Universal access to ARV treatments in South Africa: Economic and behavioral challenges

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Abstract

This article analyzes the epidemiological and economic impact of a universal testing and treatment policy of HIV in South Africa. Through the model built, several implementation scenarios of the policy are studied. Different behavioral responses in the general population are also considered. The results show that three elements are determinants for the success of such a policy: a very high testing rate, high patients’ adherence to ARV treatments and a lack of relapse in preventive behaviors in the general population facing wider availability of treatments. Screening and adherence appear as substitutable success factors while maintaining or improving prevention practices is a complementary factor for the success of the policy. Given the uncertainty about policy parameters and the heterogeneity of populations concerned such a program should be implemented flexibly with regular monitoring of the three key success parameters.

JEL Classification: I18, H51

Keywords: HIV/AIDS, antiretroviral treatments, universal HIV screening and treatment, public policy.

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1 Introduction

With 5.1 millions infected adults and a prevalence rate greater than 17% among 15-49 in 2011, South Africa is one of the countries hardest hit by HIV / AIDS. Despite a sharp increase in prevalence and incidence in the 1990s the first public programs of ARV distribution were launched very late by the South African government. Since the beginning of these programs in 2005 significant progresses have been made and the country now has the highest number of HIV patients under treatment in the world, with approximately 1.7 million patients on ART. Although the coverage of ARV treatment has increased sharply for eight years, the situation remains worrying from the point of view of screening. Indeed, in 2011, according to the latest UNAIDS data, only 27.4% of South African adults had already been tested for HIV.

For over ten years ARVs are used to minimize the risk of vertical transmission of HIV from mother to child. The preventive effect of antiretroviral treatment was confirmed in 2011 through the results of the HPTN 052 trial. This study showed the risk of transmission in discordant couples could be reduced by more than 96% thanks to the use of ARVs. ARV treatments therefore constitute a new tool for primary prevention of HIV. Theoretically, providing treatment to all HIV infected individuals could even help eradicate the disease. In line with the results of different modeling analysis concerning the effect of a wider distribution of ARVs on the HIV epidemic (Granich et al., 2009; Eaton et al., 2013), WHO changed its treatment recommendations in July 2013. The organization now advises to start treatment for people infected with HIV when the CD4 count falls below 500 against 350 as previously recommended.

The policy studied for South Africa in this article is a large scale HIV testing program repeated several years. Patients identified as HIV positive are then placed on ARV treatment regardless of their CD4 count. The scaling up of HIV testing and treatment is likely to pose significant human and economic challenges for South Africa. Costs associated with the development of a large scale testing and treatment policy are undoubtedly substantial. Economic difficulties associated with the implementation of such a policy may further be exacerbated by behavioral responses in the general population.

The model studied in this paper highlights three key elements for the success of a universal screening and treatment program of HIV in South Africa. Screening must first reach a very large part of the population repeatedly. Adherence of patients to ARV treatment must be very high to encourage a sharp decline in infectivity and allow a significant reduction in new infections. Finally, prevention behaviors in the general population should not relax
facing the greater availability of treatment. If the rate of testing / treatment initiation and the decline in infectivity can be considered as substitutable success factors, a decrease, or at least stability, in sexual risk behaviors appears as an additional factor essential for the success of such a program. From an economic point of view, taking into account the positive externality of treatment changes the traditional framework of cost-benefit analyzes related to ARVs. Indeed, the study shows that a large scale program of testing and treatment would be cost-saving, even in the case of a sub-optimal implementation, as long as preventive behaviors do not relax in population. Scaling up ARVs would indeed alter significantly the epidemiological context in South Africa by reducing drastically the number of new infections.

The implementation of a universal HIV treatment and screening program in South Africa appears desirable from both economic and public health standpoints. Nevertheless, there is a significant uncertainty about the value of implementation parameters of the policy while populations eligible for ARV treatment are probably very heterogeneous. It therefore seems essential that the implementation of such a program should be made flexibly with regular monitoring of critical success factors’ parameters. The rate of treatment initiation, patients’ adherence to ARV treatment and prevention behaviors should therefore constitute key monitoring indicators in applying such a policy.

The paper is organized as follows. Section 2 describes the modeling of the HIV epidemic in South Africa as well as how this model is affected by the introduction of a large scale screening and treatment policy. Section 3 defines the set of possible intervention scenarios and the costs associated with such a program. Section 4 is devoted to epidemiological and economic evaluation of the intervention scenarios set out in the previous section. Section 5 concludes.

2 Model

2.1 Model without ARV

The model built concerns the HIV epidemic among heterosexuals 15 to 49 years old in South Africa. At first, the epidemiological model does not include the possibility of starting ARV treatment, and therefore includes only two categories: the Susceptible category for uninfected adults and the Infected category for people infected with HIV. This model matches the reality of South Africa until 2005, since no treatments were provided by the government before this date. As in a classical epidemiological model, incidence of HIV is determined by a proportional matching. However, unlike classical models, incidence is modeled as a nonlinear function of prevalence to highlight an adaptation of preventive behaviors
to the level of prevalence. The concept of prevalence elasticity, was developed in 1996 by PY. Geoffard and T. Philipson (Geoffard et al., 1996) from a model of utility maximization related to health. In their model the authors assume that individuals seek to maximize their present and future utility based on a probability of infection that increases with the level of prevalence. Individuals will adopt risky practices as long as benefits of these behaviors are greater than the expected decrease in future utility related to HIV infection. In other words, there should exist a critical prevalence threshold below which individuals choose to be exposed to the risk of infection and above which they choose to adopt preventive behaviors. The nonlinear incidence function used in this model allows to introduce the concept of prevalence elasticity in the impact analysis of a program aiming at scaling up HIV testing and treatment in South Africa.

In the model, four parameters determine the evolution of the HIV epidemic. The transmission parameter, $\beta$, is equal to the number of sexual risk taking per period multiplied by the probability of transmission during this type of contact. The value of $\beta$ will therefore depend on both sexual risk behaviors in the population (number of partners per period, probability of condom use during sexual intercourse...) and biological parameters influencing the risk of infection (infection with another STI, kind of sexual encounter...). $\mu$ is the natural mortality rate and $\delta$ the rate of over mortality due to HIV/AIDS. The values of these two parameters are set at 0.028 and 0.072 to allow for an average of 35 years in the Susceptible category for uninfected adults and an average survival of 10 years in the Infected category for people infected with HIV but receiving no treatment. The basic reproduction rate $R_0$ is a key measure in epidemiology because it indicates the number of secondary infections caused by an infected individual in a fully susceptible population. $R_0$ therefore measures the spreading potential of the disease and, by definition, an epidemic can spread only if $R_0$ is greater than one. In the South African context, a value of $R_0$ equal to 7 was estimated (Granich et al., 2009). In the context of this simple model the value of $R_0$ is equal to $\frac{\beta}{\mu+\delta}$ and $\beta$ is set at 0.637 for the value of $R_0$ to be equal to 7.

The incidence function of this model is equal to $S(t) \cdot \frac{\beta \cdot I(t)}{(1+\alpha \cdot I(t)^2)}$. This ad-hoc modeling of incidence allows for a representation of preventive behaviours that react to the environment.

At each period, the probability of contamination of a susceptible individual is $\frac{\beta \cdot I(t)}{(1+\alpha \cdot I(t)^2)}$ where $\frac{1}{(1+\alpha \cdot I(t)^2)}$ is the probability that an individual engages in risky sexual activities and $\beta$ is the likelihood of contamination during the period when at risk contacts are undertaken.

The final model parameter, $\alpha$, measures the adaptation of preventive behaviors facing an increase in prevalence. The higher $\alpha$ is, the higher the elasticity of preventive behaviors to
prevalence will be.

The epidemiological model is represented by the following set of equations:

\[
\begin{align*}
\frac{dS(t)}{dt} &= \mu + \delta \cdot I(t) - \frac{S(t) \cdot \beta \cdot I(t)}{1 + \alpha \cdot I(t)^2} - \mu \cdot S(t) \\
\frac{dI(t)}{dt} &= \frac{S(t) \cdot \beta \cdot I(t)}{1 + \alpha \cdot I(t)^2} - (\mu + \delta) \cdot I(t)
\end{align*}
\]

The value of \( \alpha \) is chosen to obtain prevalence estimations closest to those measured in South Africa in 2002 and 2005 when HIV prevalence surveys were conducted in the general population. The following values are used for the four model parameters:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>( \beta )</th>
<th>( \alpha )</th>
<th>( \mu )</th>
<th>( \delta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values after calibration</td>
<td>0.637</td>
<td>150</td>
<td>0.028</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Table 1: Values of parameters in the model without ARV

Figure 1 presents the simulated prevalence and incidence obtained with these parameters. On the first graph, the two red dots represent the level of prevalence measured among 15 to 49 year olds in South Africa in 2002 and 2005. The black crosses represent UNAIDS estimates of prevalence among 15-49 year olds between 1990 and 2005.

2.2 Model with ARV

To simulate the effect of a large scale screening and treatment program, the model is modified to include the possibility of treatment initiation for infected individuals. In this new model, patients in the Infected category can now start ART at an annual rate of treatment initiation equal to \( \gamma \). After treatment initiation, patients present a lower mortality rate related to HIV (\( \delta' \)) and benefit from an infectivity reduced by a factor \( \epsilon \) (itself influenced by the level of adherence). There are at least three compartments in this new epidemiological model: S for susceptible individuals, U for untreated patients and T for patients on ART. Patients experiencing treatment failure or serious side effects are supposed to be immediately identified and placed under second line ARVs and thus remain in the Treated category (T). Each period, a percentage \( \theta \) of patients under treatment experience treatment failure. These patients falls within the Off treatment category (O). Once in this category patients regain their full infectivity (similar to those in the Untreated category) and a mortality related
to HIV ($\delta^n$) similar to never treated infected individuals. Patients experiencing treatment failure are likely to be put back on treatment following a rate $\tau$, equal to that of never treated infected individuals.

Movements within the various categories of the model are represented by the following graph:

Figure 1: Simulated prevalence and incidence

Figure 2: Representation of the model with ARV

The new model, called SUTOT, is represented by the following set of equations:
\[
\begin{align*}
\frac{dS(t)}{dt} &= \mu + \delta \cdot U(t) + \delta' \cdot T(t) + \delta'' \cdot O(t) - \frac{S(t) \beta \left( U(t) + T(t) + O(t) \right)}{1 + \alpha \left( U(t) + T(t) + O(t) \right)^2} - \mu \cdot S(t) \\
\frac{dU(t)}{dt} &= S(t) \beta \left( U(t) + T(t) + O(t) \right) - \left( \mu + \delta + \gamma \right) \cdot U(t) \\
\frac{dT(t)}{dt} &= \gamma \cdot U(t) + \tau \cdot O(t) - \left( \mu + \delta' + \theta \right) \cdot T(t) \\
\frac{dO(t)}{dt} &= \theta \cdot T(t) - \left( \mu + \delta'' + \tau \right) \cdot O(t)
\end{align*}
\]

The endemic equilibrium of this model is (calculation details available in Annex B):

\[
S^* = 1 + \frac{\beta \cdot (A + \epsilon + B)}{2\alpha \cdot AC} - \sqrt{\frac{(4\alpha \cdot AC) \times \left( \beta \cdot (A + \epsilon + B) - (AC) \right) + \left( \beta \cdot (A + \epsilon + B) \right)^2}{2\alpha \cdot AC}}
\]

\[
T^* = (1 - S^*) \times \frac{\gamma \cdot (\mu + \delta'' + \tau)}{(\mu + \delta'' + \tau)(\mu + \delta' + \theta + \gamma) + \theta \cdot (\gamma - \tau)}
\]

\[
O^* = \frac{\theta}{(\mu + \delta'' + \tau)} \times T^*
\]

\[
U^* = \left[ \frac{(\mu + \delta' + \theta)}{\gamma} - \frac{\tau \cdot \theta}{\gamma(\mu + \delta'' + \tau)} \right] \times T^*
\]

where:

\[
A = \left[ \frac{(\mu + \delta' + \theta)}{\gamma} - \frac{\tau \cdot \theta}{\gamma(\mu + \delta'' + \tau)} \right]
\]

\[
B = \frac{\theta}{(\mu + \delta'' + \tau)}
\]

\[
C = (\mu + \delta + \gamma)
\]

The new value of the basic reproduction rate, \( R_0 \), in this model (calculation details in Annex C) is:

\[
R_0 = \frac{\beta \times \left[ (\mu + \delta' + \theta)(\mu + \delta'' + \tau) + \epsilon \cdot \gamma \cdot (\mu + \delta'' + \tau) + \theta \cdot (\gamma - \tau) \right]}{(\mu + \delta + \gamma) \times [(\mu + \delta' + \theta)(\mu + \delta'' + \tau) - (\tau \cdot \theta)]}
\]
3 Intervention scenarios and costs

3.1 Value of model parameters

The success of the policy depends on six parameters, two biological and four related to the implementation of the program, whose values cannot be known with certainty. The section below discusses plausible values to assign to these parameters when setting up the program in favorable or unfavorable conditions.

**HIV-related mortality rate for treated patients** \( (\delta') \). The scaling up of ARVs is expected to quickly reduce the number of patients starting treatment when their immune system is already largely weakened. Life expectancy of patients on ARVs in South Africa should increase rapidly after the start of the treatment policy and reach the one estimated in developed countries ("Antiretroviral Therapy Cohort Collaboration", 2008). A value of 0.01 is assigned to \( \delta' \) in the analysis.

**HIV-related mortality rate for patients experiencing treatment failure** \( (\delta'') \). It is considered that patients experiencing treatment failure have the same HIV-related mortality that never treated patients. The value of \( \delta'' \) is set at 0.072.

**Annual rate of treatment initiation** \( (\gamma) \). \( \gamma \) represents the percentage of never treated HIV positive adults starting treatment each year. Treatment initiation involves two stages, detection through widespread screening, and linkage to care for the provision of ARV treatment. The value of \( \gamma \) is set to 0.9 for a high-performance implementation of the policy. Instead, a value of 0.5 is chosen for \( \gamma \) in the less efficient implementation scenario.

**Annual rate of treatment failure** \( (\theta) \). For the program to be most effective, it seems essential to minimize the number of patients stopping their treatment each year. The results of ARV distribution programs already in place in South Africa are very mixed concerning retention in care (Johnson et al., 2012; Wouters et al., 2012). An annual treatment failure rate between 1.5 and 4% per year is considered in the analysis \( (\theta \in [0, 0.15, 0.04]) \)

**Factor of reduced infectivity under treatment** \( (\epsilon) \). The preventive effect of ARV treatments was demonstrated in 2011 by the results of the HPTN 052 trial. This trial showed a 96% decline of new HIV transmissions in discordant couples when the infected partner ben-
efited from ARV treatment. The reduced infectivity of patients receiving ARV treatment is related to the decrease in viral load induced by the treatment and depends in part on patient’s adherence (Quinn et al., 2000). The results of the HPTN 052 must be taken with caution as they relate to patients being part of a clinical trial and receiving optimal care. In the reality of a scaling up of ARV therapies in South Africa, it seems likely that patients’ monitoring would be less efficient, potentially leading to suboptimal patients’ adherence. This would result in a reduction of treated patients’ infectivity lower than that observed in the context of the HPTN 052 trial. A range of 0.04 to 0.1 is selected for the value of $\epsilon$, corresponding to an infectivity under treatment reduced by 96 to 90%.

**Rate of treatment uptake for off treatment patients ($\tau$).** The rate of treatment uptake for off treatment patients is considered to be equal to the rate of treatment initiation for never treated patients. The value of $\tau$ thus ranges between 0.5 and 0.9.

**Transmission parameter ($\beta$).** There is a significant uncertainty regarding how the transmission parameter will be affected by the implementation of a policy aiming at scaling up HIV testing and treatment in South Africa. In particular, two questions regarding the evolution of risky behaviors, and thus the transmission parameter $\beta$, following such a policy are of major interest. The first question concerns the evolution of risky behaviors among those screened based on their HIV status, while the second relates to the modification of preventive behaviors in the general population following the greater availability of ARV treatments. To consider various possible evolutions, release or strengthening in preventive behaviors, an increase or decrease of 50% of the value of $\beta$ is considered in the analysis.

Table 2 summarizes the values of the parameters adopted for the analysis:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unfavorable values</th>
<th>Favorable values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma$</td>
<td>0, 5</td>
<td>0, 9</td>
</tr>
<tr>
<td>$\theta$</td>
<td>0, 04</td>
<td>0, 015</td>
</tr>
<tr>
<td>$\tau$</td>
<td>0, 5</td>
<td>0, 9</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>0, 1</td>
<td>0, 04</td>
</tr>
<tr>
<td>$\beta$</td>
<td>0, 9555</td>
<td>0, 3185</td>
</tr>
<tr>
<td>$\delta'$</td>
<td>0, 01</td>
<td>0, 01</td>
</tr>
<tr>
<td>$\delta''$</td>
<td>0, 072</td>
<td>0, 072</td>
</tr>
</tbody>
</table>

Table 2: Plausible values for the different parameters

Depending on the selected values for the different parameters, four implementation sce-
narios of the policy are studied and compared with a baseline scenario. These four scenarios reflect a more or less efficient policy implementation with, in parallel, different evolution of risky behaviors in the general population. For these four scenarios, the policy is evaluated over a 50 years period with an implementation starting in early 2016.

The optimistic scenario assumes a very favorable implementation of the policy with a treatment initiation rate ($\gamma$) equal to 90%, a very low rate of treatment failure ($\theta$) equal to 1.5% and an infectivity of ARV patients greatly reduced ($\epsilon = 0.04$). In addition to this very favorable implementation, the optimistic scenario also includes a 50% decrease of the transmission parameter ($\beta = 0.3185$) due to a strengthening of preventive behaviors in the population following the large-scale screening campaign.

The pessimistic scenario combines an unfavorable implementation, with an annual treatment initiation rate of only 50%, a high treatment failure rates of 4%, an infectivity under treatment only reduced by 90% ($\epsilon = 0.1$), and a release in preventive behaviors in the population resulting in an increase of 50% of the transmission parameter ($\beta = 0.9555$).

In addition to these extreme scenarios, two intermediate scenarios are considered. The favorable intermediate scenario adopts the same implementation parameters of the policy as in the optimistic scenario but assumes unchanged sexual risk behaviors in the population ($\beta = 0.637$). The unfavorable intermediate scenario adopts the same implementation parameters that the pessimistic scenario but assumes constant sexual risk behaviors in the population ($\beta = 0.637$).

These four scenarios are compared to a baseline scenario chosen to reflect the ARV distribution program currently being conducted by the South African government. Public programs of ARV distribution only started in 2005 in South Africa but were then rapidly developed. In 2011, 1.7 millions of infected adults benefited from ARV treatment in South Africa. The objective of the South African government is now to continue the scaling up of treatment to reach a target of 2.5 millions people on treatment in early 2015 \(^1\). Several evaluations are available concerning the performance of public programs of ARV distribution in South Africa. In 2011, Wouters et al. compared rates of virological success at twelve months for fourteen ARV distribution programs in South Africa. According to this article, the share of patients with undetectable viral load after twelve months of treatment varied widely by programs from 66.1 to 94.2%. In a 2012 article, Johnson estimated a 5% annual probability of treatment discontinuation among patients in South Africa, 75% of which would be linked to deaths. However, results of Wouters and al. seem less optimistic with retention rate a

\(^1\)http://www.sanews.gov.za/south-africa/savinglives-one-pill-time
twelve months ranging from 81.4 to 96%. Despite very significant progress since the first public ARV programs in 2005, the annual treatment failure rate seems relatively high in South Africa, while the share of patients with undetectable viral load remains widely variable from a program to the other. Based on these results, $\epsilon$, $\theta$ and $\tau$ are respectively set to intermediate values of 0.07, 0.03 and 0.7 in the baseline scenario. The value of $\gamma$ is then chosen to reflect the increase in the number of patients on ART between 2005 and 2011 ($\gamma = 0.08$ between 2005 and 2011) and to reach 2.5 millions of patients under treatment in 2015 ($\gamma = 0.1$).

The following table sums-up the values of parameters used in the four intervention scenarios:

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>$\gamma$</th>
<th>$\epsilon$</th>
<th>$\theta$</th>
<th>$\tau$</th>
<th>$\beta$</th>
<th>$\mu$</th>
<th>$\delta$</th>
<th>$\delta'$</th>
<th>$\delta''$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline scenario</td>
<td>0.145</td>
<td>0.07</td>
<td>0.03</td>
<td>0.7</td>
<td>0.637</td>
<td>0.028</td>
<td>0.072</td>
<td>0.01</td>
<td>0.072</td>
</tr>
<tr>
<td>Optimistic scenario</td>
<td>0.9</td>
<td>0.04</td>
<td>0.015</td>
<td>0.9</td>
<td>0.3185</td>
<td>0.028</td>
<td>0.072</td>
<td>0.01</td>
<td>0.072</td>
</tr>
<tr>
<td>Intermediate favorable scenario</td>
<td>0.9</td>
<td>0.04</td>
<td>0.015</td>
<td>0.9</td>
<td>0.637</td>
<td>0.028</td>
<td>0.072</td>
<td>0.01</td>
<td>0.072</td>
</tr>
<tr>
<td>Intermediate unfavorable scenario</td>
<td>0.5</td>
<td>0.1</td>
<td>0.04</td>
<td>0.5</td>
<td>0.637</td>
<td>0.028</td>
<td>0.072</td>
<td>0.01</td>
<td>0.072</td>
</tr>
<tr>
<td>Pessimistic scenario</td>
<td>0.5</td>
<td>0.1</td>
<td>0.04</td>
<td>0.5</td>
<td>0.9555</td>
<td>0.028</td>
<td>0.072</td>
<td>0.01</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Table 3: Parameters values in the four intervention scenario

### 3.2 Cost estimation

The scaling of HIV screening and treatment is supposed to be implemented using existing health facilities in South Africa. In 2011, 2,205 public health structures distributed ARVs in the country\(^2\). The scaling up policy would require all clinics and community health centers currently running in South Africa to be involved in the program\(^3\). The use of existing infrastructures and the potential need for further clinics construction are not taken into account in the analysis.

For each scenario, the overall cost associated with HIV is calculated and compared to the costs of other scenarios. The total cost includes screening, provision of treatment for people under ARV but also costs associated with HIV-positive people not receiving ARV treatment. The section below discusses the values of costs adopted for the different categories of expenditure.

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\(^2\) Motsoaledi, (2011, 31st May ) 'How we’re re-engineering the health system - Motsoaledi : Health Budget Vote Policy Speech presented at the National Assembly ' politicsweb.co.za

\(^3\) HID : District Health information System Database. National Department of Health. South Africa
3.2.1 Cost of the screening campaign

Tests. An intermediate cost of $50 is retained for a complete sequence of VCT (voluntary counseling and testing) (Walensky et al., 2011; McConnel et al., 2005). The cost per client tested covers the cost of program management and other recurring costs including test kits or staff ensuring the counseling sessions before and after the test. This cost also covers the distribution of condoms and targeted counselling on discordant couples.

Media campaign. To promote the success of the screening program a media campaign should be implemented across the country. It is assumed that this media campaign would run for seven years (beginning of the campaign in 2015) with an annual budget of $30 million to finance the broadcasting of TV and radio commercials as well as the establishment of targeted promotion to risk groups. In comparison, the largest HIV prevention program for young South Africans, Love Life, has an average annual budget of R180 million, about $20 millions. After six years of widespread screening, 90% (50% for scenarios 3 and 4) of untreated patients are supposed to be identified annually through targeted screening and contact tracing programs for a cost of $50 per infection detected (Menzies et al., 2009).

3.2.2 ARV distribution program

ARV treatments. As recommended by WHO, South Africa changed its treatment guidelines in 2010. Official recommendations now advise a Tenofovir based first line for all patients starting treatment. In accordance with the recommendations of the South African government, HIV positive patients screened through the VCT campaign are immediately placed under a first-line TDF+ 3TC+ EFV for which a one-day pill combination is available for a price of $172 per year per patient. Patients experiencing treatment failure or excessive side effects are supposed to be placed under second line ARVs. The preferred combination of second line therapy for patients with failure after a Tenofovir-based first line therapy is the combination AZT/3TC + ATV/r currently available at a price of $399 per patient per year. An average cost of ARV treatment per patient per year of $200 is considered in the analysis.

Prophylaxis. All ARV patients also benefit from prophylaxis including cotrimoxazole and isoniazid for TB prevention. Gutierrez et al. (2004) estimated a cost of $45 per year per

4www.lovelife.org.za
patient for the provision of both prophylactic drugs in low and middle income.

**Routine tests.** To quickly identify therapeutic failures and maintain an undetectable viral load in the majority of patients, immunological monitoring of patients on ART must be performed on a regular basis, at least twice a year. Each year, patients on ARVs must perform at least two CD4 and viral load tests in addition to treatment toxicity tests already included in official treatment guidelines published by the South African government\(^6\). Based on prices set by the "National Health Laboratory Service" for the year 2011/2012\(^7\), and including costs of transportation of samples from clinics to laboratories, a total cost of $150 per patient per year is considered in the analysis for routine tests.

**Medical staff.** Given the scarcity of medical staff in South Africa, the scaling up of ARVs will require task-shifting from doctors to nurses and from pharmacists to pharmacists assistants. The following staff norms are considered to treat 500 patients: two nurses specially trained in prescribing ARVs, a nurse assistant in charge of basic clinical monitoring (vital signs, height, weight, recording of demographic information, etc.), an administrative employee, a pharmacist assistant for the distribution of ARVs to patients, five counselors for education on ARV treatment and a clerk responsible for contract tracing of lost to follow-up patients. Based on rotary visits at different clinics, a pharmacist and a physician will be assigned to an average of 1,500 patients and a manager, responsible for the supervision of ARV clinics, 2,500 patients. Given the staff norms adopted and wage rates for medical staff in South Africa (George et al., 2012), the annual staff cost to treat 500 patients on ARV is estimated to be $144,871 ie. $290 per patient per year.

**Nurses’ training.** In agreement with Hogan et al. (2005), the cost of a specific two-week training for a nurse is set to $665. Two nurses will be trained to ensure the monitoring of an average of 500 patients per year. With an estimated 5.1 millions adults infected with HIV in South Africa\(^8\) and given staff norms described above (two nurses specifically trained in ARV prescription for 500 patients), an average of 20,400 nurses must be trained to meet the needs of the policy program. The cost of nurses’s training is thus estimated to be equal to $13,566,000 and is equally distributed between 2016 and 2017 to ensure the implementation of the policy in the best conditions in 2017.

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\(^6\)"The South African Antiretroviral Treatment Guideline". Department of Health of South Africa. 24 March 2013.
\(^7\)http://www.nhls.ac.za
\(^8\)UNAIDS Estimation
Hospitalizations. With an average of 1.7 days of hospitalization per year (Granich et al., 2012) for a cost of $130 per day, the average annual expenditure on hospitalization for patients on ARV is fixed at $221.

Opportunistic infections. Treatment cost of opportunistic infections is considered to be concentrated in the last year of life of patients under treatment. This cost has been estimated between $160 (Stover et al., 2011) and $519 (Waters et al., 2011) in low-income countries. An average cost of $350 per patient is considered in the analysis.

Management of the program. The implementation of the policy will require a major monitoring and evaluation program and will imply high logistic costs for the purchase and the management of ARV stocks. It is assumed that the management cost of the policy is equal to 5% of the total annual cost of ARV provision.

Summing up these costs, the annual expenditure for the ARV distribution program is equal to $951.3 per patient. Figure 3 shows the distribution of costs of ARV by categories of expenditures.

Figure 3: Repartition of expenditures related to ARV provision

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3.2.3 Cost related to care of HIV positive individuals not benefiting from ARV treatments

Main expenditures for untreated HIV-positive patients are related to hospitalizations and day visits in health centers. In the case of South Africa, and Granich al. (2012) estimated a value equal to 7.1 for the average annual number of hospitalization days for untreated HIV-infected patients. In the same article, the authors considered an average of 5.5 days visits per year in health facilities for untreated HIV-positive patients. In a report dated from June 2010, the average cost of a day visit to the hospital for untreated HIV-positive patients was estimated at R197,16 (about $19)\textsuperscript{10} by the "Centre for Economic Governance and AIDS in Africa". This cost estimate is similar to values used in various articles concerning South Africa (Kevany, 2006; Granich et al., 2012; Badri et al., 2005, Cleary et al., 2006.). According to these data, and considering a daily cost of hospitalization of $130 (as for treated HIV patients), the average cost associated with untreated HIV-positive patients is estimated to be $1027.5 per patient per year.

4 Results

4.1 Epidemiological evaluation of the intervention

4.1.1 Success factors of the program

Given the uncertainty on the four implementation parameters, it seems essential to identify the parameters whose influence is most important for the success of the policy. To identify the most important parameters, it is possible to look at which variables most affect the value of $R_0$ through the study of the variability of $R_0$ with respect to the different parameters.

Figure 4 depicts the elasticity of $R_0$ related to the different policy parameters. The rate of treatment uptake, $\gamma$, and the factor of reduced infectivity on treatment, $\epsilon$, seem to be the two policy parameters most important in the determination of the value of $R_0$. A 10% increase in $\gamma$ is associated with a decrease of $R_0$ from 3.4 to 4.2% depending on the initial value of $\gamma$. A 10% decrease in infectivity under treatment results in a sharp increase of $R_0$ from 4.1 to 6.3% depending on the initial value of $\epsilon$.

The rate of treatment uptake and the decline in infectivity following treatment initiation seem to be the two implementation parameters the most critical for the policy success.
Screening should thus reach a very large share of the population repeatedly. However, the current screening rate in the South African population is relatively low (27.4% in 2011 among 15-49 year olds) and few data informs us about the acceptability of a repeated screening strategy. Adherence of patients on ARV treatment must also be very high to encourage a sharp decline in infectivity and allow a significant reduction in new infections. The issue of perfect adherence among non-symptomatic patients remains problematic as the medical benefit related to ARV treatment at a level greater than 500 CD4 is still under debate. Indeed, a study of the CASCADE Collaboration in 2011 does not prove any benefit related to mortality or progression to AIDS for patients starting ARV treatment above 500 CD4 (Writing Committee for the CASCADE Collaboration, 2011).

\[\epsilon(R_0)\]

\[\epsilon(R_0, \gamma)\]

\[\epsilon(R_0, \epsilon)\]

\[\epsilon(R_0, \tau)\]

Figure 4: Elasticity of \(R_0\) with respect to the different parameter

4.1.2 Eradication, an accessible objective?

If the large scale HIV testing and treatment policy reduces \(R_0\) below 1 it means that the epidemic can be eradicated by the policy. It therefore seems essential to assess the combined influence of two key parameters previously determined on the evolution of \(R_0\). Figure 5 shows the critical values of \(\epsilon\), for which \(R_0\) is lower than 1, depending on the value of the treatment initiation rate \(\gamma\).

If the rate of treatment initiation is very high, for example 90%, a 99% reduction in infectivity
under treatment is already needed to obtain a value of $R_0$ lower than one and achieve eradication of HIV in South Africa. As the rate of treatment initiation decreases, a greater reduction in infectivity must be obtained to maintain the eradication of the disease. Thus, there seems to be a trade off between the rate of treatment initiation and the factor of reduced infectivity under treatment to control or even eradicate the disease. If infectivity on treatment is maintained at a very low level thanks to a strong adherence to treatments by patients, a smaller effort in identifying and providing treatment for HIV infected adults is necessary to obtain a reduction of $R_0$. Hence, the rate of treatment initiation and the reduced infectivity under treatment appear to be substitutable factors for the success of the policy.

More importantly, Figure 4 shows that the universal testing and treatment policy does not seem able to eradicate HIV by itself, even in particularly favorable implementation conditions. Indeed, an annual rate of treatment initiation greater than 1 is required to maintain a value of $R_0$ lower than 1 if the value of $\epsilon$ exceeds 0.014 (equivalent to a decrease of 98.6% in infectivity under treatment). This means that, apart from a perfect patients’ adherence to treatment and an infectivity under treatment close to 0, universal screening should be done more than once a year if eradication wants to be reached. Moreover, if the rate of treatment initiation is less than 71% even zero infectivity under treatment does not
allow achieving the eradication of HIV.

Zero infectivity in all patients under treatment, identifying each year 100% of people infected with HIV or developing a universal screening program repeated more than once a year appear as unrealistic hypothesis. Despite eradication hopes raised by the information on the preventive effect of ARV treatment, HIV prevention based solely on HIV treatment does not constitute in itself an eradication policy. To guarantee the eradication of the disease, it seems essential that an eradication policy based on universal screening and treatment should be backed by other preventive measures aiming at reducing the transmission parameter $\beta$. Primary prevention through treatment should thus be combined with other traditional forms of prevention. If the rate treatment initiation and the factor of reduced infectivity under treatment are two substitutable success factors of the policy, reduced sexual risk behaviors, and therefore $\beta$, appears as a complementary factor essential if eradication of HIV wants to be achieved in South Africa.

If the universal screening and treatment policy cannot succeed without a decrease in the transmission parameter, an important question is to look at the extent to which this parameter must decrease for the eradication to become possible. Figure 6 presents the transmission parameters values required to obtain a value of $R_0$ lower than one depending on different plausible values for $\epsilon$ et $\gamma$.

![Figure 6: Critical values of $\beta$ depending on $\epsilon$ and $\gamma$](image)

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If the policy benefit from favorable implementation conditions, with an annual rate treatment initiation equal to 90% and an infectivity under treatment reduced by 96%, a decline of 31% in the transmission parameter (from 0.637 to 0.44) is necessary to eradicate HIV. In the case of an unfavorable implementation scenario, a much more significant decrease in transmission parameter is necessary to obtain a value of $R_0$ lower than one. Indeed, if the rate of treatment initiation rate only reach 50% and if infectivity under treatment is only reduced by 90%, the value of $\beta$ must decrease from 0.637 to 0.25 (a decrease of 61%) for the eradication of HIV to become possible. Despite the preventive effect of ARV treatment, the theoretical model studied in this article shows that, in addition to a policy of universal testing and treatment, a relatively high decrease in the transmission parameter (and therefore risky sexual behaviors) is necessary to achieve the eradication of HIV.

4.1.3 Favorable implementation conditions

Even if this policy does not allow the eradication of HIV in South Africa, this intervention will largely influence the epidemiological context in the country. A second key element for the evaluation of such a policy is to look at the implementation conditions of the policy program that will be beneficial from an epidemiological point of view compared to baseline scenario.

Figure 7 shows the combinations of $\gamma$ and $\epsilon$ for which the value of $R_0$ is the same in the baseline and in the intervention scenario. From this graph, it appears that the implementation of the universal treatment policy is desirable from the point of view of public health in South Africa, whatever the implementation scenario, as long as preventive behaviors in the general population are not weakened by this policy. If the rate of treatment initiation is equal to 90%, and no changes in risk behaviors among the population occur, a decrease in infectivity under treatment of only 81% is enough to ensure that the intervention is preferable to the baseline scenario. If the rate of treatment initiation is only 50%, a greater, but still reasonable, decline of infectivity under treatment of 83% is necessary to obtain a favorable epidemiological effect of the intervention compared to the baseline scenario.

A second question is to know whether the policy remains desirable from the public health point of view when facing an unfavorable evolution of preventive behaviors in the population after the program implementation. Figure 8 shows the ratio of $R_0$ in the intervention and the baseline scenario for different values of $\beta$. 

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Figure 7: Values of $\gamma$ and $\epsilon$ for which $R_0$ baseline scenario = $R_0$ intervention scenario

Figure 8: Relative value of $R_0$ in the intervention scenario compared to the baseline scenario given $\beta$.

In the case of a favorable implementation of the intervention it seems unlikely that an increase in risk behaviors could counterbalance the positive effect of the intervention on the value of $R_0$. Indeed, in this case an increase of $\beta$ from 0.637 to 1.6 (a more than 150% increase) would be required for the intervention not to be desirable from an epidemiological point of view. In the case of an unfavorable implementation scenario, the risk that the intervention will lead to adverse epidemiological effects is more realistic. In this scenario, a
slight increase of $\beta$ from 0.637 to 0.75 (18% increase) could lead to a situation where the value of the basic reproduction rate is higher under the intervention scenario compared to the baseline one. A relatively low relapse in preventive behaviors following the start of the treatment program could therefore lead to an amplification of the epidemic.

4.1.4 Epidemiological impact of the intervention

Figure 9 compares the results of the four intervention scenarios and the baseline scenario in terms of prevalence, incidence, and HIV mortality.

Figure 9: Prevalence, share of infected individuals under treatment, incidence and HIV-related mortality in the four intervention scenarios and the baseline scenario.

Compared to the baseline scenario, the increase in the rate of treatment initiation allows for a rise in the share of HIV-positive people on treatment and for a reduction in HIV-related mortality in the four intervention scenarios. For prevalence and incidence, it is necessary to differentiate the first three scenarios from the pessimistic scenario where the intervention is followed by a relapse in preventive behaviors and an increase in the transmission parameter. The first three intervention scenarios allow for a decrease in prevalence and incidence compared to the baseline scenario over the 2015-2065 period. The rise of the treatment initiation rate, facing a stability or decrease in the transmission parameter, makes it possible to reduce the overall infectivity of people living with HIV. This overall decline in infectivity leads to a decrease in the number of new infections and promotes a long term decline in
prevalence, even though life expectancy of HIV-positive patients increases after treatment initiation. Moreover, in line with previously established results, only the optimistic scenario, which includes a 50% reduction in the transmission parameter, ensures a sustained decline in incidence below the 1/1000 defined in other articles as the criterion for HIV eradication (Granich et al., 2009). Under the pessimistic scenario, the increase in the transmission parameter leads to an increase in incidence in the years following the implementation of the policy. This peak of new infections can be explained by a relapse in preventive behaviors, and therefore higher sexual risk takings, at a time when the policy is not implemented efficiently enough to quickly reduce the number of infectious patients. After this peak of new infections in the early years of the intervention, incidence then stabilizes at a level equivalent to that of the baseline scenario since the effect of the increased rate of treatment initiation (and therefore the reduction in the share infectious patients) on the number of new infections is fully compensated by the increase in risky behaviors. In this scenario, the peak of new infections in the years following the implementation of the policy results in an increase in prevalence that remains higher than prevalence in the baseline throughout the intervention period.

Table 4 below reports the values of key epidemiological indicators for the baseline and the four intervention scenarios. New infections and deaths are discounted at a 3% rate per year.

<table>
<thead>
<tr>
<th></th>
<th>Baseline scenario</th>
<th>Scenario O*</th>
<th>Scenario F*</th>
<th>Scenario U*</th>
<th>Scenario P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence in 2065 (%)</td>
<td>11.91 %</td>
<td>3.74 %</td>
<td>6.05 %</td>
<td>10.81 %</td>
<td>13.99 %</td>
</tr>
<tr>
<td>Prevalence in 2065 (number)</td>
<td>3 361 192</td>
<td>1 055 352</td>
<td>1 707 707</td>
<td>3 049 843</td>
<td>3 948 127</td>
</tr>
<tr>
<td>Incidence in 2065 (%)</td>
<td>0.637 %</td>
<td>0.068 %</td>
<td>0.200 %</td>
<td>0.491 %</td>
<td>0.646 %</td>
</tr>
<tr>
<td>Incidence in 2065 (number)</td>
<td>179 755</td>
<td>19 233</td>
<td>56 384</td>
<td>138 634</td>
<td>182 348</td>
</tr>
<tr>
<td>New infections (2016-2065)</td>
<td>8 953 508</td>
<td>1 132 278</td>
<td>2 660 766</td>
<td>6 836 627</td>
<td>9 482 010</td>
</tr>
<tr>
<td>Discounted new infections (2016-2065)</td>
<td>4 352 469</td>
<td>563 602</td>
<td>1 271 026</td>
<td>3 273 408</td>
<td>4 634 913</td>
</tr>
<tr>
<td>HIV-related deaths (2016-2065)</td>
<td>4 744 873</td>
<td>1 545 352</td>
<td>1 701 970</td>
<td>3 249 808</td>
<td>4 003 238</td>
</tr>
<tr>
<td>Discounted HIV-related deaths (2016-2065)</td>
<td>2 429 175</td>
<td>954 904</td>
<td>937 524</td>
<td>1 667 658</td>
<td>2 008 075</td>
</tr>
</tbody>
</table>

Table 4: Epidemiological impacts of the intervention

* O= optimistic, F= Favorable intermediate, U= Unfavorable intermediate, P* = Pessimistic

The first three intervention scenarios allow for a decrease in prevalence and incidence in 2065 compared to the baseline scenario. Unsurprisingly, the optimistic scenario, which includes a 50% decrease of the transmission parameter in addition to a favorable implementation, is the one that results in the most significant decline in prevalence and incidence.
that respectively reach 3.74% and 0.068% in 2065 (1,055,352 people aged 15 to 49 infected and less than 20 000 new infections at that date respectively). The favorable intermediate scenario, which applies a favorable implementation but assume no change in preventive behaviors, also allows for a significant decrease of prevalence and incidence that respectively reach 6.05% and 0.2% in 2065 (1.7 million infected people and 56,384 new infections in 2065). The unfavorable intermediate scenario, which considers a less effective implementation of the intervention and no change in risk behaviors, leads to a decline in prevalence and incidence to respectively 10.81% (3,049,843 persons aged 15 to 49 infected ) and 0.491% (138,634 new infections) in 2065. In the pessimistic scenario, the prevalence is higher in 2065 compared to the baseline scenario with 3,948,127 people infected and a prevalence rate equal to 13.99% compared to 11.91% in the baseline scenario. Incidence in 2065 is also higher in this scenario compared to the baseline scenario, with a rate of 0.646%, or 182,348 new infections at this date, against only 179,755 in the baseline scenario.

Compared to the baseline scenario the four intervention scenarios allow for a reduction in the number of HIV-related deaths. In the baseline scenario 4,745,000 HIV-related deaths occur between 2015 and 2065 (2429000 discounted) compared to 1,545,000 (954,904 discounted) in the optimistic scenario, 1,702,000 (937,524 discounted) in the favorable intermediate scenario, 3,250 millions (1,668,000 discounted) in the unfavorable intermediate scenario and 4,003,000 (2,008,000 updated) in the pessimistic scenario.

Despite reduction in HIV-related mortality in all intervention scenarios, only the first three scenarios allow for a reduction in the overall number of new infections during the study period. The cumulative incidence between 2016 and 2065 reach nearly 9 millions of new infections in the baseline scenario (4352000 discounted) compared to 1,132,000 (563,602 discounted), 2,661,000 (1,271,000 discounted), 6,837 millions (3,273,000 discounted) and 9,482,000 (4,635,000 discounted) respectively for the optimistic scenario, the favorable intermediate scenario and the unfavorable intermediate scenario. In the pessimistic scenario, which combines an unfavorable scenario to a relapse in preventive behaviors, the policy leads to a perverse effect in terms of both incidence and prevalence. The decline in new infections associated to wider treatment initiation is indeed more than offset by the increase in new infections caused by the increase in risk behaviors.
4.2 Economic evaluation

4.2.1 Results of the four intervention scenarios

The table below reports the number of infections averted, the total cost of the treatment program and the cost per infection averted for the four intervention scenarios. Infections averted and costs are discounted at a 3% rate per year. This discount rate is similar to that used in other studies on South Africa (Granich et al., 2012).

<table>
<thead>
<tr>
<th></th>
<th>Baseline scenario</th>
<th>Scenario O*</th>
<th>Scenario F*</th>
<th>Scenario U*</th>
<th>Scenario P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Averted infections</td>
<td>-</td>
<td>7,821,230</td>
<td>6,292,743</td>
<td>2,116,882</td>
<td>-528,501</td>
</tr>
<tr>
<td>Averted infections (discounted)</td>
<td>-</td>
<td>3,788,867</td>
<td>3,081,444</td>
<td>1,079,061</td>
<td>-282,444</td>
</tr>
<tr>
<td>Total cost (billion of $)</td>
<td>189,798</td>
<td>115,930</td>
<td>135,821</td>
<td>176,701</td>
<td>208,837</td>
</tr>
<tr>
<td>Discounted total cost (billion of $)</td>
<td>97,152</td>
<td>67,776</td>
<td>75,837</td>
<td>90,769</td>
<td>105,142</td>
</tr>
<tr>
<td>Net cost (billion of $)</td>
<td>-</td>
<td>-69,506</td>
<td>-49,615</td>
<td>-8,735</td>
<td>23,401</td>
</tr>
<tr>
<td>Discounted net cost (billion of $)</td>
<td>-</td>
<td>-25,247</td>
<td>-17,186</td>
<td>-2,254</td>
<td>12,119</td>
</tr>
<tr>
<td>Cost per averted infection ($)</td>
<td>-</td>
<td>«cost-saving»</td>
<td>«cost-saving»</td>
<td>«cost-saving»</td>
<td>-</td>
</tr>
<tr>
<td>Cost per QALY ($)</td>
<td>-</td>
<td>«cost-saving»</td>
<td>«cost-saving»</td>
<td>«cost-saving»</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5: Economic evaluation of the large-scale HIV treatment program

* O= optimistic, F= Favorable intermediate, D= Unfavorable intermediate, P* = Pessimistic

The policy prevents 7,821,230 infections (3,788,867 discounted) under the optimistic scenario for a total cost of $115,930 billion ($67,776 discounted) compared to $189,798 billion ($97,152 discounted) for the baseline scenario. The favorable intermediate scenario avoids a lower number of infections for a higher total cost. As part of this second scenario 6,292,743 (3,081,444 discounted) new infections are avoided compared to the baseline scenario for a total cost of $135,821 ($75,837 discounted) billion. The last two intervention scenarios reflect much less favorable implementation conditions. Under the unfavorable intermediate scenario, the policy program prevents 2,116,882 (1,079,061 discounted) infections for a total cost of $176,701 ($90,769) billions. The first three intervention scenario thus present a negative cost per infection averted. The implementation of a universal testing and treatment policy for HIV in South Africa would therefore represent a cost-saving intervention, even in sub-optimal implementation conditions, a long as the intervention does not lead to a relapse in prevention behaviors in the population.

The pessimistic scenario presents a total cost of $208,837 ($105,142) billion which the is higher than the cost of the baseline scenario. In this scenario, the number of new infections
between 2015 and 2065 is also higher compared to the baseline scenario. In the context of an imperfect implementation of the policy program combined with a relatively high relapse in preventive behaviors in the general population, the scaling up policy would thus lead to both an increase in the number of new infections and the overall cost HIV. Therefore, the implementation of such a large scale HIV screening and treatment policy must be rigorously prepared to avoid any adverse effects associated with an increase in risk behaviors that would make this policy counter-productive from both epidemiological and economic point of views.

To better understand the epidemiological and economic consequences of a large scale screening and treatment policy, Figure 10 describes the evolution of the total cost by category of expenditures for the baseline and the four intervention scenarios.

In the baseline scenario the total annual cost of HIV gradually decreases from $4.4 to $3.4 billion per year between 2015 and 2065. In this scenario the share of total cost related to the provision of ARV treatments increases between 2015 and 2035 and then stabilizes at around 75%. Thanks to a significant decrease in the number of new transmissions, the total annual cost sharply declines after the end of the screening campaign (2020) under the optimistic and favorable intermediate scenarios. The total annual cost of HIV reaches respectively $1.012 and $1.641 billion in 2065 for the optimistic and favorable intermediate scenarios. In the unfavorable intermediate scenario, the annual cost decreases after the end of the screening campaign but remains high due to a number of new transmissions still elevated after the implementation of the policy. This high number of new transmissions each year does not allow for a sustainable decrease in expenditures related to the supply of ARVs. For this scenario, the annual cost of HIV is $2.958 billion in 2065 about 85% of which is related to the care of HIV patients. Finally, in the pessimistic scenario, the increase in incidence in the years following the implementation of the intervention leads to an increase in prevalence and expenditures for people living with HIV. In this last scenario, the share of total expenditure related to the provision of ARV (85%) and the overall cost of HIV (annual expenditure of $3.828 billion) is higher in 2065 than in the baseline scenario.

From a financial point of view it seems unlikely that the South African government could finance a policy program of universal access to ARV for all HIV-infected adults. Indeed, the latest National Strategic Plan against HIV only scheduled a budget of R130.7 billion ($13 billion) for various prevention and treatment programs for the 2012-2016 period. Moreover, with an annual cost over $5 billion between 2015 and 2020, this type of program far exceeds the annual budget for HIV-related programs of the South African Ministry of
Health. Funding for a large scale treatment policy should not crowds-out budgets related to other HIV prevention programs. Instead, the implementation of this intervention should help promote synergies with other prevention programs to maximize its effectiveness as seen in section 4.1.2 and 4.1.3. It therefore seems essential that the implementation of a large scale screening and treatment program should be funded, at least in part, by international donors in spite of the current crisis context in international funding for HIV (reduction in total HIV aid from $7.61 to $6.83 billion between 2009 and 2010 before a new increase to...
to $7.61 billion in 2011 \textsuperscript{11}). This considerable financial effort could still be motivated by the dynamic of long-term expenditures on HIV following such an intervention. Indeed, if the initial investment is large enough to guarantee an optimal implementation of the policy, annual expenditures on HIV should decrease rapidly in South Africa thanks to the decline in the number of new infections. The first two intervention scenarios illustrate this situation and show that, after a very expensive phase between 2016 and 2020, annual expenditures for HIV would decrease each year. Following the progressive decline in these expenditures, the financing of ARV treatment programs could then be fully covered by the South African government which would limit the country’s dependence on international aid in the fight against HIV.

### 4.2.2 Sensitivity analysis

To determine whether the large-scale treatment program remains cost-saving, or cost-effective for usual values of cost/QALY, facing adverse changes in costs of care for treated or untreated patients, sensitivity analyzes are conducted on the major expenditure categories of the program. High and low values are defined for the main cost categories based on values found in the literature. In absence of specific cost data, low and high values are respectively calculated as half or double of previously defined costs. Parameters values used in the sensitivity analysis are summarized in Table 6.

Table 7 describes changes in cost per infection averted and cost per QALY in the four intervention scenarios following adverse variations in cost used for screening, ARV treatment provision and untreated patients’ care.

<table>
<thead>
<tr>
<th>Cost parameters</th>
<th>Baseline value</th>
<th>Low value</th>
<th>High value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCT cost</td>
<td>50</td>
<td>6.49</td>
<td>101.58</td>
</tr>
<tr>
<td>ARV provision cost</td>
<td>951.3</td>
<td>475.65</td>
<td>1902.6</td>
</tr>
<tr>
<td>Cost of care for HIV untreated patients</td>
<td>1027.5</td>
<td>513.75</td>
<td>2055</td>
</tr>
</tbody>
</table>

Table 6: Cost parameters used in the sensitivity analysis

In the optimistic scenario, intervention remains cost-saving facing unfavorable (independent and simultaneous) changes in the cost of the three major expenditure categories (rising cost of screening, rising cost of ARV provision and lower cost of untreated patients’ management). In the favorable intermediate scenario, the program also remains cost-saving

\textsuperscript{11}Jennifer Kates (Kaiser Family Foundation), Adam Wexler (Kaiser Family Foundation), Eric Lief (Stimson), Benjamin Gobet (UNAIDS) Financing the Response to AIDS in Low-and Middle-Income Countries. International Assistance from Donor Governments in 2011
facing unfavorable (independent or simultaneous) variations in the cost of the three major expenditure categories. For the unfavorable intermediate scenario the intervention becomes more expensive than the baseline scenario when the cost of screening increases from $50 to $101.58, when the cost of ARV provision doubles or when the cost of care for untreated patients is reduced by 50%. Facing adverse changes in all expenditure categories, the intervention remains however very cost-effective in this scenario with a cost/QALY equal to $2540 well below GDP/head in South Africa ($7508 in 2012 according to the World Bank).

<table>
<thead>
<tr>
<th></th>
<th>Optimistic scenario</th>
<th>Scenario F</th>
<th>Scenario U</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost / IA*</td>
<td>Cost / QALY</td>
<td>Cost / IA</td>
</tr>
<tr>
<td>VCT = 6.49 $ (1)</td>
<td>-7 899</td>
<td>-1 580</td>
<td>-7 104</td>
</tr>
<tr>
<td>VCT = 101.58 $ (2)</td>
<td>-5 198</td>
<td>-1 040</td>
<td>-3 767</td>
</tr>
<tr>
<td>ARV provision = 475.65 $(3)</td>
<td>-5 600</td>
<td>-1 120</td>
<td>-5 428</td>
</tr>
<tr>
<td>ARV provision = 1902.6 $ (4)</td>
<td>-8 791</td>
<td>-1 758</td>
<td>-5 876</td>
</tr>
<tr>
<td>Untreated cost of care = 513.75 $ (5)</td>
<td>-3 761</td>
<td>-752</td>
<td>-2 146</td>
</tr>
<tr>
<td>Untreated cost of care = 2055 $ (6)</td>
<td>-12 469</td>
<td>-2 494</td>
<td>-12 441</td>
</tr>
<tr>
<td>(2) + (4) + (5)</td>
<td>-4 424</td>
<td>-885</td>
<td>-635</td>
</tr>
<tr>
<td>(1) + (3) + (6)</td>
<td>-12 641</td>
<td>-2 528</td>
<td>-13 818</td>
</tr>
</tbody>
</table>

Table 7: Sensitivity analysis results

*IA = infection averted, F = Favorable intermediate, U* = Unfavorable intermediate

The results of Section 4.1 demonstrated the possibility of perverse effects of the policy if a sub-optimal implementation is combined to a relapse in preventive behaviors in the general population. To explore this possibility more precisely, the cost-benefit ratio of the intervention is recalculated for the two intermediate scenarios for different values of $\beta$. To consider all possible evolutions in preventive behaviors following the large-scale treatment program, the value of $\beta$ is varied between -50% and 200% from its initial value. Table 8 and Figure 11 show the results of the sensitivity analysis. The universal screening and treatment policy remains cost-saving in South Africa, even facing a doubling in the value of $\beta$ (which would represent a sharp increase risk behaviors) if the implementation of the policy is favorable. On the contrary, in the case of an unfavorable implementation, such a policy is only cost-saving as long as preventive behaviors do not relax in the general population. If the increase in the transmission parameter does not exceed 30% , the treatment policy still remains a very cost-effective intervention. However, if the decline in preventive behaviors is more elevated, corresponding to an increase in $\beta$ of more than 30%, the policy becomes counter-productive with an increase in the number of infections between 2016 and 2065.
compared to the baseline scenario. This situation corresponds to the red square in Figure 12.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>β</th>
<th>Averted infections (discounted)</th>
<th>Discounted net cost</th>
<th>Cost / infection averted</th>
<th>Cost / QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scenario F</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3185</td>
<td>3 788 867</td>
<td>- 25 247 889 808</td>
<td>«cost-saving»</td>
<td>«cost-saving»</td>
<td></td>
</tr>
<tr>
<td>0.3822</td>
<td>3 655 686</td>
<td>- 23 709 669 935</td>
<td>«cost-saving»</td>
<td>«cost-saving»</td>
<td></td>
</tr>
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Table 8: Results of sensitivity analysis related to $\beta$
According to the relatively simple model studied in this paper, the success of a universal screening and treatment program of HIV in South Africa depends on three key parameters. These parameters are the rate treatment initiation, patients’ adherence on treatment, which defines their infectivity, and preventive behaviors’ change following the implementation of the intervention. Rate of treatment initiation and adherence of patients constitute substitutable success factors but the evolution of preventive behaviors is a complementary factor whose evolution is determinant to guarantee the success of the policy. These three parameters must be used as monitoring indicators around which the implementation of such a policy must be established. As part of a flexible implementation plan, these indicators should also be followed carefully to adapt the strategy according to difficulties encountered, whether related to organizational or behavioral problems.

The provision of ARVs to the greatest number of HIV infected adults in South Africa can be a beneficial intervention from both economic and public health points of view if the introduction of the program does not cause a long-term relapse in preventive behaviors among the general population. On the contrary, if unfavorable implementation conditions are combined to a sustainable decline in the practice of preventive behavior, the implementation of such a program could cause an increase in new infections, and eventually have perverse consequences from epidemiological and economic perspectives.
Despite the difficulties associated with the scaling up of ARV treatments in South Africa, extending the provision of treatments to the largest number of patients seems advisable from both an economic and public health point of view if the three key parameters defined above are correctly monitored. The expansion of ARV distribution programs should however be combined with a strengthening of primary prevention policies in order to stimulate the effect of such an intervention and to avoid any adverse effect in terms of incidence, prevalence and rising health expenditures related to HIV.

Some negative aspects related to the scaling up of ARV therapies are not discussed in this article. The wider diffusion of treatments, if accompanied by poor monitoring and patients’ adherence, could lead to the development of resistant strains more difficult and expensive to treat. From an economic point of view, this would tend to increase the cost of the intervention. Even faced with rising treatment costs related to the diffusion of resistant strains, it is likely that a policy of universal treatment would remain cost-saving or cost-effective, as evidenced by the results of the sensitivity analysis on the cost of ARV provision. The model does not take into account the role of the primary infection phase in new infections even if it has been identified as a key element for the success of treatment as prevention programs (Cohen et al., 2012). Without decomposition of population by age and sex the model does not allow to evaluate the effect of screening and treatment programs targeted at key populations as women from 25 to 29 years or men from 30 to 34, groups for which the prevalence reached respectively 32.7 and 25.8 % in 2008 in South Africa. Finally, the welfare effect of a possible stigmatization of people diagnosed with HIV is not taken into account in the analysis. This cost could nevertheless be high if no action for the integration of HIV-infected people is undertaken in parallel of the large-scale screening program.
References


[17] Gavin George and Bruce Rhodes. Is there really a pot of gold at the end of the rainbow? has the occupational specific dispensation, as a mechanism to attract and retain health workers in south africa, leveled the playing field? *BMC Public Health*, 12(1):613, August 2012. PMID: 22867099.


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Annexe A: UNAIDS prevalence data

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Annexe B: Endemic equilibrium calculus

We start by expressing $O$ and $U$ as a function of $T$:

\[
O = \frac{\theta}{(\mu + \delta'' + \tau)} \times T
\]

\[
U = \left[\left(\frac{\mu + \delta' + \theta}{\theta} - \frac{\tau \cdot \theta}{\gamma(\mu + \delta'' + \tau)}\right)\right] \times T
\]

We then replace $U$ and $O$ by these expression in the second equation of the SUTOT model and we obtain the following equation:

\[
S \cdot \beta \times \left[\left(\frac{(\mu + \delta' + \theta)}{\gamma} - \frac{\tau \cdot \theta}{\gamma(\mu + \delta'' + \tau)}\right) + \epsilon + \frac{\theta}{(\mu + \delta'' + \tau)}\right] \times S + (1 + \alpha)AC = 0
\]

To find more easily the value of $S$ from the preceding equation we pose:

\[
A = \left[\left(\frac{(\mu + \delta' + \theta)}{\gamma} - \frac{\tau \cdot \theta}{\gamma(\mu + \delta'' + \tau)}\right)\right]
\]

\[
B = \left(\frac{\theta}{(\mu + \delta'' + \tau)}\right)
\]

\[
C = (\mu + \delta + \gamma)
\]

After reorganization we obtain:

\[
(\alpha \cdot AC) \times S^2 - \left(2\alpha \cdot AC + \beta \cdot (A + \epsilon + B)\right) \times S + (1 + \alpha)AC = 0
\]

We then have:

\[
\Delta = (4\alpha \cdot AC) \times \left(\beta \cdot (A + \epsilon + B) - (AC)\right) + \left(\beta \cdot (A + \epsilon + B)\right)^2
\]

and a sufficient condition for the existence of an endemic equilibrium is:

\[
\beta \cdot (A + \epsilon + B) > AC
\]

After few rearrangements we the condition for existence of an endemic equilibrium can
be rewritten as:

\[
\beta \cdot (A + \epsilon + B) > AC
\]

\[
\beta \times \frac{\left(\mu + \delta^\prime + \theta)(\mu + \delta^\prime + \tau) + (\epsilon \cdot \gamma \cdot (\mu + \delta^\prime + \tau) + \theta \cdot (\gamma - \tau)\right)}{(\mu + \delta + \gamma) \times [(\mu + \delta^\prime + \theta)(\mu + \delta^\prime + \tau) - (\tau \cdot \theta)]^2} > 1
\]

The value of \( S \) in the endemic equilibrium is then:

\[
S^* = 1 + \frac{\beta \cdot (A + \epsilon + B)}{2\alpha \cdot AC} - \frac{\sqrt{4\alpha \cdot AC} \times \left(\beta \cdot (A + \epsilon + B) - (AC)\right) + \left(\beta \cdot (A + \epsilon + B)\right)^2}{2\alpha \cdot AC}
\]

As \( U + O + T = 1 \), we then obtain the following values for \( T^* \), \( O^* \) and \( U^* \):

\[
T^* = (1 - S^*) \times \frac{\gamma \cdot (\mu + \delta^\prime + \tau)}{(\mu + \delta^\prime + \tau)(\mu + \delta^\prime + \theta + \gamma) + \theta \cdot (\gamma - \tau)}
\]

\[
O^* = \frac{\theta}{(\mu + \delta^\prime + \tau)} \times T^*
\]

\[
U^* = \left[\frac{(\mu + \delta^\prime + \theta)}{\theta} - \frac{\tau \cdot \theta}{\gamma(\mu + \delta^\prime + \tau)}\right] \times T^*
\]
Annexe C: Basic reproduction rate calculus

We first calculate from the model the matrices $F$ and $V$ which correspond respectively to new infections and exits minus entries (other than infections) for the three infected categories of the model.

\[
F = \begin{bmatrix}
0 \\
\frac{\left(\beta \cdot S(t) \cdot U(t)\right) + \left(\beta \cdot S(t) \cdot T(t)\right) + \left(\beta \cdot S(t) \cdot O(t)\right)}{1 + \alpha (1 - S(t))^2} \\
0 \\
0
\end{bmatrix}
\]

\[
V = \begin{bmatrix}
\mu \cdot S(t) + \frac{\beta \cdot S(t) \left(U(t) + \epsilon \cdot T(t) + O(t)\right)}{1 + \alpha (1 - S(t))^2} - \mu - \delta \cdot U(t) - \delta' \cdot T(t) - \delta'' \cdot O(t) \\
\mu + \delta + \gamma \cdot U(t) \\
\mu + \delta' + \theta \cdot T(t) - \gamma \cdot U(t) - \tau \cdot O(t) \\
\mu + \delta'' + \tau \cdot O(t) - \theta \cdot T(t)
\end{bmatrix}
\]

We then consider the case of a disease free equilibrium and calculate for the three infected categories the matrices of partial derivatives $F_0$ and $V_0$. At the disease-free equilibrium we have $S = 1, T = U = O = 0$ such that:

\[
F_0 = \begin{bmatrix}
\beta & \beta \cdot \epsilon & \beta \\
0 & 0 & 0 \\
0 & 0 & 0
\end{bmatrix}
\]

\[
V_0 = \begin{bmatrix}
\mu + \delta + \gamma & 0 & 0 \\
-\gamma & \mu + \delta' + \theta & -\tau \\
0 & -\theta & \mu + \delta'' + \tau
\end{bmatrix}
\]
We then have to calculate the eigenvalue of $F_0 \times (V_0)^{-1}$ to obtain the value of $R_0$.

The value of $F_0(V_0)^{-1}$ is equal to:

$$F_0(V_0)^{-1} = \frac{1}{(\mu + \delta + \gamma) \times [(\mu + \delta' + \theta)(\mu + \delta'' + \tau) - \theta \cdot \tau]} \times \begin{bmatrix} F_0 V_0(11) & F_0 V_0(12) & F_0 V_0(13) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

With:

$$F_0 V_0(11) = \beta \times \left[ (\mu + \delta' + \theta)(\mu + \delta'' + \tau) - \theta \cdot \tau + \epsilon \cdot \gamma \cdot (\mu + \delta'' + \tau) + \gamma \cdot \theta \right]$$
$$F_0 V_0(12) = \beta \times \left[ \epsilon \cdot \tau \cdot (\mu + \delta + \gamma) + (\mu + \delta + \gamma)(\mu + \delta' + \theta) \right]$$
$$F_0 V_0(13) = \beta \times \left[ \epsilon \cdot (\mu + \delta + \gamma)(\mu + \delta'' + \tau) + \theta \cdot (\mu + \delta + \gamma) \right]$$

We can finally express $R_0$ as:

$$R_0 = \frac{T}{2} \pm \sqrt{(\frac{T}{2})^2 - D}$$
$$R_0 = \frac{1}{(\mu + \delta + \gamma) \times [(\mu + \delta' + \theta)(\mu + \delta'' + \tau) - (\tau \cdot \theta)]} \times F_0 V_0(11)$$
$$R_0 = \frac{\beta \times \left[ (\mu + \delta' + \theta)(\mu + \delta'' + \tau) + \epsilon \cdot \gamma \cdot (\mu + \delta'' + \tau) + \theta \cdot (\gamma - \tau) \right]}{(\mu + \delta + \gamma) \times [(\mu + \delta' + \theta)(\mu + \delta'' + \tau) - (\tau \cdot \theta)]}$$