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The Cost-effectiveness of Alternative HIV Intervention Portfolios in South Africa

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The Cost-effectiveness of Alternative HIV Intervention Portfolios in South Africa

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Abstract

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A dynamic compartmental model was instantiated with recent epidemiological data from South Africa to compare the effectiveness and cost-effectiveness of different portfolios of interventions to prevent HIV infection over a twenty year time horizon. We hypothesized that portfolios which combined scaling up the delivery of highly active antiretroviral therapies (HAART), increasing availability of HIV screening and counseling, and establishing widespread circumcision campaigns would be the most effective and most cost-effective strategies. Portfolios which utilized widespread circumcision for adult men were found to be the most cost-effective, while portfolios which utilized a combination of interventions were found to be the most effective, in terms of quality adjusted life years (QALYs) gained. These findings highlight the urgency of scaling up access to life-saving antiretroviral treatments, and providing concomitant investments in HIV prevention and testing programs in a generalized HIV epidemic setting such as South Africa.

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Table of Contents

Introduction…… 5

Methods……..12

Results…….20

Discussion……26

Conclusions……..32

References...…….34

1. Introduction

1.1 HIV in South Africa

South Africa remains one of the countries most severely devastated by the HIV epidemic. It is estimated that at the end of 2007 there were approximately 5.7 million people living with HIV in the country, and this number grows daily [1]. The prevalence among individuals aged 15-49 approaches 20%, demonstrating the impact of the virus on the most productive members of society. An estimated 1,000 people die from AIDS in South Africa each day, accounting for nearly half of all deaths in South Africa and 71% of deaths among individuals aged 15-49 [2].

In addition to the enormous social burden of the disease, the HIV/AIDS epidemic has had major economic consequences for South Africa. Disease-related morbidity and mortality have led to losses in the labor market, reduced labor productivity, and reduced exports [3]. Various indicators of human development have fallen sharply, as the country struggles to mount a sufficient response against the epidemic. HIV consumes a significant amount of national resources and health resources, hindering the ability of the government to address other national needs.

1.2 Current interventions for HIV

Although the situation remains urgent, progress has been made in recent years by a large coalition of non-governmental organizations, universities, international donors, governments, and more. These agencies include the Global Fund to Fight AIDS, Tuberculosis, and Malaria, the United States' Emergency Plan for AIDS Relief, and the World Bank's Multi Country AIDS Projects. Changes in South African government

policy have increased funding for provision of HIV treatment services, while also scaling up other interventions including screening and health education. The Joint United Nations Program on HIV/AIDS (UNAIDS) reports that in low- and middle-income countries, 28% of adults with advanced HIV infection were receiving antiretroviral therapy in 2007 [1]. The number of HIV positive pregnant women receiving antiretroviral therapy for reduction of mother to child transmission increased to 66%. [4] Additionally, a survey estimated that 100% of schools in South Africa included HIV/AIDS education in the past year [4].

Although these statistics demonstrate improvement, substantial work remains. A UNAIDS report estimated that $27 billion was needed for global HIV/AIDS prevention between 2005 and 2007 but that only about $18 billion would be available [5]. Recent trials for HIV vaccines and microbicidal gels have been very disappointing. With new infections occurring every day, the need for HIV services is likely to continue to grow in the most severely affected countries utilizing current strategies for treatment and prevention.

While resources available to combat the epidemic in South Africa have increased, policy makers must make difficult decisions about how to optimally distribute a finite amount of resources among a number of potentially beneficial strategies. Examples of treatment interventions include provision of antiretroviral medications for infected patients and provision of prophylaxis against opportunistic infections. Preventive interventions include HIV/AIDS education, distribution of condoms, prevention of mother to child transmission, voluntary counseling and testing services (VCT), and behavioral interventions for injection drug users such as needle-exchange and methadone

maintenance programs. More recently, male circumcision has also been demonstrated to be an effective tool for reducing heterosexual transmission of HIV among men in Africa.[6-8]

Each of these interventions has direct and indirect costs and benefits that warrant careful evaluation prior to implementation. Each intervention has the potential to improve population health by preventing new HIV infections among uninfected individuals, diagnosing infected individuals and providing a critical link to care, reducing disease-related morbidity and mortality, or some combination of the above. Whether the potential benefits of each intervention warrant their expense is an important consideration that should be evaluated prior to implementation. Moreover, by assessing the costs and benefits of implementing multiple HIV interventions simultaneously, policymakers can compare the relative trade-offs of each intervention and allocate limited resources for HIV prevention and treatment more effectively.

1.3 Mathematical models of the HIV epidemic

Policy decisions about resource allocation have significant implications for individuals infected with HIV, as well as those at risk for infection. In this setting, mathematical models of HIV epidemics have become increasingly popular tools for informing decisions about how to optimize limited resources to achieve certain goals. Epidemic models can be used to estimate factors including HIV incidence, prevalence, and mortality, in specified populations with varying degrees of granularity. Because of the vast biological, social, and political complexities of HIV epidemics these models are

intended to compare the potential gains from implementing particular interventions, rather than predict the future course of the epidemic with certainty.

Multiple papers have been published recently that aim to use HIV epidemic models to inform decisions about health policy and resource allocation in South Africa. Granich et al used a novel epidemic model of HIV to analyze a strategy of widespread screening for HIV with immediate initiation of antiretrovirals [9]. Their paper found that their proposed strategy would accelerate the transition of the epidemic from an endemic phase to an elimination phase, and that it could reduce HIV incidence and mortality to less than one case per 1000 people by the year 2016 [9]. Andersson et al used a model to examine the possible impact of a partially effective HIV vaccine on the heterosexual HIV epidemic in South Africa [10]. Their paper found that even a modestly effective vaccine could provide enormous benefits in preventing HIV infections, but also emphasized the importance of concurrent educational programs to reduce risk behaviors. Another paper found that migration patterns likely increased high-risk sexual behavior, facilitating HIV transmission in South Africa [11]. Models have also been used to analyze how different interventions might simultaneously impact the HIV and tuberculosis epidemics in South Africa [12].

While each modeling study has limitations and must be at least partially reliant on assumptions, these studies nevertheless add very meaningful analyses to debates about optimal strategies for combating HIV epidemics. These models can be combined with cost-effectiveness analyses to provide another layer of useful information to decision makers.

1.4 Cost-effective analysis for HIV resource allocation

Cost-effectiveness analysis is a useful tool for helping healthcare decision makers determine how to best allocate resources across a defined number of competing needs to maximize health outcomes for a limited budget [13]. Many of the countries most severely affected by the epidemic, such as those in sub-Saharan Africa, are among the most resource-limited in the world. Given the urgency of the situation, policy makers must often allocate resources with incomplete information, so predictive models that compare the costs and benefits of competing health interventions are important tools for guiding policy. Where information is incomplete, sensitivity analyses can offer a range of possible outcomes based upon likely scenarios.

In earlier stages of the epidemic, cost-effectiveness analysis was used to inform debate among academics and policy makers about how to distribute investment between treatment and prevention programs for HIV in sub-Saharan Africa [14]. As prices for antiretroviral therapies have declined, global funding has increased, and model sites have demonstrated success in treating HIV in resource-poor settings, the debate has shifted from a focus on treatment or prevention to a broader question of how to best structure multifaceted HIV intervention programs. In this setting, cost-effectiveness analysis has been used to compare the health benefits and associated costs of different interventions and strategies. For example, recent studies on HIV disease management have used cost-effectiveness analysis to compare the use of different antiretroviral regimens[15], compare different methods of monitoring HIV[16], and evaluate when to best start HAART [17]. Cost-effectiveness analysis has also been used as a tool to measure the efficacy of different preventative interventions in sub-Saharan Africa, such as recent

research on male circumcision[18] and the widespread treatment of sexually transmitted infections, which is thought to reduce the likelihood of HIV transmission [19].

1.4 Portfolio model of HIV interventions

While cost-effectiveness analysis has provided useful data to guide decision making on strategies to combat HIV/AIDS in resource-poor settings, a limitation of most studies is that they analyze a single intervention at a time, or directly compare two or more interventions. In reality, strategies to combat HIV/AIDS will be multi-dimensional, with a number of interventions operating simultaneously. Many of these interventions may have synergistic effects which are not captured in analyses that examine single interventions at a time. For example, it is plausible that the presence of free antiretroviral medications will impact an individual's willingness to obtain voluntary counseling and testing (VCT) services and that access to these services may influence an individual's HIV risk behaviors [20]. Similarly, in some circumstances there are diminishing returns of multiple simultaneous interventions. For example, one study may find that a certain preventive intervention may prevent one million HIV infections, and another study may find that a different intervention can prevent two million HIV infections. However, this does not imply that the two interventions will prevent three million HIV infections because the target populations often overlap, and because infectious disease transmission occurs in a non-linear manner (i.e., the likelihood of contracting HIV depends on the fraction of individuals who are also infected). Understanding how different interventions may affect the same population simultaneously is a limitation of existing HIV epidemic models.

These examples highlight the need for models that can examine multiple interventions for HIV/AIDS simultaneously. In her paper, Long describes a mathematical model that can be used to assess the effectiveness and the cost-effectiveness of a portfolio of HIV interventions. The model translates behavioral and biological factors influencing HIV transmission and disease progression into meaningful epidemic and economic outcome measures [21]. By altering the degree of each intervention, this model can estimate epidemiological and economic outcomes under different assumptions about clinical efficacy and individual behavioral responses to the interventions.

1.5 Evaluation of HIV intervention portfolio in South Africa

We proposed to use Long's intervention portfolio model to evaluate the heterosexual HIV epidemic in South Africa. By instantiating the model with epidemiologic data from South Africa, we evaluated how different portfolios of interventions impact the local epidemic. We chose to focus on three different interventions that have been shown to reduce new infections and improve the morbidity and mortality among infected individuals: male circumcision, voluntary counseling and testing (screening), and administration of highly active antiretroviral therapy. While many other possible interventions exist, we chose to examine portfolios comprised of these three since they are applicable to a generalized heterosexual HIV epidemic. Recent papers have advocated for increased funding for each of these interventions as a possible means of making a major impact on the epidemic [9]. Also, papers have called for the

needs for more mathematical models of HIV epidemics to inform critical policy decisions [9].

By using this model to examine how different portfolios of these interventions impact the epidemic in South Africa, we can then test the following hypothesis: the most effective and cost-effective strategy for improving the HIV heterosexual epidemic in South Africa is to implement a diverse portfolio offering a combination of these three interventions.

2. Methods

2.1 Overview

We applied a dynamic compartmental epidemic model for HIV in South Africa which accounts for HIV transmission and disease progression for a generalized heterosexual HIV epidemic. Although the original model described in Long's paper can account for transmission in certain high risk groups, for the purposes of this study, we focused only on heterosexual transmission and ignored transmission via injection drug use, homosexual contact, and from commercial sex workers (CSWs). We utilized the model to evaluate different portfolios of HIV interventions, each of which included a unique combination of three interventions: male circumcision, voluntary counseling and testing, and administration of highly active antiretroviral therapies (HAART). For each portfolio, we applied the model to estimate outcomes including HIV prevalence, new infections, costs, health benefits, and incremental cost-effectiveness ratios. We evaluated the cost of each strategy on these epidemic and economic outcomes, to compare the cost-effectiveness of each portfolio relative to the status quo and the next-best alternative.

2.2 Population

Our model divides the adult South African population, aged 15 to 49, into 30 compartments based on the following factors: gender, risk behavior, infection status (uninfected, asymptomatic HIV, symptomatic HIV, or AIDS) identification status (unidentified or identified), treatment status (receiving antiretroviral therapy or not), circumcision status (circumcised or not). A schematic diagram of the compartmental model is shown in Figure 1.

Individuals enter the model when they reach age 15 and exit the model at death or upon maturation beyond age 50. The mortality rate for each compartment varies and is based upon previously published demographic data [22] . The movement of individuals between compartments is determined by transition probabilities based on the rates of disease transmission and disease progression.

Disease-related mortality and disease progression rates for each compartment were based upon previously calculated data [23]. Quality of life factors for the different disease states were obtained from previously published sources [24] . These estimates allow the model to calculate the overall gain in health benefits as a result of reduced morbidity and mortality.

2.3 Disease States

Each disease stage is defined according to CD4 T-cell count where asymptomatic HIV designates an individual who is HIV positive with a CD4 T-cell count >350 cells/mm^3, symptomatic HIV designates an individual who is HIV positive and has a

CD4 T-cell count between 200 and 350 cells/mm^3, and AIDS designates an HIV positive individual with CD4 T- cell count below 200 cells/mm^3.

2.4 HIV Screening

Identification status denotes whether an individual is aware of his or her HIV status. We assume that individuals learn of their HIV status through voluntary HIV counseling and testing services (VCT), and that individuals who participate in VCT reduce their annual number of sexual partners by 20%. Individuals who receive VCT and test negatively for HIV remain identified as negative for two years before they transition back into a state where their HIV status is unknown. At this point these individuals are then eligible to be screened again.

2.5 HIV Treatment

The treatment for HIV is highly active antiretroviral therapy (HAART). We assume that in South Africa, only individuals with CD4 T-cell counts less than 200 cells/mm^3 are eligible to receive HAART, consistent with the World Health Organization's guidelines for resource limited settings [25]. HAART has been demonstrated to reduce the HIV viral load in an individual and subsequently, to reduce the infectivity of an individual and the probability that the individual will transmit HIV to a sexual partner [26]. We assume that individuals receiving HAART experience a reduction in sexual infectivity of 90%, although we varied this value in sensitivity analysis. HAART also increases an individual's life expectancy, and subsequently the length of time they can potentially infect their partners. By using a dynamic model such

as the one we developed, we can evaluate how these opposing effects can influence epidemic outcomes. Financial costs and the quality of life benefits associated with using HAART are also taken into account for cost-effectiveness analysis.

2.6 Male Circumcision

Our model also assumes that currently 40% of South African adult men are circumcised, and that all adult men are capable of being circumcised. We assume circumcision results in a 60% reduction in HIV acquisition for heterosexual males based on previously published data.[6-8]

2.7 Disease transmission

Data on sexual behaviors were obtained from a number of sources. We used an average of 2.0 sexual partners per year for both males and females, from the South African Demographic and Health Survey[27]. We also assumed both males and females use latex condoms during 30% of episodes of sexual intercourse[4], and that condoms are 90% effective in preventing transmission of HIV based upon previously published data [28].

Since our model is focused on the heterosexual HIV epidemic in South Africa, we only considered HIV transmission via heterosexual sexual contact and we ignored other modes of transmission including homosexual transmission, transmission via contaminated needles, and mother to child transmission. The annual probability of HIV transmission from male to female and from female to male is based upon previously published data. [10, 24] These probabilities are then adjusted for the three HIV disease

states used in our model (asymptomatic HIV, symptomatic HIV, AIDS) and also for the presence of interventions (VCT, HAART, circumcision).

Each of these stratifications allows for more precise modeling of an individual's likelihood of acquiring or transmitting HIV and we adjust model parameters for each compartment accordingly.

2.8 Model Implementation

The model is represented by a system of ordinary differential equations to track the number of people in each health state, or compartment, over time. We instantiated the model based on population compartment sizes in 2007 and assumed a 20-year time horizon.

Parameters for the model were obtained from a combination of published primary and secondary data, calculations, and assumptions. Table 1 shows all input parameters used in the model and their sources. Our model assumed a South African adult population (defined as individuals aged 15-49) of 12,530,300 men and 13,464,600 women based upon South African census data. The HIV prevalence among these groups was 16.1% for men and 19.6% for women. Men and women were separated into compartments based on previously published sources, as shown in Table 1. Using the mathematical programming language Matlab, we numerically solved the system of equations for different HIV intervention portfolios in South Africa.

We began with a "base case" scenario that represented the current use of the three interventions discussed, examined over a 20-year time horizon, and based on available 2007 data. In this base case, we assumed that 28% of all South African adults

with HIV and CD4 counts less than 200 cells/mm^3 received antiretroviral treatment upon becoming eligible, and an additional 5% entered treatment programs annually. We also assumed that 25% of all South African adults were tested for HIV and received the test results in the past two years. Finally, we estimated that 40% of adult males are circumcised and that this percentage will remain relatively constant. Under these base case assumptions, we then projected HIV prevalence, new HIV infections, and total costs and health benefits (measured in quality-adjusted life years or QALYs) incurred in the population, over the 20-year time horizon. For each intervention portfolio, we then estimated the change in HIV prevalence, HIV infections prevented, incremental costs, incremental health benefits, and the incremental cost-effectiveness ratio (ICER) compared to the base case scenario.

2.8.1 HAART focused portfolios

To create different scenarios to compare to the base case scenario, we altered the composition of the portfolio of interventions. First, we examined hypothetical scenarios for changes in the percentage of HIV patients receiving HAART to explore how strategies that favor treatment scale up may affect the epidemic in South Africa. For these scenarios, the fraction of patients screened for HIV and the fraction of adult males circumcised remained constant with the base case. We created two separate "HAART-focused" scenarios. In the first scenario, we assumed that HAART access increases to 50% of the eligible HIV infected population (CD4 count <200 cells/mm^3). We also created an "optimistic" scenario to examine HAART scale-up in South Africa. In this case, we assumed that HAART access increases to 75% coverage. Again, we assumed

that the fraction of patients screened for HIV and the fraction of adult men circumcised remained constant.

2.8.2 Screening Focused Scenarios

Next, we created scenarios that examined how intervention strategies that favored increased HIV screening impacted epidemic outcomes. First, we created a "moderate" screening scenario, where we assumed that 50% of the adult South African population would be screened for HIV every two years. For these screening focused scenarios, we held the percentage of South Africans receiving antiretroviral therapy, and the percentage of South African men circumcised constant from the base case. We also created an additional "optimistic" screening focused scenario, where we assumed that 75% of the adult South African population is screened for HIV every two years, and otherwise followed the same assumptions as for the "optimistic" scenario.

2.8.3 Circumcision Focused Scenarios

Next, we evaluated scenarios that favored widespread male circumcision. In the base case scenario, we assumed that 40% of the adult South African male population is circumcised, and that this remains constant over the 20-year time horizon. This means that each year as new fifteen year olds enter the adult population, we assume that 40% are circumcised. In the first circumcision focused portfolio, we assumed that every year 10% of the uncircumcised adult male population will become circumcised, in addition to the 40% background circumcision rate. In the second "optimistic" scenario, we increased the marginal circumcision rate to 20%. For both of these scenarios we held constant the

percentage of HIV infected individuals receiving antiretrovirals, and the percentage of adults screened for HIV every two years.

2.8.4 Combination Scenarios

Finally, we evaluated different combinations of two or three interventions.. For each combination we considered a "moderate" and "optimistic" scenario.

First, we evaluated portfolios that favored a combination of increased antiretroviral administration and increased screening. In these scenarios we assumed that the percentage of South African adult men who are circumcised stays constant at 40%. In the moderate scenario, we assumed that 50% of eligible HIV infected individuals receive antiretroviral therapy, and 50% of South African adults undergo HIV screening every two years. In the optimistic scenario, we increased both interventions to 75% coverage. We then evaluated portfolios that favor a combination of increased antiretroviral administration and widespread circumcision, while maintaining only 25% HIV screening rates. In the moderate scenario, we increased antiretroviral therapy coverage to 50%, and increased the marginal circumcision rate to 10%. In the optimistic scenario, we increased the fraction of individuals receiving each intervention to 75% and 20%, respectively. The next combination of interventions favored increased screening for HIV and increased male circumcision.. In these two scenarios, the percentage of eligible individuals on HAART remained at 28%. In the moderate scenario, we assumed that 50% of adults are screened for HIV every two years, and an additional 10% of uncircumcised men are circumcised. In the optimistic scenario, these fractions increased to 75% and 20%, respectively.

Finally, we explored scenarios for portfolios which utilized all three interventions. In the moderate scenario, we assumed that 50% of eligible HIV infected South Africans receive HAART, 50% of adults are screened for HIV every two years, and 10% of uncircumcised men undergo circumcision each year. In the optimistic scenario, the fraction of individuals receiving each intervention increases to 75% (HAART), 75% (screening), and 20% (male circumcision).

We used the Matlab software to solve for each of these 14 scenarios to estimate how each portfolio affected the overall South African HIV epidemic, population-wide health benefits and costs, and incremental cost effectiveness, relative to the base case scenario.

2.9 Student Contribution

Robert Stavert contributed by performing epidemiological research, conducting the literature review, gathering data on the South African HIV epidemic to be instantiated in the model, discussing relevant clinical assumptions, developing the scenarios evaluated by the model, and reviewing the results and conclusions. All of this work was performed together with Elisa Long who created the original dynamic compartmental model used in this analysis.

3. Results

In the base case scenario, we estimated that approximately 10.6 million people would become newly infected with HIV in South Africa over 20 years. At the end of the

20-year horizon, the HIV prevalence was 14.67% among men and 16.67% among women (Figure 2).

3.1 HAART focused portfolios

The scenarios for HAART focused intervention portfolios resulted in the smallest number of infections prevented, compared to the base case scenario. The moderate HAART focused scenario prevented 114,000 HIV infections (1.1% of projected new infections) compared to the base case, and the optimistic scenario prevented 242,000 cases (2.3% of projected new infections) over twenty years (Figure 3). The moderate HAART focused strategy added 4.8 million QALYs, at a cost of $434 per QALY gained (Figure 4), and the optimistic scenario added 10.3 million QALYs at a similar cost per QALY gained (Figure 5). HIV prevalence among men declined modestly to 14.6% in the moderate scenario and 14.4% in the optimistic scenario (Figure 2). Among women, these values were 16.5% and 16.4% respectively. HAART's minimal reduction on HIV prevalence is in part due to infected individuals living longer as a result of treatment. Therefore, it is important to include in our analysis a universal metric, such as quality-adjusted life years, to account for the effect of reduced mortality on health benefits.

3.2 Screening focused portfolios

The screening focused intervention portfolios prevented more infections than the HAART focused portfolios, but were more costly. The moderate screening focused portfolio prevented 824,000 infections (7.8% of projected new infections) compared to the base case, and increased QALYs by 7.6 million at a cost of $433 per QALY gained

(Figures 3 and 4). In the moderate scenario the HIV prevalence in 20 years was 13.19% for men and 14.99% for women (Figure 2). In the optimistic scenario, 1,387,000 infections (13.1% of projected new infections) were prevented, adding 13 million QALYs at a cost of $499 per QALY gained (Figures 3 and 5). Screening-focused strategies offered a greater reduction in HIV prevalence than HAART-focused portfolios. After 20 years, HIV prevalence decreased to 13.19 % (moderate scenario) or 12.2% (optimistic scenario) among men and 15.0% (moderate scenario) or 13.9% (optimistic scenario) among women (Figure 2).

3.3 Circumcision-focused portfolios

Among the portfolios focused upon a single intervention, the circumcision-focused portfolios prevented the largest number of HIV infections. The moderate scenario prevented 1,470,000 infections (13.8% of projected new infections), adding over 13 million QALYs for only $55 per QALY gained (Figures 3 and 4). HIV prevalence fell to 11.1% in men and 14.1% in women at the end of the 20 years (Figure 2). Although circumcision primarily benefits men through reduced HIV acquisition, HIV prevalence notably decreases among women as well, due to reduced secondary transmission. Preventing one male HIV infection also prevents infection among future female partners, hence, HIV prevalence among women also decreased. The optimistic scenario was even more successful with 2,188,000 infections prevented over 20 years, with a net gain in 19 million QALYs and a cost-effectiveness ratio of $62 per QALY gained (Figures 3 and 5). HIV prevalence substantially decreased to 9.7% and 12.8% for men and women respectively (Figure 2).

3.4 Combination Portfolios

We first considered intervention portfolios that include implementing two of the three interventions simultaneously. In general, the number of infections prevented for a two-intervention strategy was *less* than the sum of implementing the interventions individually. For example, under moderate assumptions, expanded screening prevented 824,000 infections and expanded circumcision prevented 1,470,000 infections. However, a portfolio that implemented these programs simultaneously prevented only 2,160,000 infections (compared to 2,294,000 if implemented independently). We find a similar result with QALYs gained: screening adds 7.6 million QALYs, circumcision adds 12.7 million QALYs, and the combination strategy adds 19.3 million QALYs. The benefits of implementing programs simultaneously are non-additive because the target populations for each intervention may overlap, and an infection cannot be prevented more than once. These results illustrate the need for using a dynamic epidemic model to appropriately evaluate the effects of multiple infectious disease interventions.

Finally, we considered portfolios that scaled-up efforts of all three interventions. In the moderate scenario, this portfolio prevented 2,257,000 new HIV infections (21.2% of projected new infections) and increased QALYs by 23 million at a cost of $251 per QALY gained relative to the base case (and $484 relative to the circumcision-focused strategy) (Figures 3 and 4). HIV prevalence decreased to 9.9% among men and 12.6% among women (Figure 2). Under optimistic assumptions, this portfolio averted 3,414,000 HIV infections (32.1% of projected new infections), more than with any other strategy (Figure 3). As expected, this strategy increased QALYs by the greatest amount

(38 million) at a cost of $305 per QALY gained relative to the base case (and $561 relative to the circumcision-focused strategy) (Figure 5). The favorable cost-effectiveness ratios are largely driven by the relative inexpensiveness of male circumcision. This strategy also offered the greatest reduction in HIV prevalence after 20 years: 8.1% among men and 10.7% among women (Figure 2). These were the lowest prevalence rates of all the scenarios examined.

3.5 Sensitivity Analysis

We used sensitivity analyses to further evaluate areas of our model where there is a degree of uncertainty about the data or about future events. One such area is the impact of VCT on behavioral risk reduction. In the base-case of our model, we assume that individuals who undergo VCT reduce their number of sexual partners by 20%, as has been done in previously published studies [24]. In order to test the sensitivity of our findings to this assumption, we varied the risk reduction of individuals who undergo VCT from a minimum, where individuals do not change their risk behaviors at all after VCT, to a maximum where individuals reduce their sexual partners by 40% after VCT. All intervention portfolios examined remain cost-effective, including the three-intervention combination portfolio, when there is no change in risk reduction after VCT. Under these circumstances, the cost-effectiveness of the screening focused portfolios decreases as the ICER is $4,122, demonstrating the importance of the educational component of screening interventions. As the effectiveness of VCT in reducing risk behaviors rises, programs that use this intervention become relatively more cost-effective compared to the base case. When risk reduction is 10% the ICER of the moderate screening-focused portfolio is

$730, and when risk reduction is 40% the ICER of the moderate screening-focused portfolio is $278. This finding again demonstrates the importance of adequately funding screening programs so that individuals who undergo VCT can receive helpful education about how to reduce the likelihood of acquiring HIV and transmitting it to a sexual partner.

Sensitivity analysis was also used to consider the effect of increased sexual activity among men who underwent circumcision. Studies have reported increases in sexual risk taking behavior in populations where antiretroviral therapies become widely available [29]. There is concern that this trend may also apply to areas where male circumcision is applied as a preventive measure, although preliminary data indicates that this is not the case [30, 31]. We examined scenarios where male circumcision results in increased sexual activity from a range of 0% change in sexual activity to a 30% increase in sexual activity in individuals newly circumcised. Our findings demonstrate that as sexual activity increases, overall costs increase, HIV prevalence increases, and the effectiveness of portfolios decrease. However, even in the most pessimistic scenario where circumcision results in a 30% increase in sexual activity, the circumcision based portfolio still remains very cost-effective and has an ICER of $216, compared to an ICER of $55 when we assume 0% increase in sexual activity. Similarly, the ICER of the moderate portfolio that combines all three interventions increases from to $251 from $422. Thus, even in the event that circumcision leads to a substantial increase in sexual activity, portfolios with circumcision-based plans remain highly cost-effective.

In our initial scenarios, we assumed that HAART reduces the sexual infectivity of an individual by 90%. There is some uncertainty about the degree to which HAART

reduces infectivity, and there is also likely to be some variance from individual to individual depending on factors such as adherence, HIV genotype, and an individual's genotype. We varied the impact of HAART on infectivity from 90% in the base case to a minimum of 50% reduction in infectivity. This analysis results in fairly minimal changes in the overall costs and effectiveness of the portfolios studied. The ICER of a HAART-focused portfolio decreases from $552 to $434 as reduction in infectivity changes from 50% to 90%. Similarly, the ICER of the portfolio comprised of a combination of three intervention changes from $259 to $251. Portfolios that include expanding access to HAART remain cost-effective even with only a 50% reduction in sexual infectivity because of the significant health benefits accruing among infected individuals receiving HAART. These findings demonstrate that the intervention portfolios are fairly robust to changes in the impact of HAART on infectivity.

4. Discussion

In this study, we evaluated the costs, health benefits, and cost-effectiveness of expanded HIV screening, increased HIV treatment, and/or increased male circumcision using a dynamic HIV intervention portfolio model. Our results highlight the significant opportunities that may exist to improve upon the current set of interventions aimed at controlling the generalized HIV epidemic in South Africa. The base case scenario projected that close to 11 million new HIV infections may occur in adults over a 20 year time horizon. Our model can be applied to compare the relative costs and benefits of implementing various combinations of these three interventions, which may help policy makers allocate resources among competing interventions. Our results highlight the

urgency of increasing select HIV interventions, in order to most effectively mitigate the South African epidemic.

Of the portfolios that focused on a single type of intervention, the circumcision-based portfolios were significantly more effective and less expensive than the portfolios which scaled up antiretroviral treatment and screening for HIV. The cost of implementing circumcision programs is relatively low compared to other interventions, and circumcision is a single, safe event, if done in the appropriate healthcare setting, and an inexpensive mechanism for reducing HIV transmission. This finding is consistent with previous studies that have demonstrated that male circumcision is a highly cost-effective tool in South Africa. One recent study found that "Male circumcision can lower health system costs. This finding is robust across a wide range of plausible parameter input values for South Africa, including lower effectiveness, higher costs, and lower HIV incidence. This analysis also suggests that male circumcision is amongst the most economically efficient of HIV prevention strategies in sub-Saharan Africa."[18] In our single intervention portfolios, the ICER of circumcision strategies was $55-$62, compared to $433-$499 for screening- and HAART-based strategies, further supporting the idea that widespread male circumcision should increasingly be considered as a strategy in South Africa.

These findings also create opportunities for further research in this area. Epidemic modeling could be used to identify specific subpopulations to target for the most effective delivery of a circumcision campaign, for example men from particular age groups, men from particular locations in the country, or men with particular risk factors. The possibility of pursuing widespread circumcision as a prevention strategy also

demands that further research be undertaken to understand the personal and social meanings of this intervention in the variety of cultures and subcultures of South Africa.

Portfolios that used circumcision in combination with other interventions were more effective in preventing HIV infections than strategies that used individual interventions only, however they were also more costly. The HAART and circumcision portfolios prevented 1.6 to 2.4 million HIV infections with an ICER of $151 to $177, while the screening and circumcision portfolios prevented 2.2 million to 3.2 million infections at an ICER of $209 to $262. These findings demonstrate that while pursuing circumcision alone as a strategy may be effective, even further gains can be obtained by using circumcision in conjunction with other interventions. However, as circumcision is used with other interventions the overall costs of programs escalate.

Additionally, when circumcision is added to existing portfolios of interventions, the portfolios become more effective and more cost effective. When the circumcision intervention is added to the HAART portfolio, the number of infections prevented increases substantially from 114,000-242,000 to 1.6-2.4 million, and the ICER decreases from $434-$433 to $151-$177. A similar effect is noted when a circumcision intervention is added to the screening portfolio. In that case, the number of new infections prevented increases from approximately 824,000-1.4 million to 2.2 million-3.2 million. The ICER falls from $433-$499 to $209-$262. This finding suggests that adding a widespread circumcision intervention to the treatment and screening interventions currently in place may offer significant benefits.

In the final scenario created, we examined a strategy that used a combination of all three interventions. This strategy was the most effective overall in averting HIV

infections but with a slightly higher incremental cost-effectiveness ratio: $251-$305 relative to the base case (or $484-$561 relative to circumcision-focused strategies). The World Health Organization suggests that health interventions are "very cost-effective" if they cost less than gross domestic product (GDP) per capita, and "cost-effective" if they cost less than three times GDP per capita [32]. Based on these guidelines, this particular HIV intervention portfolio falls significantly below the WHO's threshold. These findings again suggest that the largest number of infections is prevented with portfolios that are multifaceted and that it is possible to avert large numbers of infections with moderate increases in overall program cost.

Our study model and findings are limited by a number of factors. Because of limited data, we did not stratify certain populations who may have a higher risk of acquiring or transmitting the HIV virus than the general population. In particular, we do not have separate compartments for commercial sex workers, intravenous drug users, or men who have sex with men. Individuals in each of these groups may influence the shape of the HIV epidemic in South Africa in ways that are unaccounted for in our model.

A few studies have recently attempted to learn more about the HIV epidemic among men who have sex with men in sub-Saharan Africa and found that as in other regions of the world, African men who have sex with men also have sex with women [33]. This means that men who have sex with men are likely to shape the heterosexual HIV epidemic in South Africa. However, the extent of this influence is not clear.

Similarly, data on injection drug use behavior in South Africa are very limited, but some information is beginning to emerge. According to a UNAIDS review, injection

drug use is an increasingly important factor in HIV epidemics in the region, and one study found 28% of drug users tested in South Africa to be HIV positive [34]. In addition, in other areas of sub-Saharan Africa a majority of drug users interviewed were found to share needles with other drug users, and were also found to be sexually active [34]. As more data on these high risk groups become available, incorporation of this data into our epidemic model will allow for more precise estimates of how these groups influence the HIV epidemic in South Africa and the success and costs of different interventions.

Our model is also limited by the ability of the model to predict future events. One such area is projection of the use and costs of second line antiretroviral therapies. Currently, the cost of second line therapies for HIV far exceeds cost for first line therapies in South Africa. A recent WHO report found that the current prices for the most common first line antiretroviral regimens in lower middle income countries fell in a range from about $140 per patient per year to $380 per patient per year [35]. However, prices for the most common second line antiretroviral therapies were in the range of about $1300 to $2700 per patient per year [35]. Currently, South Africans on second line antiretrovirals make up a small minority of South African patients on HAART. However, as treatment plans are scaled up and more patients with HIV are treated with HAART, for longer periods of time, the number of patients who must be treated with second line HAART increases rapidly. Another WHO report estimates that approximately 3% of patients receiving HAART, per year, must switch from first line to second line therapies, as patients develop strains of HIV that are resistant to first line therapies, or because they are unable to tolerate the toxicities of particular medications [36].

Depending on how this is projected over time, the cost of second line therapies has a major impact on the overall cost of scaling up treatment. One report estimates that by the year 2010, second line antiretrovirals will make up 90% of the cost of providing antiretroviral therapies to low and middle income countries [37]. Projecting the use and costs of second line antiretrovirals in South Africa twenty years into the future is very challenging, as the prices of second line antiretrovirals are a subject of debate and negotiation between drug manufacturers, governments, and non-governmental organizations. Although it is reasonable to predict that prices for second line antiretrovirals in South Africa are likely to decline during the twenty year time horizon of our model, the extent and timing of this decline is difficult to predict and significantly impacts the cost of scaling up treatment. In the future, the model can be used to demonstrate the effect of second line antiretrovirals on the overall cost of scaling up antiretroviral therapy as prices for these therapies change and more data emerges about antiretroviral switch rates.

Another opportunity to expand the data provided by our model would be to create different scenarios depending on when HAART is initiated. In our model, HAART is initiated only in for a percentage of patients whose CD4 T-cell count is below 200 cells/ mm^3; patients with CD4 counts above 200 cells/mm^3 are not candidates for HAART even if they otherwise meet WHO recommendations for HAART initiation. Initiating HAART earlier in the course of an individual's HIV disease provides a greater opportunity to reduce HIV-related morbidity and the likelihood of transmitting the virus to partners. Future studies could examine how varying the criteria for HAART initiation impacts the effectiveness and cost of the portfolios of interventions described in this study.

5. Conclusions

In this paper we describe the results of a study that uses a deterministic computer model to explore the impact of different portfolios of interventions on the adult heterosexual HIV epidemic of South Africa. Our study finds that portfolios which incorporate widespread circumcision as a preventive intervention are generally more effective and cost-effective than other portfolios that exclusively focus on expanded HIV screening and/or treatment with HAART. Portfolios that combine a scale up of voluntary counseling and testing resources, scale of up antiretroviral administration, and widespread circumcision campaigns were the most successful overall in reducing new infections and adding QALYs over the 20-year time horizon explored. We also find that the costs and benefits of implementing multiple HIV interventions simultaneously are non-additive, and a dynamic epidemic model such as the one we have implemented is necessary in order to accurately estimate the effect of compound interventions on epidemic and economic outcomes. In the absence of a clinical trial offering a similar amalgamation of interventions, a mathematical model is the best tool for estimating the costs and benefits of a portfolio of HIV interventions. In this study, we included only three interventions; however, our modeling framework could be extended to include additional interventions (e.g., a preventative vaccine, microbicide, genetic therapy) should they become available in the future.

While the findings of this paper are intended to inform debates and discussions about the optimal use of limited resources to combat the HIV epidemic in South Africa, there are multiple limitations inherent in a mathematical model. Mathematical models are

limited by the quality of the data used to generate estimates, and are based upon events which have happened in the past and may not be necessarily predictive of the future.

Mathematical models may also not sufficiently account for costs and benefits that are difficult to quantify. For example, increasing the availability of HAART in South Africa is likely to have significant societal benefits not accounted for in the metrics of our model, such as an increased life expectancy for parents, greater social stability, and greater productivity leading to economic gains. Despite these shortcomings, the findings of this study can be helpful as policy makers face difficult choices in allocating resources to combat the HIV epidemic in South Africa. We hope that in the future we can apply this model to assess a variety of different HIV intervention portfolios in different settings.

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Table 1: Model Input Parameters, Values, Source

Parameter	Value	Source
Demographic Parameters		
Total population (15-49 year olds)		
Males	12,530,300	[38]
Females	13,464,600	[38]
HIV prevalence		
Males	16.1%	[38]
Females	19.6%	[38]
Fraction of HIV-infected individuals		
Asymptomatic HIV (CD4 >350)	50%	[39]
Symptomatic HIV (CD4 200-350)	30%	[39]
AIDS (CD4 <200)	20%	[39]
Mortality rate (non-HIV-related)		
Male	0.028	[10]
Female	0.028	[10]
Maturation rate		
Male	0.0162	[38]
Female	0.0185	[38]
Entry rate (includes growth rate)		
Male	0.0623	[38], [34]
Female	0.0587	[38], [34]
Disease Parameters		
Disease mortality rate		
Asymptomatic HIV (CD4 >350)	0.01	[22]
Symptomatic HIV (CD4 200-350)	0.02	[22]
AIDS (CD4 <200)	0.45	[22],[40]
AIDS (CD4 <200) on HAART	0.11	[22], [39]
Disease progression rate		
Asymptomatic HIV (CD4 >350)	0.1745	[22]
Symptomatic HIV (CD4 200-350)	0.2755	[22]
AIDS (CD4 <200)	--	
AIDS (CD4 <200) on HAART	--	
Quality-of-life factor		
Uninfected	1.0	[41]
Asymptomatic HIV (CD4 >350)		

Parameter	Value	Source
Unidentified	0.91	[42], [24]
Identified – First Year	0.84	[24], [43]
Identified – Subsequent Years	0.89	[24]
Symptomatic HIV (CD4 200-350)		
Unidentified	0.79	[24], [43], [44], [45]
Identified	0.72	[42]
AIDS (CD4 <200)		
Unidentified	0.72	[24]
Identified	0.72	[44], [45], [43]
Identified and on HAART	0.82	[45]
Sexual Behavior Parameters		
Annual probability of HIV transmission per sexual partnership ($F_{HIV+} \rightarrow M_{HIV-}$)		
Asymptomatic HIV (CD4 >350)	0.05	[24], [10], [46]
Symptomatic HIV (CD4 200-350)	0.08	[24], [10], [46]
AIDS (CD4 <200)	0.10	[24], [10], [46]
Annual probability of HIV transmission per sexual partnership ($M_{HIV+} \rightarrow F_{HIV-}$)		
Asymptomatic HIV (CD4 >350)	0.10	[24], [10],[46]
Symptomatic HIV (CD4 200-350)	0.15	[24], [10],[46]
AIDS (CD4 <200)	0.20	[24],[10],[46]
Average number of sexual partners per year		
Males	2.0	[27]
Females	2.0	[27]
Condom usage		
Males	30%	[47]
Females	30%	[47]
Condom effectiveness	90%	[10]
Screening & Identification Parameters		
Fraction of uninfected population identified (HIV-tested in past 2 years)	25%	[48]
Identification duration if uninfected (years)	2	[27]
Fraction of infected population identified	35%	[48]

Parameter	Value	Source
Annual probability of symptom-based case finding if infected		
Symptomatic HIV (CD4 200-350)	0.1	[24]
AIDS (CD4 <200)	0.2	[24]
Reduction in sexual behavior due to screening		
Uninfected	20%	[24]
HIV-Infected	20%	[24]
Treatment Parameters		
Fraction of eligible individuals receiving HAART at CD4 <200	28%	[34]
Reduction in sexual infectivity due to HAART	90%	[24], [9], [49]
Circumcision Parameters		
Fraction of males circumcised	40%	[34], [48], [27]
Reduction in HIV acquisition due to circumcision (heterosexual males)	50%	[7], [6], [8]
Cost Parameters (2008 USD)		
Annual HIV-related healthcare costs		
Asymptomatic HIV (CD4 200-350)	$574	[22]
Symptomatic HIV (CD4 >350)	$852	[22]
AIDS (CD4 <200)	$4,257	[22]
AIDS (CD4 <200) on HAART	$736	[22]
Annual non-HIV-related healthcare costs	$856	[1]
Annual cost of HAART	$142	[35]
Cost of testing and counseling	$74	[50]
Cost of circumcision	$64	[18]
Annual discount rate	3%	[51]

Table 2: Benefits and Costs of HIV Screening, Treatment, and Male Circumcision in South Africa

Portfolio Strategy	HIV Infections Prevented	Incremental Costs (billions)	Incremental QALYs (millions)	ICER relative to	
				Base Case	Next Best
HAART-focused					
Moderate	113,656	$2.10	4.85	$434	Dominated
Optimistic	242,075	$4.45	10.28	$433	Dominated
Screening-focused					
Moderate	824,040	$3.30	7.62	$433	Dominated
Optimistic	1,387,800	$6.48	12.97	$499	Dominated
Circumcision-focused					
Moderate	1,470,789	$0.70	12.73	$55	$55
Optimistic	2,187,508	$1.20	19.31	$62	$62
Combination					
Moderate	2,256,555	$5.89	23.45	$251	$484
Optimistic	3,413,878	$11.50	37.64	$305	$561

Under the base case, approximately 10.8 million HIV infections occur over 20 years.
Incremental costs and quality-adjusted life years (QALYs) are relative to the base case.
Incremental cost-effectiveness ratio (ICER) is relative to the base case or the next-best alternative, assuming all strategies are either moderate or optimistic.
Combination portfolios include increased HAART, screening, and circumcision.

Figure 1: Schematic Diagram of Intervention Portfolio Model

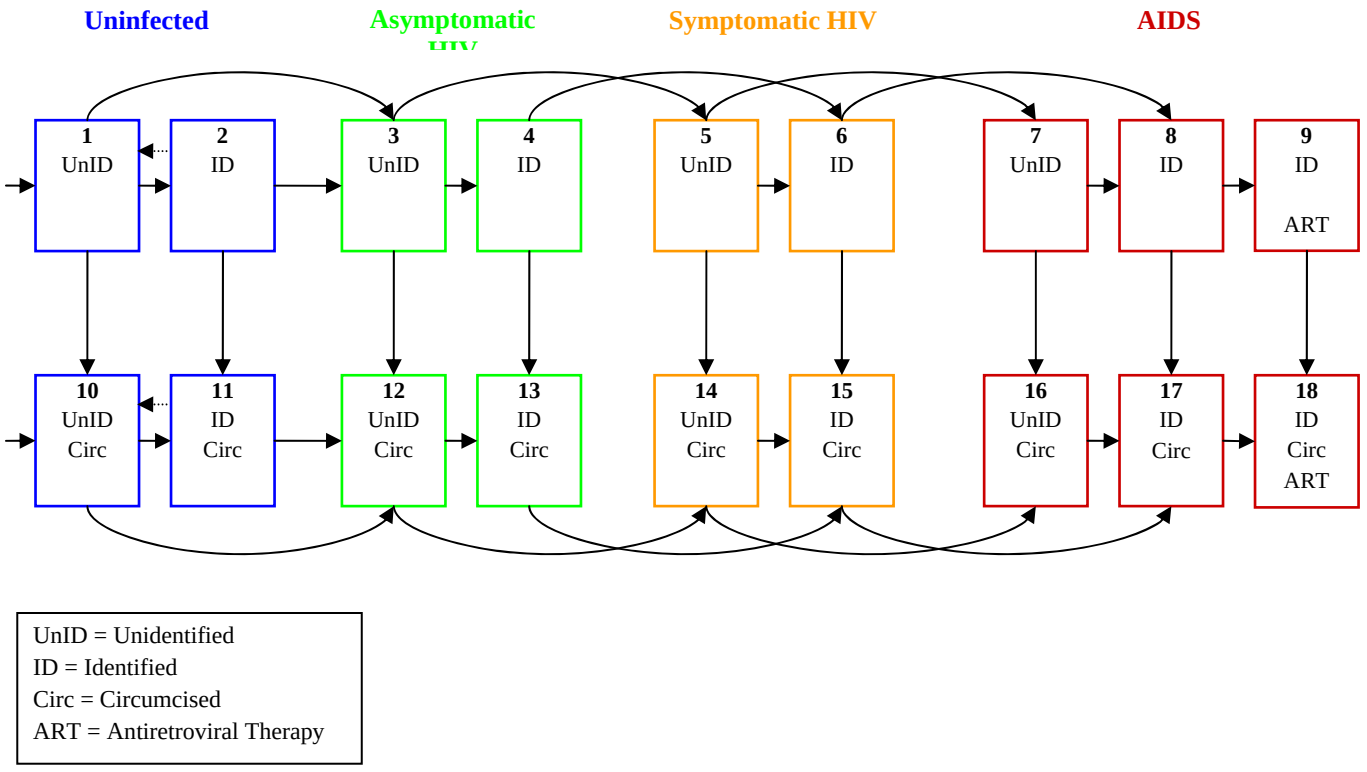

Figure 2: HIV Prevalence in Men and Women by Intervention Portfolio

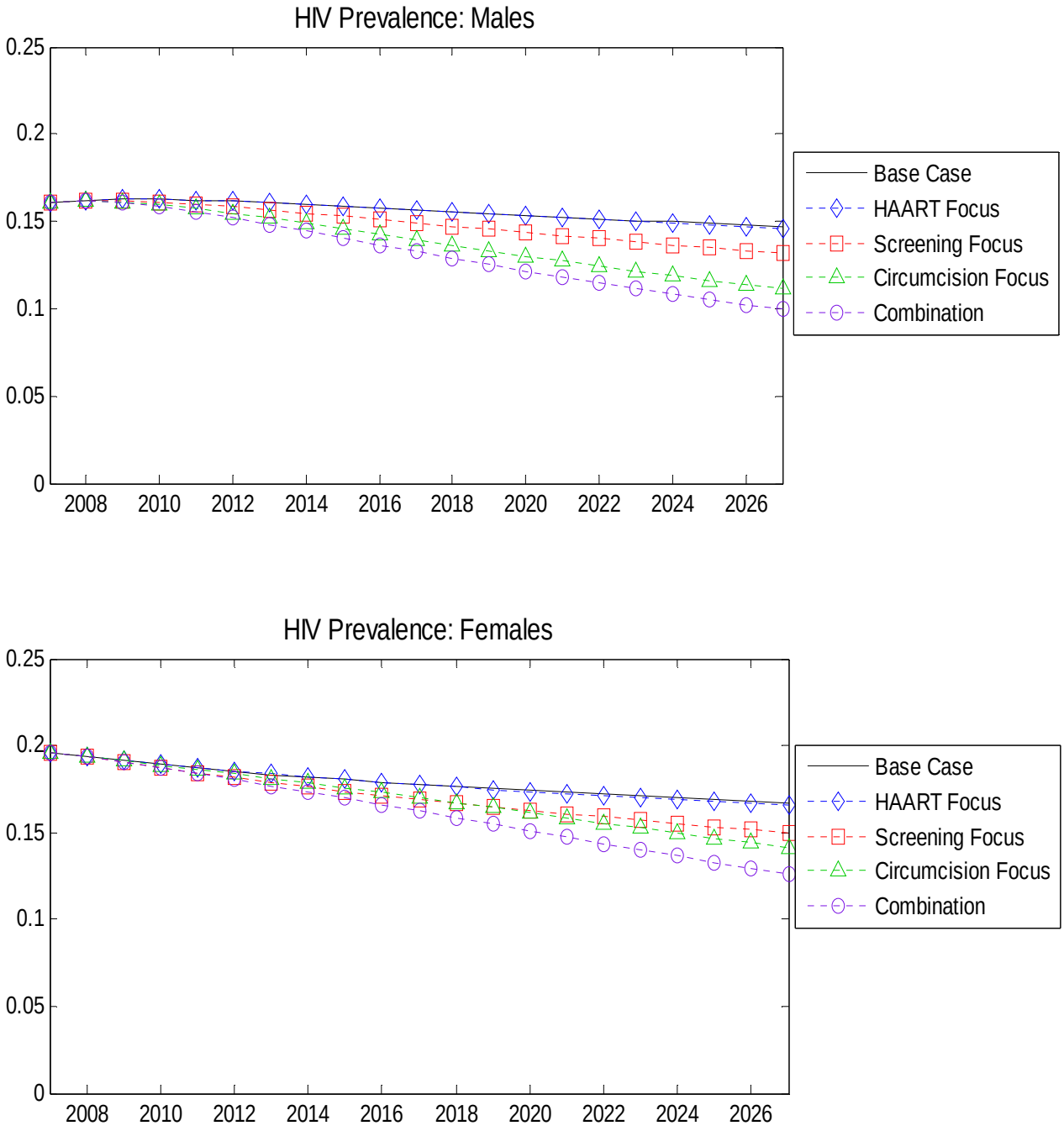

Figure 3: Percentage of HIV infections Averted Relative to Base Case

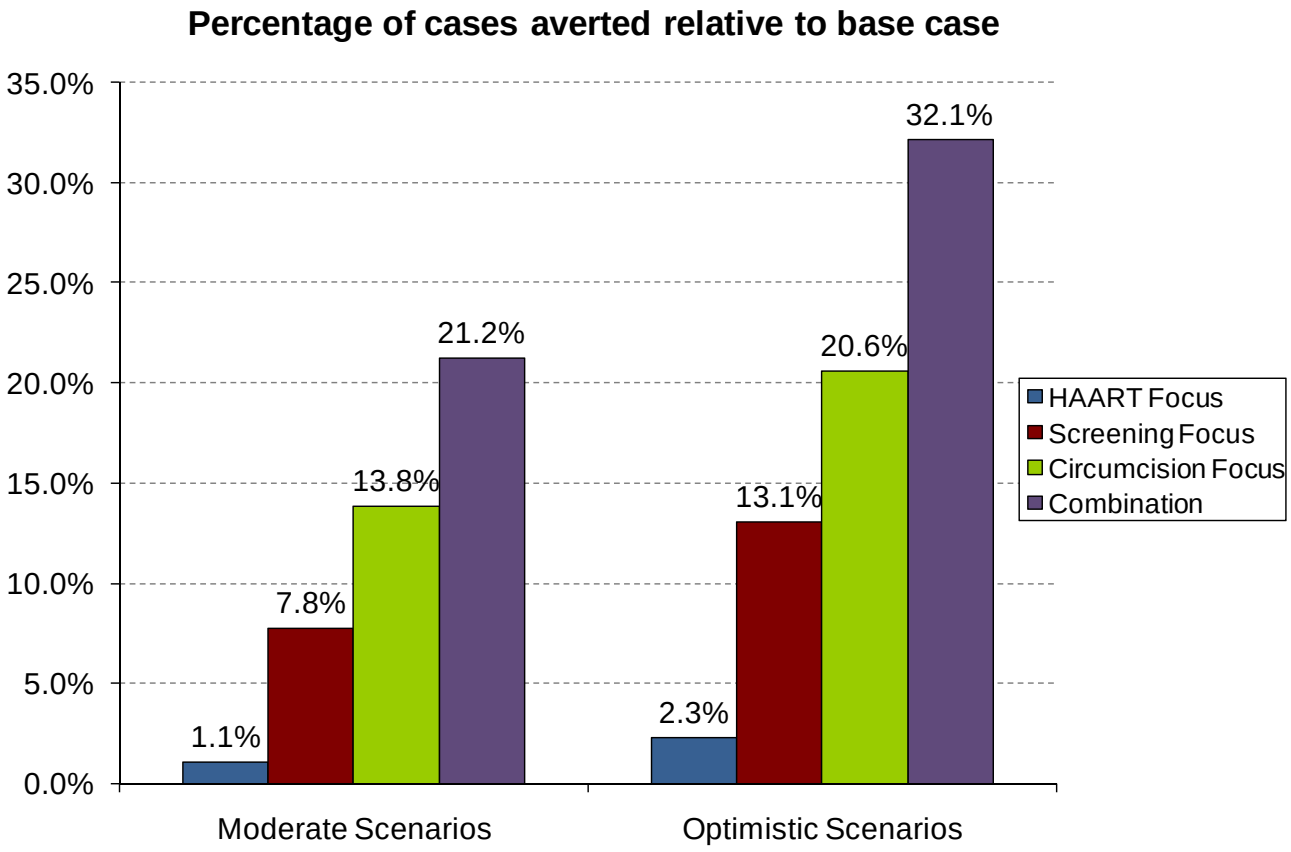

Figure 4: Cost-Effectiveness Analysis and Efficiency Frontier for Moderate Scenarios

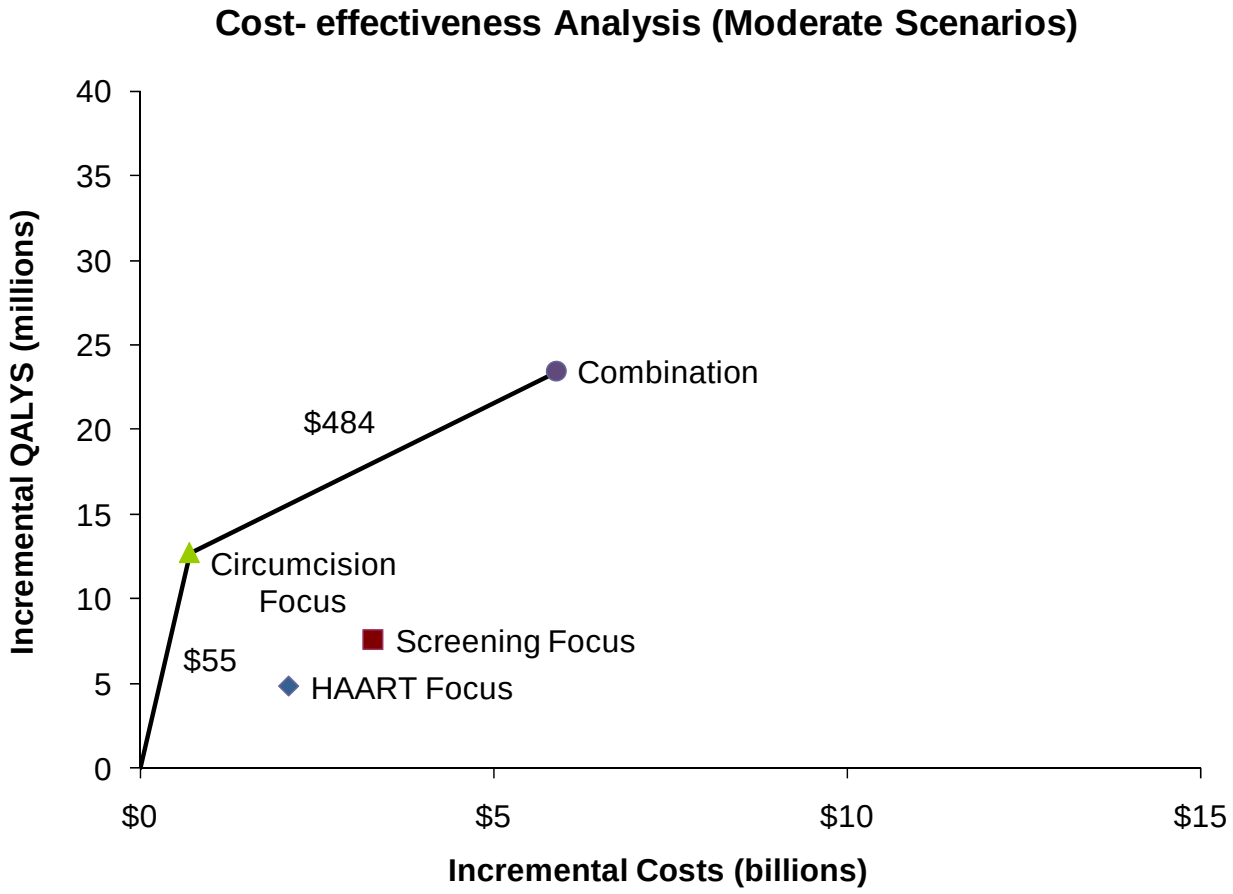

Figure 5: Cost-Effectiveness Analysis and Efficiency Frontier for Optimistic Scenarios