TasP). However, it is unclear how TasP can be financed, given flat-lining support for global HIV programs. We assess whether TasP is indeed a game changer or if comparable benefits are obtainable at similar or lower cost by increasing coverage of medical male circumcision (MMC) and antiretroviral treatment (ART) at CD4 <350/μL. We develop a new mathematical model and apply it to South Africa, finding that high ART coverage combined with high MMC coverage provides approximately the same HIV incidence reduction as TasP, for $5 billion less over 2009–2020. MMC outperforms ART significantly in cost per infection averted ($1,096 vs. $6,790) and performs comparably in cost per death averted ($5,198 vs. $5,604). TasP is substantially less cost effective at $8,375 per infection and $7,739 per death averted. The prevention benefits of HIV treatment are largely reaped with high ART coverage. The most cost-effective HIV prevention strategy is to expand MMC coverage and then scale up ART, but the most cost-effective HIV-mortality reduction strategy is to scale up MMC and ART jointly. TasP is cost effective by commonly used absolute benchmarks but it is far less cost effective than MMC and ART. Given South Africa's current annual ART spending, the $5 billion in savings offered by MMC and ART over TasP in the next decade, for similar health benefits, challenges the widely hailed status of TasP as a game changer.

combination HIV prevention | treatment-as-prevention prioritization

On the eve of the 2011 United Nations (UN) General Assembly's High Level Meeting on AIDS, HIV activists and the press described the results of the HIV Prevention Trials Network (HPTN) 052 study (1) as a "game changer" in the fight against AIDS (2–4). The study provides convincing evidence that early initiation of antiretroviral treatment (ART) can reduce HIV transmission by 96% in HIV sero-discordant couples (1). While questions remain about the effectiveness of ART in reducing HIV transmission in general populations (5), the Joint United Nations Programme on HIV/AIDS (UNAIDS) has forcefully argued that treatment as prevention (TasP) has the potential to shape the future of the HIV epidemic (6).

This optimism is understandable, but it is unclear how TasP can be funded, given flat-lining financial support for global HIV programs (6). Although the UN General Assembly pledged in June 2011 to close the $6 billion gap between global HIV funding and the estimated need for 2015 (7), by World AIDS Day 2011, this pledge seemed to lack traction as The Global Fund to Fight AIDS, Malaria and Tuberculosis announced funding cuts, and other HIV programs faced uncertain prospects (8).

It is also not clear how TasP should be implemented. TasP has commonly been understood as testing entire populations frequently for HIV and initiating ART immediately in everyone found to be HIV infected, even if they are not eligible for ART under the revised World Health Organization (WHO) ART eligibility threshold (i.e., CD4 cell count <350/μL) (9, 10). Under this definition, HIV treatment provided to HIV-infected persons with CD4 ≥350/μL is TasP and treatment provided to HIV-infected persons with CD4 <350/μL is ART under current guidelines (or simply ART), a definition we use in this paper. If resources are available for frequent HIV testing and treatment uptake is high, implementation of TasP may increase ART initiation in disease stages earlier than CD4 <350/μL. However, scaling up ART in earlier disease stages may be difficult, as the pressure to achieve universal ART coverage by 2015 (given current ART coverage of 50%) (9) may direct scarce resources toward those currently eligible for treatment.

Compounding such uncertainties is the fact that we do not yet have reliable estimates of the resources needed for implementing TasP, nor of its population-level benefits (11). UNAIDS has recently projected global resource needs for HIV at $20–22 billion per year by 2020 (12, 13), based on its strategic investment framework that does not include the cost of TasP. Predictive models for estimating TasP benefits and resource needs are currently under exploration (14). However, most of these models focus only on TasP, rather than its effect in combination with other prevention interventions, such as medical male circumcision (MMC). The effect of TasP in combination with MMC is particularly important for policymaking, because MMC has been shown to be effective in randomized trials in Sub-Saharan Africa (15–17), and MMC coverage remains low—2.7% across a sample of 14 countries in Sub-Saharan Africa in 2010 (18)—implying substantial scope for scaling it up.

In this study, we assess whether TasP can be a game changer in the fight against HIV, or if comparable benefits can be obtained through combinations of MMC and ART. Even if TasP alone is cost effective for prevention in comparison with external benchmarks, such as a threshold maximum cost per infection averted, it is not clear how it compares to alternative options. Together, MMC and ART, or MMC with limited TasP coverage, may reduce HIV incidence comparably at the same or lower cost.

In carrying out this assessment, we take an optimistic view of the benefits obtainable under TasP. We assume, for instance, that the HIV transmission reduction obtained when TasP is brought to scale will be the same, ~96%, as in the HPTN 052 trial (1). This reduction is very high, because the HPTN 052 trial was conducted within a highly motivated and ART-adherent group, whereas in general populations about a quarter of patients do not adhere adequately to ART (19, 20). Further, this TasP transmission reduction does not account for several significant foreseeable issues in TasP scale-up, such as TasP enrollment and retention, and the potential development of drug-resistant HIV strains (21, 22). We also set the costs of TasP equal to ART costs, increasing the

Author contributions: T.B., D.E.B., and S.H. designed research, performed research, contributed new reagents/analytic tools, analyzed data, and wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

[1]To whom correspondence should be addressed. E-mail: shumair@hsph.harvard.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1209017110/-/DCSupplemental.

Table 1. Cumulative discounted new infections, HIV deaths, and costs over 2009–2020 and the incremental cost effectiveness relative to the base case

Coverage, %			Cumulative discounted 2009–2020 (in millions)			ICER 2009–2020	
ART	TasP	MMC	Infections	Deaths	Costs	$/IA	$/DA
50	—	45	2.76	3.57	8,520	—	—
50	—	60	2.63	3.54	8,660	1,087	4,639
50	—	80	2.46	3.50	8,847	1,096	5,198
60	—	45	2.47	3.23	10,341	6,366	5,353
60	—	60	2.36	3.20	10,479	4,906	5,328
60	—	80	2.21	3.17	10,663	3,909	5,463
70	—	45	2.18	2.86	12,319	6,560	5,410
70	—	60	2.08	2.85	12,456	5,819	5,484
70	—	80	1.95	2.82	12,640	5,120	5,553
80	—	45	1.88	2.51	14,450	6,790	5,604
80	—	60	1.80	2.49	14,588	6,356	5,650
80	—	80	1.70	2.47	14,772	5,890	5,710
70	20	45	2.11	2.80	13,150	7,157	6,061
70	20	60	2.02	2.78	13,266	6,439	6,051
70	20	80	1.90	2.76	13,420	5,726	6,066
80	40	45	1.76	2.40	15,969	7,482	6,391
80	40	60	1.69	2.39	16,073	7,103	6,411
80	40	80	1.60	2.37	16,212	6,672	6,455
80	60	45	1.65	2.31	17,265	7,937	6,987
80	60	60	1.60	2.30	17,354	7,619	7,001
80	60	80	1.52	2.29	17,473	7,245	7,020
80	80	45	1.50	2.20	19,063	8,375	7,739
80	80	60	1.45	2.20	19,148	8,153	7,780
80	80	80	1.39	2.19	19,263	7,881	7,827

ART, antiretroviral treatment under current World Health Organization guidelines; DA, deaths averted; IA, infections averted.; ICER, incremental cost-effectiveness ratio; MMC, male medical circumcision; TasP, treatment as prevention.

possibility that our analysis confirms TasP to be a game changer, because TasP is likely to require additional program components that are not part of current ART programs, such as intensified HIV testing campaigns (11).

In estimating the effects and costs of TasP, ART, and MMC, and their combinations, we contribute a new model of the HIV epidemic for hyperendemic countries in which the primary mode of transmission is heterosexual (Fig. 1). Unlike most models that focus on sexual transmission, our model combines both behavioral and biological variables (e.g., number of partners, transmission probability per sex act) to overcome the difficulty of obtaining model parameters by fitting a curve to historical disease trends—because historical data are not yet available for large-scale implementation of TasP alone or in combination with MMC. The model analytically derives the number of new HIV infections, and using published evidence, produces reasonable national HIV incidence for South Africa without requiring curve fitting (23). Our model is formulated under a parsimonious set of assumptions. A recent, detailed comparison of our model with 11 other HIV models, some of which rely on more assumptions and include features such as a population age structure, shows that our model produces comparable results under a range of ART initiation thresholds (14). Further, the HIV incidence reduction obtained under TasP in our model is broadly consistent with the results from other models that have been used to study TasP (24) (additional discussion is provided in *SI Appendix*).

We apply our model to South Africa, which we have chosen for this study, motivated by a number of reasons described in *SI Appendix*. We explore a range of scenarios involving different combinations of TasP, ART, and MMC coverage levels (Table 1). The lower bounds for these coverage levels, our base case, are the current coverage estimates for South Africa (TasP 0%, ART 50%, and MMC 45%) (25). The upper bound is "universal coverage" for each intervention, which we take to be 80%, following the UNAIDS strategic framework (12).

For combined interventions, we explore all combinations of coverage levels of the individual interventions, except that the coverage levels for TasP and ART are coupled such that a coverage level of x% for TasP implies that the coverage level for ART is $\min((b+x)\%, 80\%)$, where b is the base case coverage level for ART. We couple TasP and ART coverage levels because we believe that ART coverage will increase along with TasP coverage. This increase will likely occur because TasP will be supported by interventions to increase HIV testing and ART uptake (26), which would presumably increase treatment coverage in all disease-stage groups. For each scenario, we record the HIV incidence, mortality rate among HIV-infected people, HIV prevalence, and the resources required to achieve the desired coverage levels. Resource needs are estimated assuming coverage levels are constant across time, which is a standard way of comparing interventions (14). Cumulative costs and health outcomes are discounted using a discount rate of 3%, as recommended in ref. 27.

Some assumptions need to be kept in mind when interpreting our results. First, because ART is highly effective in stopping the progression of HIV, we assume that a person on ART does not move to the next stage of the disease until she stops receiving ART. For instance, if a treatment-naive person in the fifth year since she had acquired HIV were to start receiving ART, she would stay in the fifth-year state until death or until she stops receiving ART. This assumption is conservative in favor of TasP, because later stages of HIV (CD4 <200 μL) are much more infectious than earlier stages—with the exception of the very early acute infection stage (1–4 mo) which we distinguish in our model.

Second, we assume that for a circumcised man having sex with an HIV-infected partner who is receiving ART, MMC gives additional protection over and above that offered by the partner receiving ART. Therefore, the per sex act HIV acquisition probability of the circumcised man is 40% of the reduced transmission probability of the partner when receiving ART, rather than 40% of the partner's transmission probability when not receiving ART. The rationale for this assumption is that the protection offered by MMC, and that offered by ART, operate through different biological mechanisms. This assumption weighs the benefits more toward TasP, because regardless of the MMC coverage levels, a partner receiving ART can further significantly reduce a man's HIV acquisition probability. A discussion of other modeling assumptions is provided in *SI Appendix*.

Results

Summary statistics reveal the magnitudes of variation in health outcomes and costs across scenarios. In 2020, the largest variation in outcomes across all scenarios (as a percentage of the minimum value) occurs in HIV incidence (0.81–0.29%); less variation in HIV-related mortality (9.8–4.5%), and little variation in prevalence (10.8–9.8%). Yearly costs across all scenarios in 2020 vary in the ratio 2.5:1 ($1.8–$0.7 billion); and the discounted cumulative costs over 2009–2020 vary in the ratio 2.25:1 ($19.2–$8.5 billion). Detailed time-varying differences in HIV incidence, mortality, prevalence, and yearly costs for all scenarios are documented in *SI Appendix*, Figs. S1–S4.

Our results show that significant cost savings could be achieved through an appropriate combination of interventions over the next decade (2009–2020), without compromising the overall prevention benefits (Fig. 2) or mortality benefits (Fig. 3). These figures show scenarios sorted by cumulative cost, revealing that HIV incidence decreases at a decreasing rate as cumulative costs increase. Fig. 2 also reveals that for roughly half of the scenarios with significant cost variation (roughly $14 billion to $19 billion),

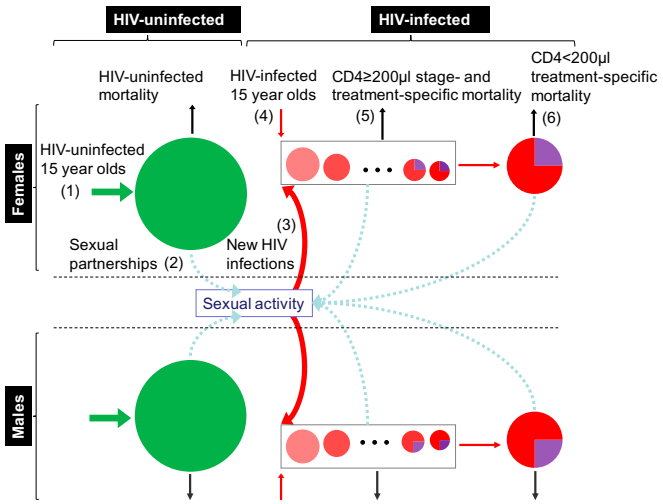

Fig. 1. The HIV infections model. New 15-y-old HIV-uninfected individuals flow into the HIV-uninfected pools (1). HIV-uninfected individuals participate in sexual activity with HIV-uninfected as well as HIV-infected individuals (2), giving rise to new HIV infections (3), which together with new HIV-infected 15 y olds (4), add to the HIV-infected pool. HIV-infected people progress through different stages of HIV infection (5) until reaching CD4 count <200 μL (6) (purple color indicates people receiving ART).

HIV incidence varies in a relatively narrow range between 0.4% and 0.3%. Fig. 3 shows the same pattern for mortality among HIV-infected individuals, i.e., half of the scenarios with significant cost variation ($14 billion to $19 billion) have less than 1% mortality variation, between 5.2% and 4.4%.

Table 1 suggests that over the next decade, TasP implementation is the most expensive option among all interventions, followed by increases in ART coverage and then increases in MMC coverage. For each scenario, Table 1 shows discounted cumulative costs, discounted cumulative new infections, and discounted cumulative deaths over 2009–2020, with scenarios shown sorted by TasP, ART, and MMC coverage levels. With a few exceptions, this scenario sorting results in monotonically decreasing new infections and monotonically increasing costs. Further, the difference in cumulative new infections till 2020 between universal ART and MMC coverage only (80%, 0%, and 80%) and universal coverage for all interventions (80%, 80%, and 80%) is 300,000, whereas the cost difference is roughly $4.5 billion. The HIV incidence in 2020 in these two scenarios is 0.34% and 0.29% respectively, suggesting that the incremental benefits of TasP are comparatively smaller once MMC and ART have been scaled up, while the additional costs of TasP remain substantial.

Table 1 also lists the incremental cost effectiveness for each scenario in terms of infections averted relative to the base case over 2009–2020. These ratios show that although TasP is cost effective if compared with commonly used external benchmarks (e.g., one to three times the South African per-capita GDP of $8,070 in 2011 per life-year saved), it is the most expensive option among the alternatives both for preventing new HIV infections and averting HIV-related deaths. Scaling up MMC only to universal coverage is several times more cost effective per additional infection averted ($1,096 per infection averted) than other interventions—ART scale-up alone is roughly six times less cost effective than universal MMC coverage in terms of HIV prevention ($6,790 per infection averted), and ART scale-up and TasP implementation without an increase in MMC coverage is a roughly eight times less cost-effective prevention strategy ($8,375 per infection averted). In terms of deaths averted, ART and MMC are much more cost effective relative to the base case over 2009–2020 ($5,710 per death averted) than ART and TasP without increased MMC coverage ($7,739).

In Tables 2 and 3, we show the incremental cost-effectiveness results by first ranking all interventions in order of their incremental cost effectiveness for averting infections relative to the base case over 2009–2020 and then determining the cost effectiveness of the other interventions relative to the most cost-effective intervention in the prior step (in terms of infections averted in Table 2 and in terms of deaths averted in Table 3). The most cost-effective prevention scenario in terms of both infections and deaths averted (Table 1) is 50% ART coverage and 60% MMC coverage. Compared with this new base case, the most cost-effective scenario is 50% ART coverage and 80% MMC coverage in terms of infections averted. Because these two scenarios are roughly similar in their cost effectiveness, we show only the initial cost-effectiveness results and then the results based on the comparison of all other interventions to the new base case of 50% ART coverage and 80% MMC coverage (Table 2). Relative to this new base case, ART scale-up is more cost effective than ART scale-up and TasP implementation jointly. These results suggest that for both HIV prevention and averting HIV-related deaths, the most economically rational priority ordering for increasing intervention coverage is MMC, ART, and then TasP. Once universal access to MMC and ART is attained, TasP offers a comparatively small reduction in either HIV incidence or HIV-related mortality while substantially increasing costs.

Over a longer horizon, we find that MMC scale-up alone becomes even more cost effective for both HIV prevention and averting HIV-related deaths. For infections averted, MMC is increasingly more cost effective than the other interventions over time (by an order of magnitude by 2030) and becomes cost saving in 2040 (*SI Appendix*, Table S5). None of the other interventions achieve such significant variation in their cost effectiveness for averting infections over time. *SI Appendix*, Table S6 also shows that whereas in 2020, MMC scale-up is roughly similar to ART in its cost effectiveness for deaths averted, it becomes much more cost effective by 2030. By 2040, MMC scale-up becomes cost saving over the base case, because it results in fewer cumulative discounted deaths with a smaller cumulative discounted cost. For the other interventions, the cost effectiveness of deaths averted does not change substantially over time.

Finally, the differences in relative cost effectiveness of different combinations of interventions persists under variations of parameters, such as sexual activity levels (which could change, e.g., due to aging of the HIV-infected population). Sensitivity analysis reveals that when sexual activity is 75% (or 50%) of normal, in 2020 the incremental cost effectiveness of ART and MMC (both at 80%) is $7,924 per infection averted ($11,980 for

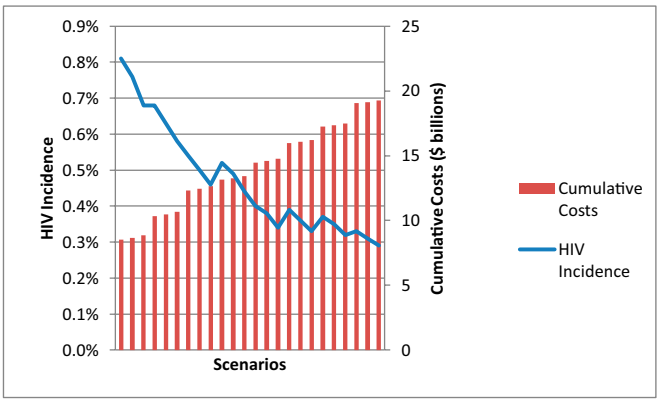

Fig. 2. HIV incidence in 2020 and cumulative discounted costs 2009–2020 across all scenarios.

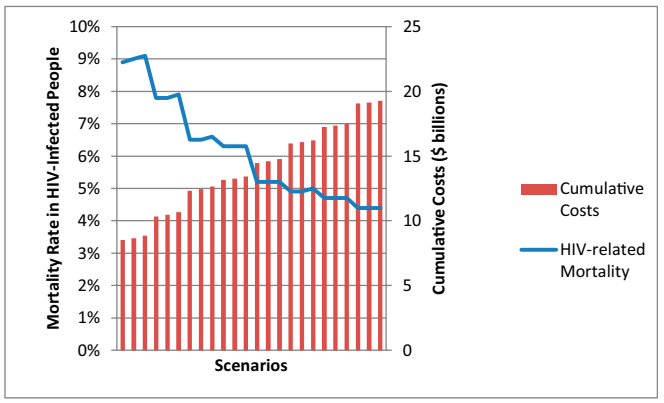

Fig. 3. Mortality in HIV-infected people in 2020 and cumulative discounted costs 2009–2020 across all scenarios.

50%) and that of ART and TasP (both at 80%) is $11,010 per infection averted ($16,159 for 50%). These numbers concretize our intuition that any reduction in sexual activity is likely to affect all interventions in the same direction and by a similar magnitude, preserving their cost-effectiveness rankings.

Discussion

We compare the health effects and costs of different combinations of three interventions to reduce HIV incidence and HIV-related mortality in South Africa: increased coverage of (*i*) TasP, (*ii*) ART under the current WHO eligibility guidelines, and (*iii*) MMC.

We find that a combination of high ART and high MMC coverage provides approximately the same substantial HIV incidence reduction as TasP. However, the combination of high ART and high MMC coverage is considerably less expensive than TasP, requiring approximately $5 billion less in cumulative discounted costs over 2009–2020. Compared with the estimated annual cost of treatment for South Africa (approximately $650 million using unit costs of $530 per person per year on ART), the savings are substantial.

Further, in terms of cost per infection averted, increased MMC coverage (at about $1,100 per infection averted) outperforms high ART as well as high TasP coverage (at about $6,800 and $8,400 per infection averted, respectively). In addition, the cost effectiveness of MMC increases over time and, unlike ART or TasP, MMC becomes cost saving after 2040 (*SI Appendix*, Tables S5 and S6).

Our study yields two insights about why MMC is more cost effective than TasP. First, the costs of MMC are roughly one-ninth of the annual cost of ART and these costs accrue only once for MMC, whereas the costs of ART and TasP accrue over patients' lifetimes. Second, even though the direct beneficiaries of MMC are men, after some delay, women also benefit substantially as HIV prevalence decreases among men. These results would also hold, as we have confirmed in sensitivity analysis, if HIV prevalence for South Africa were only one-fourth of its current level, suggesting that they generalize to countries with less severe epidemics. Further, the high transmission probability reduction we have assumed for TasP suggests that our finding that TasP is substantially less cost effective than ART and MMC is conservative, and robust to minor variations in the transmission probability reduction we have assumed for MMC.

Whereas the result that MMC is more cost effective for HIV prevention than ART and TasP is understandable, before our analysis it seemed plausible that TasP could be more cost effective due to three significant advantages it enjoys over MMC: first, a very high reduction in HIV transmission probability (~96% reduction) (1) compared with much lower reduction in acquisition probability due to MMC (~60% reduction) (28); second, TasP immediately benefits both men and women, whereas MMC initially benefits only men; and, third, the number of men who need to be circumcised for universal MMC coverage is much larger than the number of people in need of ART and TasP (roughly 16 million men eligible for MMC vs. 2.4 million eligible for ART and 2.4 million eligible for TasP in 2009). However, as our findings show, these advantages are outweighed by the substantial unit cost disadvantage of TasP.

In terms of cost per death averted, high MMC coverage is similar to high ART coverage. Whereas ART initially outperforms MMC in avoiding HIV-related deaths, in the longer run, the averted HIV infections due to increased MMC coverage reduce HIV-related deaths to an extent that is commensurate with the ART scenario at a lesser cost. The difference in cost effectiveness between TasP and either MMC or ART is very large for averting both HIV infections and HIV-related deaths. The incremental cost-effectiveness rankings are thus the same for the prevention outcome, HIV infections averted, and the final health outcome of HIV disease, HIV-related deaths. The lesser cost effectiveness of TasP in averting deaths can be explained by the fact that the mortality reduction benefits of TasP are far less than the mortality reduction benefits of ART. The comparison of TasP, ART, and MMC in terms of cost per HIV-related death averted suggests that a robust policy recommendation is to continue to scale up ART while simultaneously accelerating the scale-up of MMC. Only when ART and MMC have been scaled up to high levels should policy makers consider introducing TasP.

Our model captures the effects of the three HIV interventions on both HIV incidence and HIV-related mortality. The final and arguably the most important outcome of HIV disease is HIV-related deaths. Both HIV treatment and prevention ultimately serve the purpose of reducing the mortality effects of the HIV epidemic; thus, comparing HIV interventions with different treatment and prevention effects in terms of their cost effectiveness in averting deaths is a reasonable approach to assessment.

In this study, we do not consider other effects of HIV interventions, such as effects on morbidity or on economic and social outcomes. All three interventions will have such effects. In the case of MMC, these effects will occur with a delay determined by the latency period of HIV and will include a reduction in all those effects that an averted HIV infection would have led to had it not been averted, such as employment loss and morbidity. In the case of ART, these effects will occur sometime after treatment initiation, as has been found in several studies (29, 30). The effects of

Table 2. Incremental cost effectiveness of infections averted over 2009–2020

Coverage, %			ICER 2009–2020 for infections averted		
ART	TasP	MMC	Relative to base case	Relative to ART, 50%; MMC, 80%	Relative to ART, 80%; MMC, 80%
50	—	45	—	—	—
50	—	60	1,087	—	—
50	—	80	1,096	—	—
60	—	80	3,909	7,272	—
70	—	80	5,120	7,495	—
80	—	80	5,890	7,765	—
70	20	80	5,726	8,207	—
80	40	80	6,672	8,621	15,773
80	60	80	7,245	9,203	15,501
80	80	80	7,881	9,785	14,894

See Table 1 legend for acronym definitions.

Table 3. Incremental cost effectiveness of deaths averted over 2009–2020

Coverage, %			ICER 2009–2020 for deaths averted		
ART	TasP	MMC	Relative to base case	Relative to ART, 50%; MMC, 80%	Relative to ART, 80%; MMC, 80%
50	—	45	—	—	—
50	—	60	4,639	—	—
50	—	80	5,198	—	—
60	—	80	5,463	5,513	—
70	—	80	5,553	5,586	—
80	—	80	5,710	5,741	—
70	20	80	6,066	6,140	—
80	40	80	6,455	6,525	14,894
80	60	80	7,020	7,114	14,970
80	80	80	7,827	7,953	16,180

See Table 1 legend for acronym definitions.

TasP on morbidity and quality of life, and on economic and social outcomes, in South Africa are currently largely unknown, but in the longer run may be similar to those of ART (11). Thus, incorporating morbidity and social and economic impacts of the interventions into the model is unlikely to change their cost-effectiveness rankings. However, such extensions are likely to improve the cost effectiveness of all interventions in *absolute* terms, further supporting our conclusion that all interventions—TasP, ART, and MMC—are cost effective compared with the commonly used benchmarks of cost effectiveness and should be scaled up in the absence of resource constraints. It is when resource limitations preclude immediate implementation of all three interventions that our comparative cost-effectiveness results become policy-relevant.

It is also important to note other reasons that strengthen our main conclusion that ART and MMC together are more cost effective than ART and TasP. We used the extremely high effect size found in the randomized controlled trial of TasP in serodiscordant, stable couples (1). It is likely that TasP in routine treatment settings in Sub-Saharan Africa will be less effective because of lower treatment retention and adherence levels than in trial settings. In routine settings, the actual effectiveness of TasP will depend strongly on the capacity available for HIV testing and on post-ART initiation monitoring. The absence of such capacity could lead to the development of drug resistance at earlier stages of HIV, through lower treatment retention and adherence and less timely switching of antiretroviral regimens, decreasing the benefits from TasP. Moreover, we have not counted the costs of additional HIV testing and counseling needed for TasP, which may be incurred when TasP is brought to scale. Our main conclusion that TasP is less cost effective than MMC, ART, or a combination thereof also accords with the caution advocated by other researchers about the benefits and costs of TasP (21, 31, 32). What makes our results particularly relevant for policy decisions is that we show clearly that two existing interventions that are already being scaled up, when combined, can achieve similar benefits to TasP at a much lower cost.

One important practical consideration with respect to interventions for increasing MMC and ART coverage is that our model captures only the recurrent costs of the interventions, but does not take into account any additional start-up investment costs that may be necessary to scale up MMC and ART. To substantially increase MMC and ART coverage, additional human and physical resources may be required. Of course, in comparison with the two existing interventions, TasP will likely require even larger start-up investments because it involves components that are not part of current ART programs, e.g., frequent testing and retesting for HIV and ensuring high ART uptake among HIV-infected people who are not yet suffering significant symptoms (11). It is thus unlikely that incorporating investment costs into a cost-effectiveness comparison will change the intervention ranking or our main conclusions.

When formulating policies to further increase MMC and ART coverage, it is also important to consider potentially accompanying interventions that may improve public health over and above the effects of the core interventions. For MMC, it will be important to identify those approaches to pre- and post-MMC counseling that can avert unprotected sexual activity during the recovery period (33) and can reduce HIV-related risk-taking behaviors (34). For ART, it will be important to provide sufficient capacity to enroll and counsel HIV-infected people who do not yet meet the treatment eligibility criteria in pretreatment cohorts. Whereas such pretreatment cohorts are currently part of standard HIV treatment and care in South Africa, they commonly suffer from high levels of nonretention (35), and the opportunity they offer for HIV prevention targeted specifically at HIV-infected populations remains largely unused (36).

Our findings have a number of potentially important policy implications. The first is to accord a much higher priority to MMC scale-up in South Africa, along with ART scale-up, as suggested by the ordering of the three interventions in terms of their cost-effectiveness in preventing HIV infections and averting HIV-related deaths. There is substantial opportunity to do so, as MMC coverage in South Africa still lags substantially behind ART coverage—more than 1 million people in South Africa are receiving ART but only a quarter million men have received MMC (37)—despite the progress made by recent MMC campaigns (18). Further, our results suggest that instead of viewing MMC and ART as separate interventions, it is important for policy makers to realize the synergy between MMC and ART—increased upfront investments in MMC will also increase the ability to provide high ART coverage in the long run, because averted infections due to MMC imply fewer people needing ART in the future.

Second, TasP is an effective HIV prevention intervention but it is not a game changer, because MMC with ART can achieve similar HIV incidence reductions at substantially lower cost. Moreover, the benefits of using ART in combination with MMC are achievable over the short-to-medium term. Within the next decade, ART and MMC can achieve comparable reductions in HIV incidence for about $5 billion less than TasP, based on our current knowledge. As only about half of those needing ART are currently receiving treatment in South Africa (38), increasing ART coverage in this population group should precede an extension of treatment to people in earlier disease stages.

The findings of our model should be reassuring for policy makers, because under current conditions the decision to implement TasP can be delayed, while vigorously scaling up MMC and ART. During the delay, results of the large cluster-randomized trials of TasP in Sub-Saharan Africa are likely to become available, which will further inform decision making on TasP strategies (39).

Materials and Methods

We formulate a discrete-time mathematical model with yearly time increments and two main population classes: men and women aged 15 and older. Each population class is divided into people without HIV infection, and HIV-infected people differentiated by the number of years since HIV acquisition (Fig. 1). The years since HIV acquisition model the decline in CD4 cell count over time, e.g., 5 y after infection, an untreated person's CD4 cell count falls below 350/μL. HIV-uninfected men are further subdivided into pools of circumcised and uncircumcised men. HIV-infected men are further subdivided into pools of those uncircumcised and not receiving ART, uncircumcised and receiving ART, circumcised and not receiving ART, and circumcised and receiving ART. HIV-infected women are subdivided into pools of those receiving ART and those not receiving ART. Pools can differ from each other with respect to mortality rate, HIV transmission probability per sex act (for HIV-infected people), and HIV acquisition probability per sex act (for HIV-

uninfected people). These data depend on the treatment (and for men, circumcision) status of individuals.

During each year, new sexually transmitted HIV infections are computed under the following assumptions: each HIV-uninfected person has a probability distribution for the number of partners over the year; each partner is randomly drawn from the pools of opposite sex partners; each partner engages with her in a given number of sex acts; and each sex act with an HIV-infected partner can result in an infection independently of all other sex acts during the year. In addition to sexual infections, exogenous inflows of new 15 y olds also occur into the pool of HIV-uninfected individuals and the pool of HIV-infected people in the first year of their infection. The precise mathematical formulation of this model and the data sources used for model inputs are provided in *SI Appendix*.

ACKNOWLEDGMENTS. We thank Barry Bloom for detailed and thoughtful comments on an initial version of the manuscript, Robert Oelrichs and Anderson Stanciole of the World Bank's Global HIV/AIDS Program for their feedback on early versions of the model, and the PNAS editor and two anonymous referees for very helpful comments. This paper has also benefited from comments by participants at the International AIDS and Economic Network 2012 meeting and the AIDS 2012 conference.

1. Cohen MS, et al.; HPTN 052 Study Team (2011) Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 365(6):493–505.
2. Editorial L (2011) HIV treatment as prevention—it works. *Lancet* 377(9779):1719.
3. Sidibé M (May 15, 2011) The 4th decade of AIDS: What is needed to reshape the response. *UN Chronicle* Vol. XLVII No. 1.
4. Economist (June 2, 2011) AIDS: The 30 years war. *The Economist*.
5. Hammer SM (2011) Antiretroviral treatment as prevention. *N Engl J Med* 365(6): 561–562.
6. UNAIDS (2011) AIDS at 30. (Joint United Nations Programme on HIV/AIDS, Geneva).
7. United Nations (2011) Political declaration on HIV/AIDS: Intensifying our efforts to eliminate HIV/AIDS. UN General Assembly High Level Meeting on HIV/AIDS, June 8–11, 2011, New York.
8. BBC World News (November 30, 2011) HIV funding cut as science brings "decisive moment." BBC World News. Available at www.bbc.co.uk/news/health-15946803.
9. UNAIDS (2010) *Getting to Zero: 2011–2015 Strategy* (Joint United Nations Programme on HIV/AIDS, Geneva).
10. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG (2009) Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: A mathematical model. *Lancet* 373(9657):48–57.
11. Bärnighausen T, Salomon JA, Sangrujee N (2012) HIV treatment as prevention: Issues in economic evaluation. *PLoS Med* 9(7):e1001263.
12. Schwartländer B, et al.; Investment Framework Study Group (2011) Towards an improved investment approach for an effective response to HIV/AIDS. *Lancet* 377(9782): 2031–2041.
13. UNAIDS (2011) *How to Get to Zero: Faster. Smarter. Better. UNAIDS World AIDS day report* (Joint United Nations Programme on HIV/AIDS, Geneva).
14. Eaton JW, et al. (2012) HIV treatment as prevention: Systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Med* 9(7):e1001245.
15. Auvert B, et al. (2005) Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 Trial. *PLoS Med* 2(11):e298.
16. Bailey RC, et al. (2007) Male circumcision for HIV prevention in young men in Kisumu, Kenya: A randomised controlled trial. *Lancet* 369(9562):643–656.
17. Gray RH, et al. (2007) Male circumcision for HIV prevention in men in Rakai, Uganda: A randomised trial. *Lancet* 369(9562):657–666.
18. WHO and UNAIDS (2011) *Progress in Scale-Up of Male Circumcision for HIV Prevention in Eastern and Southern Africa: Focus on Service Delivery: 2011* (World Health Organization, Geneva).
19. Kalichman SC, et al. (2010) Adherence to antiretroviral therapy and HIV transmission risks: Implications for test-and-treat approaches to HIV prevention. *AIDS Patient Care STDS* 24(5):271–277.
20. Mutevedzi PC, et al. (2010) Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: Does rapid expansion affect patient outcomes? *Bull World Health Organ* 88(8):593–600.
21. Shelton JD (2011) HIV/AIDS. ARVs as HIV prevention: A tough road to wide impact. *Science* 334(6063):1645–1646.
22. Cohen MS, Muessig KE, Smith MK, Powers KA, Kashuba ADM (2012) Antiviral agents and HIV prevention: Controversies, conflicts, and consensus. *AIDS* 26(13):1585–1598.
23. Bärnighausen T, Bloom D, Humair S (2010) *The Sustainability of Antiretroviral Treatment: The Case of South Africa*. Oral presentation at International AIDS and Economics Network, August 16–17, 2010, Vienna.
24. Wagner B, Blower S (2009) Voluntary universal testing and treatment is unlikely to lead to HIV elimination: A modeling analysis. *Nature Precedings* Available at http://hdl.handle.net/10101/npre.2009.3917.1.
25. Njeuhmeli E, et al. (2011) Voluntary medical male circumcision: Modeling the impact and cost of expanding male circumcision for HIV prevention in eastern and southern Africa. *PLoS Med* 8(11):e1001132.
26. Bärnighausen T (2010) The role of the health system in HIV treatment-as-prevention. *AIDS* 24(17):2741–2742.
27. WHO (2003) *Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis*, eds Edejer T-T, et al. (World Health Organization, Geneva).
28. Williams BG, et al. (2006) The potential impact of male circumcision on HIV in Sub-Saharan Africa. *PLoS Med* 3(7):e262.
29. Bor J, Tanser F, Newell M-L, Bärnighausen T (2012) In a study of a population cohort in South Africa, HIV patients on antiretrovirals had nearly full recovery of employment. *Health Aff (Millwood)* 31(7):1459–1469.
30. Rosen S, et al. (2010) Economic outcomes of patients receiving antiretroviral therapy for HIV/AIDS in South Africa are sustained through three years on treatment. *PLoS ONE* 5(9):e12731.
31. Wagner BG, Kahn JS, Blower S (2010) Should we try to eliminate HIV epidemics by using a 'Test and Treat' strategy? *AIDS* 24(5):775–776.
32. Wagner B, Blower S (2010) Costs of eliminating HIV in South Africa have been underestimated. *Lancet* 376(9745):953–954.
33. Herman-Roloff A, Bailey RC, Agot K (2012) Factors associated with the early resumption of sexual activity following medical male circumcision in Nyanza province, Kenya. *AIDS Behav* 16(5):1173–1181.
34. Peltzer K, Simbayi L, Banyini M, Kekana Q (2012) HIV risk reduction intervention among medically circumcised young men in South Africa: A randomized controlled trial. *Int J Behav Med* 19(3):336–341.
35. Lessells RJ, Mutevedzi PC, Cooke GS, Newell M-L (2011) Retention in HIV care for individuals not yet eligible for antiretroviral therapy: Rural KwaZulu-Natal, South Africa. *J Acquir Immune Defic Syndr* 56(3):e79–e86.
36. Kennedy CE, Medley AM, Sweat MD, O'Reilly KR (2010) Behavioural interventions for HIV positive prevention in developing countries: A systematic review and meta-analysis. *Bull World Health Organ* 88(8):615–623.
37. South African Department of Health (DoH) (2012) National Strategic Plan on HIV, STIs and TB, 2012–2016. (DoH, Pretoria).
38. WHO UNAIDS, UNICEF (2010) *Towards Universal Access: Scaling up Priority HIV/AIDS Interventions in the Health Sector*. Progress Report 2010. (World Health Organization, Geneva).
39. Granich R, et al. (2011) ART in prevention of HIV and TB: Update on current research efforts. *Curr HIV Res* 9(6):446–469.