The impact of antiretroviral therapy on the HIV epidemic in South Africa

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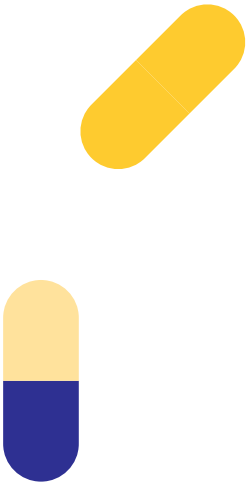

1. General Introduction

1.1 HIV epidemiology and prevention

The Human Immunodeficiency Virus (HIV) is the cause of Acquired Immune Deficiency Syndrome (AIDS), a lethal disease characterized by the destruction of the immune system [1,2]. At the end of 2010, there were about 34 million people infected with HIV worldwide [3]. The epicenter of the HIV pandemic lies in sub-Saharan Africa (figure 1.1): with only 12% of the world's population, 68% of all people living with HIV live in the subcontinent [3]. Although the number of new infections worldwide declined over the past decades, there were an estimated 2.7 million acquired the infection in 2010 [3]. Especially countries in Eastern and Southern Africa are heavily affected by the pandemic. In countries like Botswana or Swaziland prevalence levels in the adult population are as high as 20 to 25%. South Africa is the country with the largest HIV-infected population worldwide. With prevalence levels of about 15% in the population aged over 15 years, the country has about 6 million people living with HIV [3]. Over the past few years, the number of new infections in the country declined [4,5], yet incidence levels remain considerable [6]. In mid-2010, about 1.5 million people infected with HIV were receiving antiretroviral therapy (ART), while a further 1.5 million are estimated to be eligible for treatment.

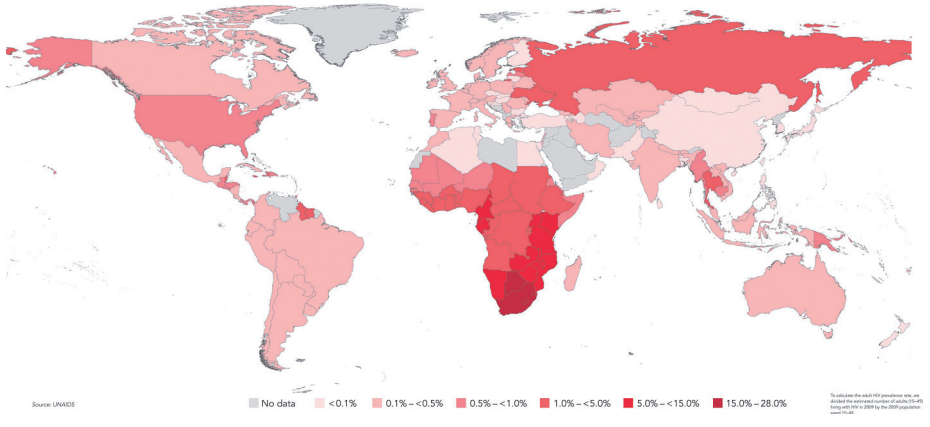

Figure 1.1. Global HIV prevalence. Source: UNAIDS [3]

HIV is primarily transmitted through unprotected sex acts, but can also be transmitted from mother to child during pregnancy or breast feeding, through needle sharing for medical purposes or injecting drugs, and blood transfusions with infected blood [7]. In South Africa, as well as the whole of sub-Saharan Africa, the majority of new infections in adults are caused by unsafe sex in heterosexual contacts, while many infected mothers pass on their infection to their unborn child through mother-to-child transmission [8]. In this thesis, we will focus on the heterosexual transmission of HIV.

Interventions to reduce sexual transmission of HIV in sub-Saharan Africa can roughly be divided into 3 categories: 1) biomedical interventions; 2) behavioral interventions; and 3) structural interventions [7,9]. Biomedical interventions reduce the efficiency of transmission of HIV during

a sex act, and include condoms [10], male circumcision [11-13], pre- and post-exposure prophylaxis [14,15], vaccines [16], microbicides [17], and syndromic treatment for STIs [18]. Behavioral interventions aim to reduce the number of - or increase the use of condoms during - high risk sex acts such as concurrent partnerships and visits to sex workers [19]. Finally, structural interventions aim to reduce poverty, gender disparities, and improve retention in the educational system, with the goal to improve knowledge on HIV, empower women to stay in school, delay sexual debut and empower women to make their own choices in their sexual life [20,21].

Yet despite the many promising interventions that have been developed over the past decades, a limited number of them were proven to be effective in randomized trials or real world situations. Over 90% of all HIV prevention trials reported no significant reduction in HIV incidence in the intervention arm [22]. Up to 2010, only 5 trials demonstrated effectiveness of an intervention: Three independent trials have shown that male circumcision can effectively reduce HIV incidence in men [11-13], and mathematical modeling studies have shown that the results from these trials can be translated into a highly effective and cost-effective public health intervention [23-27].

Another trial - on syndromic treatment of sexually transmitted infections (STIs) in Mwanza, Tanzania - showed a substantial reduction in HIV incidence in the intervention arm [28], yet many other trials failed to replicate this positive finding [29-32]. Mathematical modeling studies suggest that syndromic treatment of STIs also has the potential to have a high public health impact [33-36], and the intervention was implemented in South Africa in 1995. However, in 2008, White et al concluded that the intervention failed to produce significant results in the country [37].

Finally, the RV144 ALVAC/AIDSVAX vaccine is the only HIV vaccine that was demonstrated to be effective in a randomized trial up to now. The trial was conducted in Thailand, and showed a 39% reduction in HIV incidence in the intervention arm 2 years after vaccination [16]. In contrast to male circumcision and STI treatment, the population level impact and cost-effectiveness the RV144 vaccine in a high endemic setting have never been evaluated.

Recently, ART was added to the quiver of HIV prevention opportunities, as it became clear that the drugs not only result in a longer and healthier life for the infected individual [38-41], but can also effectively reduce their infectiousness. Cohen et al showed in a randomized controlled trial that HIV incidence in serodiscordant couples was reduced by 96% due to ART [42]. This study - which was labeled as 'scientific breakthrough of the year 2011' by the journal Science [43] - confirmed hypotheses from earlier observational studies showing reductions of about 90% in incidence [44,45]. These promising findings created renewed excitement that the ever growing HIV epidemic in South Africa could be stopped through scaling-up access to treatment, implying the need for careful evaluation of the public health implications of these findings.

In this thesis, we will examine the public health implications of effects of ART on survival and transmission in South Africa by using a mathematical model. In addition, we also examine the public health implications of RV144-like vaccines in South Africa, and the impact of the ART scale-up on the age composition of the HIV epidemics in all 43 sub-Saharan African countries.

In the remainder of this introductory chapter, we will first discuss HIV pathogenesis and the effects of ART on disease progression and transmission in more detail, followed by a description of mathematical modeling methods and the study site in South Africa. We close this chapter by formulating the main aim and research questions addressed in this thesis.

1.2 Pathogenesis and antiretroviral therapy

Pathogenesis

HIV is a retrovirus, consisting of two identical RNA strands [46]. The virus is transmitted through contact with body fluids from an infected individual, and can pass the mucus membranes in the genitals and rectum, or may pass through cuts or sores upon contact [7]. In the body, the virus targets CD4-receptor-bearing cells, including T-helper cells, monocytes, dendritic cells, and microglia, which are important cells in the immune system of the host [1,2,47-49]. The CD4 protein acts as a binding site for the viral gp120 envelope glycoprotein, which allows the virus to enter the cell (steps 1 and 2 in figure 1.2). Within the host cell, the RNA of the virus is translated to DNA through the reverse transcriptase enzyme, and the viral DNA is subsequently incorporated in the host DNA (steps 3 and 4 in figure 1.2) [46]. Next, the DNA transcription mechanism of the host is used to make new viral RNA strands, which are assembled and released by the cell to infect other CD4+ cells (step 5, 6, and 7 in figure 1.2) [46]. The protective mechanisms within the host cell senses an infection, in response to which the cells eventually goes into apoptosis, or programmed cell death [50].

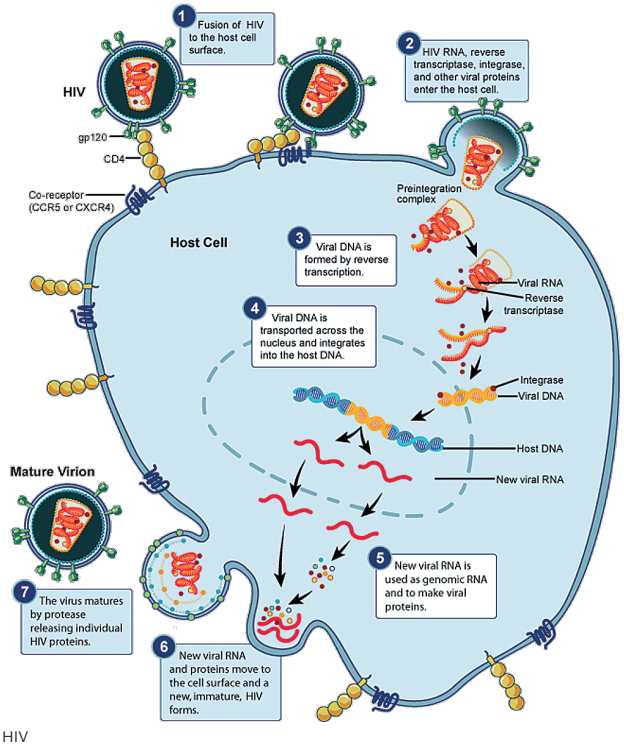

Figure. 1.2. Life cycle of HIV

During the first few months after an individual got newly infected - the so-called 'acute phase' or 'primary infection' - high viral loads are found in the patient as the virus is allowed to replicate and infect CD4 T cells unchallenged (red line in figure 1.3) [51]. CD4 T cells die at high rates, and the circulating number of CD4 T cells (CD4 cell count) declines rapidly (blue line in figure 1.3). However, after several weeks or months, the adaptive host immune system fights back through the development of virus-specific CD8 T cells which eventually reduce HIV viral loads [47,48]. A period of clinical latency starts (figure 1.3), which last for about 6 to 8 years on average [52]. Although this asymptomatic phase is characterized by relatively low viral loads and recovering CD4 cell counts, viral replication continues at high rates, exceeding the body's capacity to produce virus specific CD8 T cells [47,48]. As a result, the immune system gradually begins to fail, levels of circulating CD4 T cells decline, and HIV viral loads increase again (fig 1.3). CD4 T cells have essential regulatory and effector functions in the immune system. Hence, the gradual destruction of the CD4+ T cells eventually results in overall immune failure, and the system is no longer able to fight other pathogens that would not cause disease in a healthy individual. Full blown AIDS develops as the damaged immune system is no longer capable of producing CD8 T cells, viral loads exponentially increase, and numerous specific and non-specific symptoms occur. Common opportunistic infections in patients with AIDS include herpes simplex virus (HSV), varicella-zoster virus, Toxoplasma gondii, JC-virus, and Cryptococcus neoformans. The average survival time of a patient with AIDS is about 1 year [53].

In addition to indicating clinical progression, the HIV viral load in an individual also predicts the transmission potential of the virus during an unprotected sexual contact, as higher viral loads are associated with higher probabilities of HIV transmission [54,55]. Consequently, transmission probabilities vary during the course of the disease. Acute infection - which is characterized by very high viral loads - thus has a relatively high transmission potential, while the asymptomatic phase has the lowest transmission potential because here viral loads are significantly reduced [56]. As viral loads increase again during the symptomatic phase, transmission probabilities also go up. Finally, the high viral loads in the AIDS stage again predict high transmission probabilities, yet sexual activity is usually substantially lower due to severe symptoms [57].

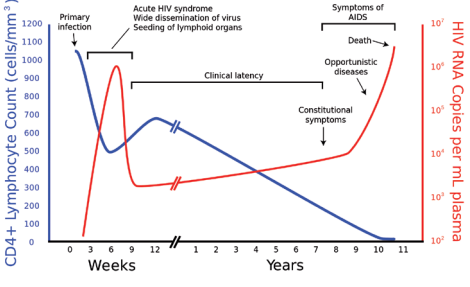

Figure 1.3. HIV natural history in an infected individual. The blue line gives the progression of CD_4 cell counts during the course of the diseases, while the red line indicated progression of viral loads.

Antiretroviral therapy

Although HIV cannot be cured, effective combination antiretroviral therapy (ART) prolongs the life of an infected individual close to general life expectancy [41,58,59]. ART works by inhibiting viral replication, and different types of antiretrovirals that target different parts in the HIV lifecycle are given in combination in order to maximize effect. As viral loads are decreased due to the interruption of viral replication under successful treatment, the immune system is allowed to recover and usually patients on successful therapy will have increased CD4 cell counts after a few months [60], which in turn is associated with better health and prolonged survival [61].

Because ART effectively reduces viral loads, individuals on treatment are also substantially less infectious. ART drugs are already widely used and recognized as a highly cost-effective intervention to prevent transmission from an infected mother to her unborn child [62], and it is becoming evident that ART also effectively reduces the sexual transmission of HIV. Several observational studies showed that transmission probabilities are about 90% lower in stable discordant couples in which the infected partner is on treatment [44,45,63], and Montaner et al show that a lower community viral load due to ART is associated with a lower incidence of HIV [64]. Finally, one randomized controlled trial has shown that ART can reduce HIV transmission rates to up to 96% if treatment adherence and viral suppression are perfect [42].

The combination of increased survival and decreased per-act transmission probability will result in a substantial change in HIV epidemics as treatment access is increased. Some of these changes have already been observed in high-income countries. Here, ART has been available since the mid-90s and - due to reduced transmission and increased survival - the HIV epidemics have aged: about 30% of HIV-infected people in the United States was aged over 50 years in 2008, while this proportion was only 17% in 2001 [65]. This has important consequences for the organization of care, as HIV-infected elderly often require specialized care because of multiple co-morbidities. In addition, HIV-infected people show signs of 'accelerated aging', resulting in higher rates of non-communicable diseases such as cardiovascular diseases, non-AIDS related malignancies, osteoporosis, and liver- and kidney failure [66-68]. In South Africa and SSA, ART only became widely available at around 2004. Since then, the ART scale-up has expanded rapidly, from only 300,000 people on treatment in 2003 to nearly 5 million in end 2010 [69]. Given the size of the epidemic in SSA, changes in the age-composition of the HIV-infected population will have important implications for the organization of care in the sub-continent. In this thesis, we will examine how ART will change the age composition of the HIV epidemics in SSA and South Africa.

Treatment initiation

The timing of treatment initiation for HIV-infected individuals is subject to an important and ongoing debate [59,70-72]. Once initiated on treatment, an infected individual should continue ART for the rest of his/her life in order to maximize viral suppression and reduce resistance development, which makes ART very resource intensive. In addition, HIV-infected individuals live for many years without any symptoms and low levels of circulating virus. Treatment for these

individuals will produce less clinical benefits compared to patients who are at later stages of the disease and experience symptoms. On the other hand, patients at late stage of infection who initiate treatment often incur more health care costs as they require additional care for symptoms and opportunistic infections, while starting treatment in the asymptomatic period is relatively cheap [73,74]. Finally, the public health benefits of reduced transmission probabilities are an argument to treat all HIV-infected individuals, regardless of disease stage or CD4 cell count. However, the huge amount of resources required to treat all infected individuals in countries like South Africa might not outweigh these benefits.

Currently, treatment initiation is guided by the level of immunosuppression of the patient, which is measured by the number of circulating CD4 cells in the blood. A typical healthy individual will have about 1100 CD4 (95% CI: 610 to 2100) cells per micro liter of blood (cells/μL) [75]. In the past, guidelines specified that treatment should be initiated when the CD4 cell count drops below 200 cells/μL. However, in 2009 the WHO changed its guidelines to provide treatment for all HIV-infected individuals with a CD4 cell count of ≤350 cells/μL because of evidence that this will improve clinical outcomes for the patient [76]. As treatment will reduce infectiousness and increase survival, it seems obvious that an increase in number of people on treatment through earlier initiation will have both clinical and public health benefits. However, an increase in the number of people on treatment will also increase overall treatment costs. It is therefore important to determine whether the benefits of the new WHO treatment guidelines outweigh the need for more financial resources, and thus whether it would make sense for South Africa to adopt these guidelines. In this thesis, we address the potential financial and epidemiological impact of the new WHO treatment guidelines compared to continued treatment initiation at ≤200 cells/μL in South Africa.

In addition, we also examine the costs and effects of treating all HIV-infected individuals, regardless of CD4 cell count, in order to substantially reduce transmission. Universal test and treat (UTT), an intervention that involves annual screening and immediate ART for all HIV-infected individuals regardless of clinical staging and CD4 cell count, has been proposed to eliminate the HIV epidemic in South Africa within as little as 7 years [77]. However, this mathematical modeling study by Granich and colleagues was heavily criticized [78-84], and subsequent modeling studies of this promising intervention gave different results [85-87]. In this thesis, we will examine the implications of differences in model structures and assumptions, so as to arrive at the best possible predictions of the long-term impact of UTT and determine whether expanded access to ART can eliminate HIV in South Africa.

1.3 Mathematical modeling of HIV and ART

Mathematical modeling can be used to determine the epidemiological and public health impact of ART and to compare the relative impact of various strategies [88], and several studies have already explored the impact of ART on HIV epidemics in SSA [77,86,87,89-91]. In 2002, Velasco-Hernadez et al were the first to suggest that widespread use of ART can reduce R0 to below 1 (suggesting that the infection will eventually die out), even in high endemic settings [91],

yet Baggaley et al concluded in 2006 that ART cannot be seen as a direct transmission prevention measure, regardless of the extent of the ART roll-out [89]. However, in 2009, Granich et al showed that universal screening of all adults and immediate ART for all HIV-infected people could eliminate the HIV epidemic in South Africa in no less than 7 years [77].

Although many have investigated the impact of ART in high endemic settings using mathematical models, most of these models are population based deterministic models that incorporate only limited or no heterogeneity in risk of HIV between individuals. These models are often easy to solve and can be used to investigate steady-state situations, yet they ignore random chance and individual heterogeneities. HIV epidemics and HIV transmission events are complex, and the probability of acquiring HIV depends on a lot of factors, including consistency in condom use, the STI status of the individual, circumcision status of the male partner, and the underlying sexual network. In addition, chance plays a role, as the probability of an HIV transmission event during an unprotected sex act in a serodiscordant couple relatively low [56]. Dodd et al showed, in a simple deterministic model, that the rate of mixing between low-risk and high-risk individuals is an important determinant of the amount of incidence reduction achieved by widespread ART use [86]. Therefore, to adequately investigate the impact of ART on the HIV epidemic in South Africa and other countries in SSA, a detailed, stochastic microsimulation model is needed that tracks individuals rather than population groups, and allows for heterogeneities in HIV risk between individuals.

STDSIM

STDSIM is an event driven microsimulation model of the spread and control of HIV that has been used extensively in the past to evaluate behavioral interventions [92,93], syndromic treatment for STIs [35,36], male circumcision [27], to explain different HIV epidemics in sub-Saharan Africa [94], and to determine the impact of mobility and migration on HIV epidemic dynamics [95]. The model simulates the life-history of several thousands of individuals in a dynamic population, in which they can have sexual relationships with someone from the opposite sex. During unprotected intercourse within these relations, HIV and other STIs can be transmitted. There are three different types of relationships in the model: (i) long term ('steady') relationships, resembling marriage; (ii) short term ('casual') relationships; and (iii) one-off contacts between a female commercial sex worker (CSW) and a male client. Together, the population thus forms a dynamic sexual network in which HIV spreads. In this thesis, we will use the STDSIM model to determine the impact of ART on HIV epidemics in South Africa and other countries in SSA.

The model consists of four modules: demography, sexual behavior, transmission and natural history, and interventions. The demography module implements the processes of birth, death, and migration. Processes for initiation and dissolution of sexual relationships, for mixing according to age preference, for sexual contacts within relationships and for sexual contacts between female sex workers and their male clients are defined in the sexual behavior module. In the transmission and natural history module, transmission probabilities per sexual contact are specified for HIV and 5 other STIs: chancroid, chlamydia, gonorrhea, syphilis and HSV-2. Finally, the interventions module

specifies the timing and effectiveness of control measures in curbing transmission (e.g. condom use, circumcision, STI treatment, lower partner change rates) or enhancing survival (e.g. antiretroviral therapy). Model runs start in the year 1910 with a predefined initial population composition. For the purpose of the research questions in this thesis, we expanded the model to include the possibility to provide ART based on CD4 cell counts of HIV-infected individuals. We used data from the Africa Centre for Health and Population Studies in rural KwaZulu-Natal, South Africa, to quantify our model (see 1.4 for description of the data).

A description of the ART component of STDSIM, together with a description of how the model was quantified to represent a rural South African area can be found in Supplement I – Quantification of STDSIM to rural KwaZulu-Natal. A detailed description of all modules of STDSIM, as well as their application in quantifying the national South African HIV epidemic are described in Supplement II – STDSIM and its application to South Africa.

1.4 The Africa Centre for Health and Population Studies

The Wellcome Trust Africa Centre for Health and Population studies is a research center in rural KwaZulu-Natal, South Africa (figure 1.4) that maintains a population based cohort of about 85,000 people in which all relevant demographic and epidemiological data on HIV are collected on an annual basis [96]. The surveillance area is located near the market town of Mtubatuba in the Umkanyakunde district of KwaZulu-Natal, and covers about 438 square kilometers [97]. The area is characterized by a very high HIV prevalence [98] and incidence [6]. HIV prevalence peaked in women aged 25-29 at around 50% in 2004 [96].

The Centre also runs - in cooperation with the South African Department of Health - the Hlabisa HIV Treatment and Care Program, an ART treatment program consisting of 17 primary health care clinics (PHCs) and one district hospital, spanning an area with a population size of about 228,000 people [99]. The local hospital (Hlabisa hospital) has nearly 300 beds. In the HIV Treatment and Care Program, all HIV-infected people are monitored and relevant data on their clinical progression are recorded. The scale-up of ART treatment started in late 2004, and in 2010 nearly 20% of all HIV-infected people in the area were initiated on treatment [100,101]. As a result of the rapid and effective scale-up, mortality rates in the population aged 25-49 years has declined substantially [102]. The various databases developed and maintained at the Africa Centre are a valuable source for data on demographic structure, HIV prevalence, sexual behavior, and ART coverage that are essential in model quantification. In this thesis, we will use that data to quantify model parameters and validate model output. The quantification of the model to the HIV epidemic in rural KwaZulu-Natal is described in Supplement I – Quantification of STDSIM to rural KwaZulu-Natal.

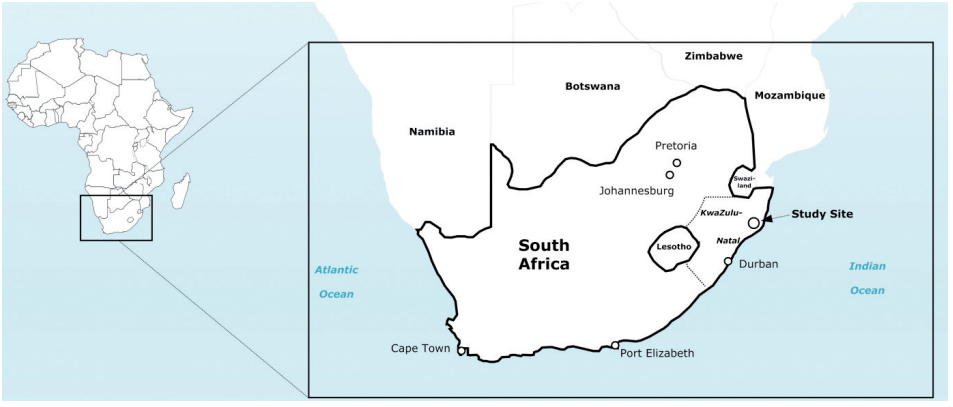

Figure 1.4. Location of study site in South Africa

1.5 Aims

The overall aim of this thesis is to investigate the impact of ART on HIV epidemic dynamics in South Africa and other countries of sub-Saharan Africa. We formulate the following research questions:

1. When should treatment with ART for HIV infected individuals be initiated in order to optimize public health benefits and resource allocation?
2. What financial and human resources are needed for universal access to treatment under different ART treatment strategies in South Africa?
3. Can ART eliminate the HIV epidemic in South Africa?
4. What is the impact of ART on the age composition of the HIV epidemic in sub-Saharan Africa?

In addition to the main aims, we also investigate the potential impact of the RV-144 vaccine, the only HIV vaccine demonstrated to be effective in a randomized controlled trial [16], on the HIV epidemic in KwaZulu-Natal, South Africa. We use the STDSIM model quantified with data from the Africa Centre to address aims 1, 3, and 4. In addition, we performed a time-motion study on health care workers in HIV clinics within the Hlabisa HIV Treatment and Care Program to address aim 2, and developed a quantification of the HIV epidemics in all sub-Saharan African countries to further investigate aim 4.

1.6 Structure of the thesis

Chapters 2 and 3 address research questions 1 and 3. In chapter 2, we compare the epidemiological and financial impact of the WHO treatment guidelines of starting ART at a CD4 cell count of ≤350 cells/μL to continued treatment at ≤200 cells/μL in rural KwaZulu-Natal. In chapter 3 we look at the impact of UTT and ART at ≤350 cells/μL in South Africa as a whole, and look at both

the occurrence and timing of elimination and the cost-effectiveness of UTT compared to ART at ≤350 cells/μL.

Chapter 4 addresses research question 2. We performed a time-motion study in ART clinics in South Africa to determine the doctor- nurse- and counselor-time needed for delivering ART to individual patients, and extrapolate these results to make estimates regarding the number of doctors, nurses and counselors needed in South Africa to achieve universal access under different eligibility criteria.

Chapter 5 describes the study on the impact of the RV-144 vaccine on the HIV epidemic and ART treatment costs in KwaZulu-Natal, South Africa.

Chapters 6 and 7 address research question 4. In chapter 6, we explore the impact of the current ART roll-out on the age composition of the HIV epidemic in rural KwaZulu-Natal, and in chapter 7 we determine the impact of different scale-up scenarios on the age-specific HIV prevalence and trends in total numbers of infections in 43 SSA countries.

The answers to the research questions, a general discussion, a critical appraisal of STDSIM, and overall conclusions and recommendations are given in chapter 8.

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2. The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa

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Supplementary material at: Supplement I: Quantification of STDSIM to rural KwaZulu-Natal

Abstract

Background

Since November 2009, WHO recommends that adults infected with HIV should initiate antiretroviral therapy (ART) at CD4 cell counts of ≤350 cells/μl rather than ≤200 cells/μl. South Africa decided to adopt this strategy for pregnant and TB co-infected patients only. We estimated the impact of fully adopting the new WHO guidelines on HIV epidemic dynamics and associated costs.

Methods and Findings

We used an established model of the transmission and control of HIV in specified sexual networks and healthcare settings. We quantified the model to represent Hlabisa sub-district, KwaZulu-Natal, South Africa. We predicted the HIV epidemic dynamics, number on ART and program costs under the new guidelines relative to treating patients at ≤200 cells/μl for the next 30 years. During the first five years, the new WHO treatment guidelines require about 7% extra annual investments, whereas 28% more patients receive treatment. Furthermore, there will be a more profound impact on HIV incidence, leading to relatively less annual costs after seven years. The resulting cumulative net costs reach a break-even point after on average 16 years.

Conclusions

Our study strengthens the WHO recommendation of starting ART at ≤350 cells/μl for all HIV-infected patients. Apart from the benefits associated with many life-years saved, a modest frontloading appears to lead to net savings within a limited time-horizon. This finding is robust to alternative assumptions and foreseeable changes in ART prices and effectiveness. Therefore, South Africa should aim at rapidly expanding its healthcare infrastructure to fully embrace the new WHO guidelines.

2.1 Background

WHO has recently (November 2009) adopted new guidelines calling for earlier initiation of antiretroviral therapy (ART) for people infected with HIV [1]. Under the old guidelines, patients with a CD4 cell count of ≤200 cells/μl were eligible to initiate ART. The revised guidelines call for ART initiation when CD4 cell counts fall to ≤350 cells/μl. In April 2010 [2], South Africa adopted the new WHO treatment guidelines for pregnant women and for patients with TB co-infection, but decided at this time that the country could not expand the eligibility to all patients as this would overburden the healthcare infrastructure. For non-pregnant and non-TB HIV infected patients, the old strategy of ART at CD4 cell counts ≤200 cells/μl remains [3].

Little is known about what impact the new WHO treatment guidelines will have on HIV epidemic dynamics and costs, especially in the long run. On the one hand ART reduces mortality and morbidity of the individual [4-6], and may reduce transmission of HIV through the accompanying reduction in viral load and thus infectivity [7-9]. On the other hand, longer survival of HIV patients increases the duration of infectiousness. While initial costs of adopting the new guidelines will be greater because of the increased number of people now eligible for treatment, in the long run costs may be saved because of the reduced number of new infections. Moreover, the initial costs per patient are generally lower when treatment is initiated earlier as patients require less additional care, e.g. for treatment of opportunistic infections [10, 11].

With an estimated 5.7 million people living with HIV and an overall HIV prevalence of 18% in adults, South Africa is home to the largest population living with HIV in the world [12]. Within South Africa, KwaZulu-Natal (KZN) is the most heavily affected area, with prevalence rates in 2004 of about 24% for the adult population, peaking at 51% in women aged 25-29 years [13, 14]. The Africa Centre Demographic Information System (ACDIS) contains high quality data on demography, sexual behavior, and HIV status of about 85,000 people in the largely rural Umkhanyakunde District of KZN [15]. ART rollout in this area has expanded dramatically in the past years [16], with about 7,500 people initiating ART by end 2008 [17], and a substantial decline in HIV-related and overall mortality [18].

In this paper we estimate the long-term impact of the full WHO guidelines on the dynamics of the HIV epidemic and healthcare costs in the Hlabisa sub-district of Umkhanyakunde in KZN, South Africa. We use STDSIM, an established microsimulation model that simulates the spread of HIV and other STIs in a population of individuals interacting through a network of sexual relationships [19, 20]. We quantify the potential net costs and life-years saved due to the new WHO guidelines compared to treating patients at ≤200 cells/μl.

2.2 Methods

Quantification of the model

We used data from ACDIS [15] and Hlabisa Treatment and Care Program [16] to represent demography, sexual risk behavior, and the ART rollout in the Hlabisa sub-district. A detailed

description of the model, quantifications, and data used can be found in the Supplement I: Quantification of STDSIM to rural KwaZulu-Natal

In the model, HIV patients are put on ART when they seek care and their CD4 cell counts are at a given threshold (≤200 or ≤350 cells/μl). We assumed ART to decrease infectivity by 92% [7, 21, 22]. The survival on ART was assumed to be three times the ART naïve survival [6]. Health seeking behavior was fitted such that the modeled CD4 cell count at the first test accurately reflects data from the Hlabisa Treatment and Care Program [16]. We assumed a dropout rate (proportion of patients on ART stopping treatment permanently) of 1.27% per year, reflecting 5% of patients lost to follow-up after four years, as reported by Houlihan et al [16]. The ART component of the model is illustrated in figure I.1 (see Supplement I: Quantification of STDSIM to rural KwaZulu-Natal). In the model, ART is introduced in 2004, and rolled-out in accordance with the actual rollout among the 17 primary care clinics in Hlabisa sub-district.

Costs

We analyzed costs from the perspective of the Hlabisa Treatment and Care Program. In the absence of detailed local data, we used published data from the public sector ART programs in Cape Town, South Africa, consisting of ART costs stratified by CD4 cell count at initiation and number of years on treatment (table 2.1) [10, 23].Cost values reported in these studies include costs for ART provision, treatment of opportunistic infections, outpatient visits, and inpatient days -, and consist of costs for equipment, medication, wages of healthcare personnel, logistics and infrastructure. We excluded non-healthcare costs, such as patient time and lost wages. Costs of patients on ART were stratified by CD4 count at initiation, which reflects the fact that patients who start treatment at lower CD4 counts are sicker and therefore in need of additional health resources (inpatient and outpatient visits, and non-ART medication). This increased medical cost of starting at a lower CD4 cell count is most prominent in the first year of ART, and decreases in subsequent years [10]. We assumed this difference to disappear after three years. In addition, we added a one-time pre-ART cost, reflecting the cost of care surrounding treatment initiation [10]. For patients seeking care with CD4 cell counts between 201 and 350 cells/μl and not eligible for treatment, we included costs for HIV testing and treatment for opportunistic infections [23]. For patients testing with CD4 cell counts of >350 cells/μl, we only assumed annual costs for CD4 monitoring [10]. Finally, we added a one-time cost of dying (hospitalization prior to death) for all HIV-related deaths, irrespective of ART status or CD4 count at ART initiation [10].

ART costs were updated to reflect present ART price levels [24]. All other costs were standardized to January 2010 prices using South Africa's consumer price index [25]. We then converted all costs into US dollars using the average exchange rate for January 2010 of US$1 to R 7.42 [26]. Costs in future years were discounted at an annual rate of 3% [27].

CD4 count (cells/µl) at ART initiation	Per patient annual ART costs (US$)			
	Pre-ART	First year	Second and third year	Subsequent years
0-100	495	3,664	1,435	1,095
101-200	495	3,060	1,284	1,095
201-350	495	2,304	1,095	1,095

Table 2.1. Overview of costs input values used in this study. The perspective of the Hlabisa Treatment and Care Program was chosen. Costs are stratified by CD4 count at antiretroviral therapy (ART) initiation, and include costs of diagnostic testing, ART provision, treatment of opportunistic infections, outpatient visits, and inpatient days. In addition, some costs were included for patients seeking care but not (yet) eligible for ART: (1) 1,165 US$ per year for patients with CD4 counts of 201-350 cells/µl, reflecting costs of testing and treatment of opportunistic infections; and (2) 104 US$ for patients with CD4 cell counts of >350 cells/µl reflecting costs of CD4 cell count monitoring. Furthermore, a one-time cost of dying of 1,197 US$ was included for each HIV-related death, irrespective of being on treatment and CD4 count at initiation.

Simulations

We predicted the impact of increasing the threshold for treatment initiation to ≤350 cells/µl starting by mid-2010, versus continuing with treatment initiation at ≤200 cells/µl, on HIV epidemic dynamics, number of people on ART, and associated annual costs for adults aged 15+ in the Hlabisa Treatment and Care Program in the Hlabisa sub-district until 2040. We then calculated the cumulative net costs and cumulative number of life-years saved by starting treatment at higher CD4 counts. To roughly compare the new WHO strategy to the current South African strategy, we also assumed a scenario that a fraction of 19% of the patients with CD4 cell counts of 201-350 cells/µl is eligible for treatment in the ≤200 cells/µl scenario (see Supplement I: Quantification of STDSIM to rural KwaZulu-Natal).

To correct for the stochasticity of the model, we used the average result of 1000 runs. We also presented the results of 50 individual runs to visualize the variation in model predictions. Each run was based on about 35,000 simulated individuals. Absolute values (number of people on treatment, annual costs, and life-years saved) were multiplied by 6.5 to represent the situation of Hlabisa sub-district, which has 228,000 inhabitants [16].

Sensitivity analysis and scenario analysis

We performed a univariate sensitivity analysis on all key parameters. Our assumption that ART reduces infectiousness by 92% is based on the most recent evidence [7, 21, 22]. However, others have assumed a reduction of 99% [28], while less reduction has also been opted [29]. Therefore, we also ran the model using reductions of 80% and 99% respectively. Dropout rates in the Hlabisa sub-district are relatively low (1.27% per year), likely due to the experimental nature of the area. Therefore, we also assumed a dropout rate of 10% per year, which is more representative for the rest of South Africa [30], and a lower value of 1% per year. Furthermore, we made predictions for a 10% higher and 10% lower overall partner change rates (see Supplement I: Quantification of STDSIM to rural KwaZulu-Natal) to reflect the results for different endemicity levels, where 10% lower leads to an HIV prevalence close to that for South Africa as a whole. All other parameters (health seeking rates, survival on ART, ART costs, costs of dying, costs of not on ART) were varied by a factor 2/3rd to determine the lower bound, and 3/2nd to determine the upper bound.

We also performed a multivariate sensitivity analysis on 5 parameters related to the HIV epidemic and ART (overall partner change rates, survival on ART, infectivity on ART, dropout rates, and health seeking behavior rates). For each parameter we randomly selected values from Weibull (for durations) or Beta distributions (for proportions). The average of each distribution is our point estimate, and 2.5% and 97.5% values represent the lower and upper bounds chosen in the univariate sensitivity analysis. We ran 1,000 randomly selected combinations of parameters drawn from the distributions and used the 25th and 975th value to represent the bounds of the 95% confidence interval over our main outcome.

Furthermore, we assumed 4 scenarios of foreseeable future developments that could influence ART programs: (1) development of more effective ART (99% reduction in infectiousness, and increased survival by a factor 4 relative to ART naïve HIV patients); (2) further reduction in ART prices (reduced ART costs by 20%); (3) risk compensation in response to reduced threat of HIV (condom use of 10% in casual contacts); (4) resistance development (increased ART costs by 20% due to more need of second- and third-line treatment options). All scenarios are assumed to take effect in 2015.

2.3 Results

Our model was able to accurately simulate the demographic structure, sexual behavior dynamics, and HIV and STI prevalence in the Hlabisa sub-district both before and after the ART rollout in 2004 (figure 2.1). Two differences between model and data can be seen. First, the model predicts about 25% more men in the 60+ age group than observed (figure 2.1A), possibly as a result of a higher background mortality rate in this group compared to the Coale-Demeney life table used. However, the contribution of this age group to the overall HIV epidemic in the area is limited, so this discrepancy will not affect our main results. Second, the reported number of recent sexual partners of women is much lower than predicted by the model (figure 2.1B). This is likely a result of underreporting, something that is commonly observed in studies on reported sexual risk behavior [34-37]. The prevalence of classic STIs, which is often viewed as a more accurate indicator of risk behavior, accurately fits the data for women (figure 2.1C). As a consequence of the good fit of the underlying demography (figure 2.1A), risk behavior (figure 2.1B) and co-factors (figure 2.1C), the predicted HIV prevalence is very close to that observed, both over time (within 0.3% to 0.9% between 2004 and 2009; figure 2.1D) and within age and sex groups (figure 2.1E). Furthermore, the cumulative number of people initiating treatment in the model accurately reflects the actual treatment initiation numbers observed in the program (figure 2.1F). Finally, the model accurately fits CD4 cell count distributions as observed in the Hlabisa Treatment and Care Program, both at the time of initial testing (figure 2.1G) and one year after initiating ART (figure 2.1H).

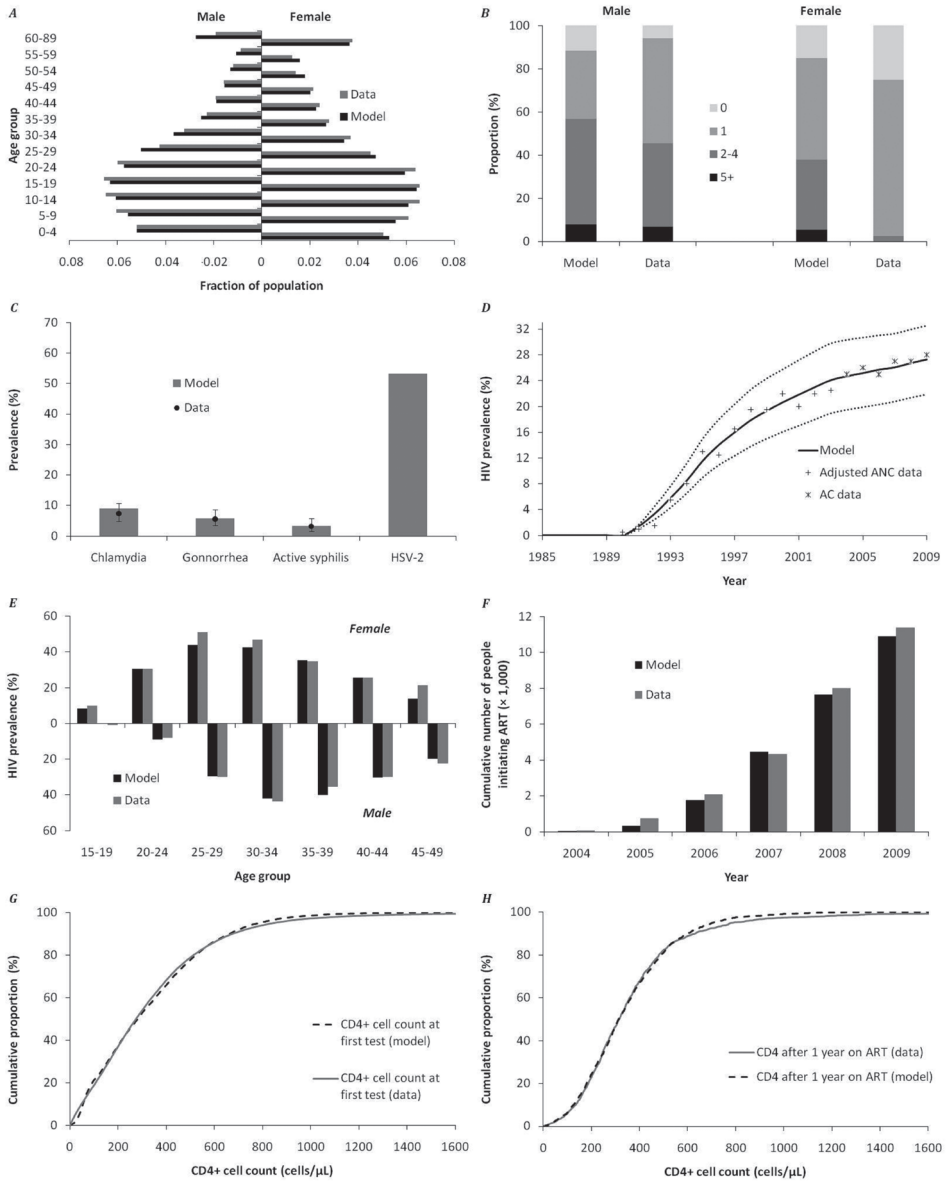

Figure 2.1. Comparison of model predictions with data of the HIV-epidemic and ART rollout in Hlabisa sub-district of the Umkhanyakunde district in KwaZulu-Natal (KZN), South Africa. A: Modeled and actual demographic structure in 2006. Data derived from Muhwava & Nyirenda [31]; B. Total number of partners in the last 12 months in men and women aged 20-49 years in the model versus total number of reported partners derived from Todd et al [32] C. Modeled and observed prevalence of classic STIs in women aged 15-49 in KZN. Data derived from White et al [33]. D: Modeled and actual HIV epidemic in KZN. Antenatal Care (ANC) data were adjusted by applying a 1:0.6 ratio of ANC prevalence versus Africa Centre (AC) prevalence in 2004 to all data points. ANC data derived from UNAIDS [12], AC data from Bärnighausen et al [13]. Prevalence in 2005-2009 is from unpublished ACDIS sero-surveillance data (age specific data, adjusted for population age-structure). Dotted lines represent the predicted HIV-prevalence when assuming a 10% increase and 10% decrease in the assumed overall partner change rate ('promiscuity factor'). The latter roughly reflects the HIV epidemic of South Africa as a whole (prevalence of 18% in 2004) E: Modeled and actual age- and sex-specific HIV prevalence in 2004. Data derived from Bärnighausen et al [13]; F. Cumulative number of people initiating treatment in the Hlabisa Treatment and Care Program, model versus unpublished data [16]; G. Cumulative distribution of CD4 cell counts at first test, model compared to data for 2007 to 2009. Data derived from the Hlabisa Treatment and Care Program [16]. H. Cumulative distribution of CD4 cell counts after 1 year on ART, model compared to data. Data derived from the Hlabisa Treatment and Care Program [16].

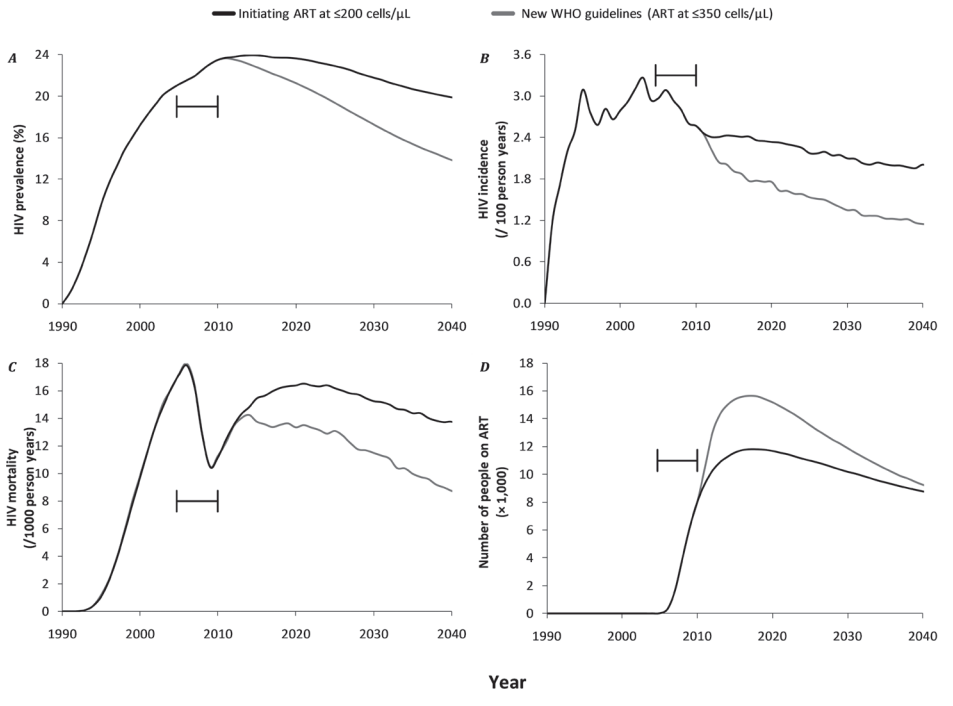

Figure 2.2. Projected impact of ART at CD4 cell counts of ≤200/µl (black) and the new WHO treatment guidelines of ART at CD4 cell counts of ≤350/µl (gray) on HIV epidemic dynamics in the Hlabisa sub-district of the Umkhanyakunde District, KwaZulu-Natal, South Africa, 1990-2040. A. HIV prevalence; B. HIV incidence; C. HIV mortality; D. Total number of people on ART. The results reflect the average of 1000 model runs and concern adults (≥15 years). The bar indicates the timing of the initial start of ART distribution in the first clinic (end 2004) till full coverage of all 17 clinics in the area (mid 2010).

Figure 2.2 indicates that continued initiation of ART at CD4 cell counts of ≤200 cells/µl will result in a modest decline of the HIV epidemic over the coming years. After peaking at 24% in 2015, HIV prevalence in adults (aged 15+) is predicted to reduce to 20% in 2040 (figure 2.2A). Incidence will continuously decrease from 2.6/100 person years in 2010 to 2.0/100 person years in 2040 (figure 2.2B). Although mortality rates were almost halved over the period 2004-2009, which is consistent with observations [18], we predict a rebound in 2010, associated with mortality in patients on ART (figure 2.2C). We expect that by 2018 the number of people on ART would have peaked at 11,000, up from 8,000 on treatment in 2010 (figure 2.2D). The new WHO guidelines of treating patients at ≤350 cells will have a more substantial effect on the epidemic, reducing prevalence to 14% and incidence to 1.5/100 person-years in 2040. Although initially the number of people on ART will peak at about 16,000 in 2018, it will rapidly decline to nearly the same number on treatment in 2040 compared to treatment at ≤200 cells/µl (figure 2.2D).

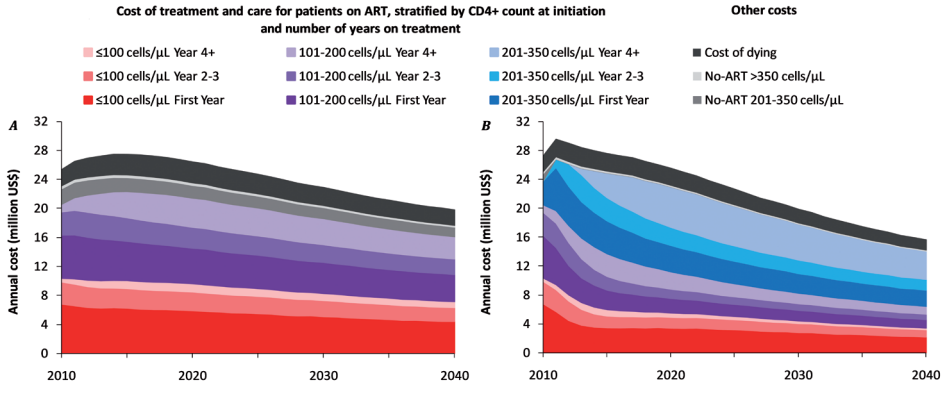

Figure 2.3. Projected cost of the ART treatment and care program in the Hlabisa sub-district of the Umkhanyakunde District, KwaZulu-Natal, South Africa, 2010-2040. A. Annual cost when ART is initiated at ≤200 cells/µl. B. Annual cost when ART is initiated at ≤350 cells/µ. All ART costs concern adults aged 15+ and are stratified by CD4 cell count at initiation and number of years on ART.

Figures 2.3A and 2.3B show the annual costs of treating patients at ≤200 cells/µl and ≤350 cells/µl respectively. Even though the average number of people on ART during the first five years (2011 to 2015) is predicted to be 28% higher under the new guidelines (14,000 versus 11,000, figure 2.2D), the average estimated annual costs are only 7% higher (US$28.6 million versus $26.8 million). This is because costs are mostly incurred by people initiating treatment at ≤100 cells/µl, and under the new WHO guidelines there will be significantly fewer people in this category (figure 2.3B in red). We predict that annual costs of treating patients at ≤350 cells/µl or ≤200 cells/µl will become equal in 2017 (figure 2.3), and the cumulative net costs will reach a break-even point in 2026 (figure 2.4A). Thereafter putting people on ART starting at CD4 cell counts of ≤350 cells/µl will lead to net cost-savings. This break-even point is subject to stochasticity in the model and may be reached between 2020 and 2033 (gray lines in figure 2.4). In addition to these cost-savings, the new WHO treatment guidelines will yield about 160,000 life-years saved by 2040 (figure 2.4B).

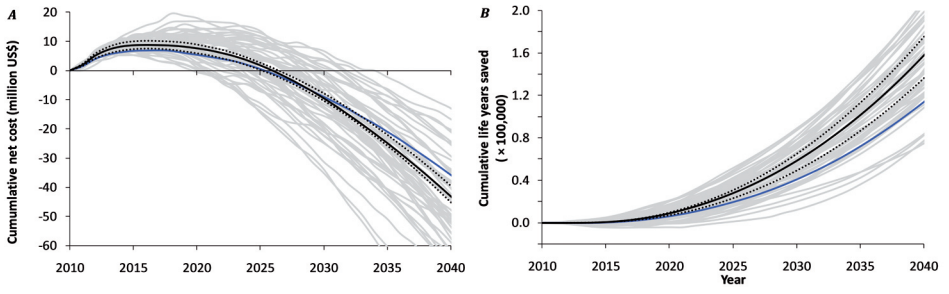

Figure 2.4. Projected net cost and life-years saved of implementing the new WHO treatment guidelines (ART at CD4 cell counts of ≤350/µl) versus the old treatment guidelines (ART at CD4 cell counts of ≤200 cells/µl) in the Hlabisa sub-district of the Umkhanyakunde District, KwaZulu-Natal, South Africa, 2010-2040. A. Cumulative net cost of treating patients at ≤350 cells/µl compared to ≤200 cells/µl. Negative values reflect net cost-savings. B. Cumulative number of life-years saved when treating patients at ≤350 cells/µl compared to ≤200 cells/µl. The black continuous line shows the average of 1000 model runs. Grey lines represent 50 individual runs to illustrate the random variation in model output. Both dotted black lines represent the results for increased and decreased levels of endemicity, when assuming a 10% higher and 10% lower overall partner change rate respectively (see also figure 2.1D). The blue line represents the results of treating patients at ≤350 cells/µl versus a strategy of treating patients at ≤200 cells/µl, together with 19% of patients that report with CD4 of 201-350 cells/µl. This 19% is a crude estimation of the proportion of pregnant women and TB co-infected patients among HIV-patients with CD4 of 201-350, who are since recently eligible to receive ART under the current South African strategy

These findings are not very sensitive to alternative assumptions of key parameters (table 2.2). Changes in cost values have the highest impact on the timing of the breakeven point, but this is limited to only 7 years. The cumulative number of life-years saved is most affected by changes in partner change rates. Similar changes in commercial sex work visits and circumcision rates had less effect on the cumulative number of life-years saved (results not shown). Multivariate sensitivity analysis shows that the uncertainty around our point estimate of the breakeven point ranges between 2023 and 2031 (table 2.2). Alternative scenarios of future developments regarding availability of more effective ART, further reductions in ART prices, risk compensation, and increased resistance development in the near future also have limited impact on both the timing of the breakeven point and the number of life-years saved (table 2.2).

When comparing the new guidelines with the scenario that 19% of HIV patients with CD4 cell counts of 201-350 receive ART (crudely reflecting the current South African policy of providing ART to pregnant and TB co-infected HIV patients), our model explorations show there will still be a break-even point around 2026 (blue line figure 2.4A). The number of life-years saved by 2040 will then be about 120,000 (blue line in figure 2.4B).

Parameter	Value	Timing of breakeven point	Cumulative number of life years saved in 2040 (x 1000)
Baseline	-	2026	158
Univariate sensitivity analysis			
Partner change rates*			
Lower bound	10% decrease	2025	136
Upper bound	10% increase	2026	175
Dropout rates			
Lower bound	1% per year	2026	160
Upper bound	10% per year	2027	138
Health seeking rates*			
Lower bound	Factor 2/3	2030	142
Upper bound	Factor 3/2	2025	165
Infectivity while on ART			
Lower bound	80% reduction	2029	162
Upper bound	99% reduction	2024	158
Survival on ART			
Lower bound	Factor 2/3	2026	155
Upper bound	Factor 3/2	2026	156
ART costs***			
Lower bound	Factor 2/3	2018	N.A.
Upper bound	Factor 3/2	2033	N.A.
Cost of dying			
Lower bound	Factor 2/3	2028	N.A.
Upper bound	Factor 3/2	2025	N.A.
Cost not on ART			
Lower bound	Factor 2/3	2032	N.A.
Upper bound	Factor 3/2	2018	N.A.
Discounting			
Lower bound	1%	2026	N.A.
Upper bound	7%	2031	N.A.
Multivariate sensitivity analysis			
Lower bound	N.A.	2023	112
Upper bound	N.A.	2031	181
Scenario analysis****			
More effective ART	infectiousness on ART reduced by 99%, survival to 4 times ART-naïve survival	2022	145
Further reduction in ART prices	Reduce ART costs by 20%	2022	N.A.
Risk compensation	Condom use reduced to 10%	2027	168
Resistance development	Increase ART costs by 20%	2027	N.A.

Table 2.2. Sensitivity analysis and scenario analysis. Timing of the breakeven point (year) and cumulative number of life-years saved (x 1000) of treating patients according to the new WHO guidelines compared to ≤200 cells/µl are shown. The breakeven point shows when cumulative net cost savings will occur.

* Effects of 10% increase and decrease in partner change rates are displayed as dotted lines in figure 2.1D, 2.4A and 2.4B.
** Applied to all 5 health seeking rates (rh(1) to rh(5), see Supplement I: Quantification of STDSIM to rural KwaZulu-Natal
*** Applied to all cost values displayed in table 2.1
**** All scenarios changes is the scenario analysis take effect in 2015
N.A. = Not Affected

2.4 Discussion

We show that starting ART at ≤350 cells/μl, as recently recommended by WHO [1], will lead to only a modest increase in program costs, but significantly more patients on ART in this rural setting of KwaZulu-Natal, South Africa. Compared to ART initiation at ≤200 cells/μl, initiating ART according to the new WHO guidelines will result in cumulative net cost-savings starting around 2026. This break-even point is robust to alternative assumptions in key parameter values. In addition to net cost-savings, the new guidelines produce a substantial increase in number of life-years saved as well as a more profound decrease in HIV prevalence and incidence.

Our baseline predictions concerning the Hlablisa sub-district could be too optimistic for South Africa as a whole, where dropout rates are higher [30], health seeking behavior is less [12], and endemicity levels are slightly lower [12]. However, the sensitivity analysis shows that these differences have a limited impact on the timing of the breakeven point and the number of life-years saved (table 2.2). This can be explained by the fact that we compare two scenarios (ART at ≤200 cells/μl versus ≤350 cells/μl), which are both largely affected in the same way, so that the comparison between the two remains relatively unchanged. This demonstrates that our main finding of limited initial investments with a breakeven point within a limited time horizon is generalizable to South Africa as a whole.

We realize that the comparative strategy of starting ART at ≤200 cells/μl does not fully represent the current South African policy, since very recently the country announced that pregnant women and TB patients co-infected with HIV should initiate ART at ≤350 cells/μl [2, 3]. However, our model explorations show that when including 19% (roughly the proportion of pregnant women or TB co-infected) of the patients with CD4 between 201-350 in the ≤200 scenario will lead to the same general finding: i.e. modest initial frontloading needed to adhere to the WHO guidelines of treating all with CD4 ≤350 cells/μl, resulting in net cost-savings around the year 2026. The initial investments of expanding the program to include all patients with CD4 cell counts of 201-350 cells/μl are likely to be even less than predicted by our model, because especially TB co-infected patients require more additional care and thus are more expensive than other HIV-infected patients. On the other hand, the projected number of life-years saved in this comparison is somewhat overestimated since ART for pregnant women is beneficial for both the mother and her unborn child [38].

Our baseline calculations are based on the premise that assumption will not change in the future, but it is conceivable that there may be developments that would influence the epidemiological and economic impact of ART. The development of new, more effective ART and further reduced ART prices might improve the distribution and effectiveness of ART [39], while concerns exist regarding risk compensation [40] and resistance development [41]. However, the scenario analysis shows that each of these possible future developments has limited impact on both the timing of the breakeven point and the number of life years saved (table 2.2).

Thus, it is clear that from an economic point of view South Africa should adopt the full WHO guidelines as soon as possible, given the expected net savings within a limited time-horizon. However, there are limitations regarding infrastructural and human resources, which are already stretched under the current efforts of South Africa to provide treatment and care for HIV-infected patients [43, 44]. This was also the reason why South Africa decided not to adopt the full WHO guidelines. Infrastructural expansion may require increased funding, resulting in the postponement of the breakeven point. However, model explorations show that, when adding 10% to the overall annual costs in the first five years of treating patients according to the new WHO guidelines in order to reflect the costs for infrastructural expansion, net cost savings will occur only 6 years later (results not shown). The expected savings achieved by adopting the full WHO guidelines could be a basis to ensure sufficient resources for infrastructural development and increase the pool of health workers through task shifting, decentralization, increased training, and higher salaries [43, 45].

The effect of ART on HIV epidemic dynamics and costs has been explored in a number of other modeling studies [21, 28, 46-48]. However, our microsimulation model allows more accurate modeling of sexual networks, transmission dynamics and STI co-factor effects. It is striking that our model gives such a good representation of the demographic and epidemiological situation of this setting, while only three parameters (overall partner change rate and two parameters for health seeking - see Supplement I: Quantification of STDSIM to rural KwaZulu-Natal) were used to calibrate the model. Moreover, it is reassuring that our model predicts a stable HIV incidence over the period 2003-2007 (figure 2.2B), as reported by Bärnighausen et al [14] and the strong decline in HIV-related mortality during the first years of ART rollout (figure 2.2C) is consistent with Herbst et al [18].

In conclusion, our study provides a strong argument in favor of immediately adopting the new WHO treatment guidelines, rather than starting ART at ≤200 cells/μl, or only implementing the guidelines for specific groups. This is provided that increased efforts are undertaken to increase human resources and healthcare infrastructure. In addition to a reduction in transmission and mortality, and a substantial increase in life-years saved, cumulative net cost-savings for treating patients with CD4 cell counts of ≤350 cells/μl will occur after about 16 years. We show that the new WHO guidelines are beneficial from a financial, epidemiological, and societal point of view, regardless of future developments, and South Africa should therefore aim at rapidly expanding its healthcare infrastructure to fully embrace the new WHO guidelines.

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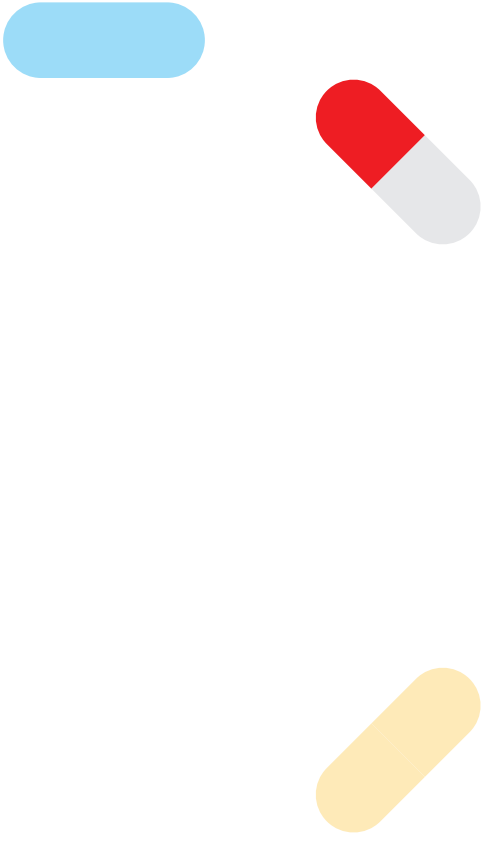

3. Expanded access to antiretroviral therapy leads to elimination of HIV in South Africa, even without universal test and treat

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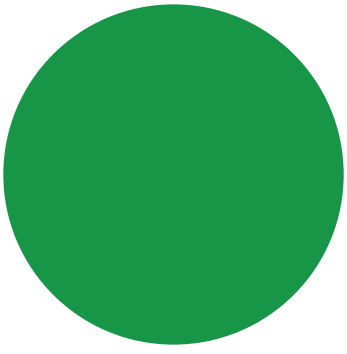

Abstract

Background

Expanded access to antiretroviral therapy (ART) using universal test and treat (UTT) has been suggested to eliminate HIV in South Africa within 7 years. However, the underlying model was criticized widely, and other modeling studies did not always confirm this finding. It is important to better understand the implications of differences in model structures and assumptions, so as to arrive at the best possible predictions of the long-term impact of UTT.

Methods and findings

We developed 9 structurally different mathematical models of the South African HIV epidemic in a stepwise approach of increasing complexity and realism. The simplest model resembles the deterministic model developed by Granich et al, while the most comprehensive model is the stochastic microsimulation model STDSIM, which includes sexual networks and HIV stages with different degrees of infectiousness. Similar to Granich et al, we defined UTT as annual screening and immediate ART for all HIV infected adults, starting in 2012 and scaled-up to 90% coverage by 2019. All models predict elimination, yet those that capture more processes underlying the HIV transmission dynamics predict elimination after 20 to 25 years. Importantly, the most comprehensive model predicts that the current strategy of ART at CD4 count ≤350 cells/μL will also lead to elimination, be it 10 years later compared to UTT. Still, UTT remains cost-effective as many additional life-years will be saved.

Conclusions

Our results confirm previous predictions that the HIV epidemic in South Africa can be eliminated through universal testing and immediate treatment at 90% coverage. However, more realistic models show that elimination is likely to occur at a much later point in time. Also, UTT is a cost-effective intervention, but less efficient than previously predicted because the current ART treatment policy in South Africa alone will already drive HIV into elimination.

3.1 Background

South Africa is home to the largest HIV-infected population worldwide, with nearly 6 million people living with HIV in 2010 [1]. Although extensive efforts to curb the epidemic may have resulted in some decline in the number of new HIV infections among young adults in the past few years [2,3], incidence levels remain considerable. Commitments to achieve universal coverage [4], coupled with a proof of concept that antiretroviral therapy (ART) can be used to prevent onward transmission [5] created renewed excitement that a turning point in the ever growing HIV epidemic could be achieved by expanding access to treatment. 'Treatment as prevention' (treatment of all HIV positive individuals with ART, regardless of CD4 cell count, in order to reduce transmission) - a hypothesized HIV prevention intervention that is currently being tested in community randomized trials [6] - was conceptually designed by mathematical models [7-13]. In 2009, Granich et al suggested that the HIV epidemic in South Africa could be driven into an elimination phase (defined as an incidence of below one new infection per 1,000 person-years) after just 7 years of annual HIV screening and immediate ART for all HIV infected patients (universal 'test-and-treat' - UTT) [9].

In response to these results, other modeling studies also examined the potential impact of a UTT intervention in various settings [14-19]. But there are as many different conclusions as there are models that investigated the issue. As models are profoundly different in many aspects – structure, parameterization, and assumptions about the intervention – it is hard to determine which factors are responsible for the differences [20]. There are several obvious reasons for these discrepancies, such as differences in time horizon of the analysis [14,19], less optimistic assumptions regarding programmatic efficacy [14,18], or alternative assumptions on HIV natural history and heterogeneity in transmission and ART effectiveness [17]. For example, Granich et al assumed a 99.4% reduction in infectiousness of those on ART [9], but later studies suggested that this reduction is likely to be too optimistic [5,21-23]. The HPTN052 trial showed a reduction of 96% [5], with trial participants completely adhering to treatment, which is unlikely in large-scale interventions. A Cochrane review including all observational studies and the trial reported a reduction in transmission of about 86% [23]. Also, the ongoing treatment roll-out according to the recent WHO treatment guidelines of ART at CD4 cell counts of ≤350 cells/μL [24] will already have a profound impact on the HIV epidemic [25,26], making it important to compare the impact of UTT with the current treatment scale-up. Nevertheless, these obvious differences explain only part of the variation between model predictions [20]. As modeling remains essential to further inform public health decision-making, it is vital to better understand the reasons for the discrepancies between models.

We examined the impact of model structure and parameterization on the estimated impact of UTT in South Africa in a highly controlled experiment as follows: we developed 9 structurally different models of the South African HIV epidemic with a standardized core set of assumptions but with gradated degrees of model complexity and realism that span from the very simplest to one of the most comprehensive representations of HIV epidemics (figure 3.1). In all models, we examined the impact of the UTT-intervention suggested by Granich et al [9] and related this to a baseline of no

UTT (i.e. no ART in the simplest models, and ART roll-out at ≤350 cells/μL as currently applied in South Africa in the most detailed model).

3.2 Methods

We developed 4 structurally different main models and 5 sub-models of the South African HIV epidemic through a stepwise approach of increasing complexity and realism (figure 3.1). Model A fully resembles the deterministic 'Granich' model [9], but now simulated using an event-driven stochastic approach. Similar to Granich et al, a prevalence density function is used to account for the scale-up of background prevention interventions - such as increased condom use - to arrive at the observed steady state HIV prevalence [9]. Model B is an age-structured model with age-related demographic projections and variability in infectiousness during disease progression, allowing for the commonly used relative high transmissibility during the acute stage [17]. Model C allows for sexual network structures and heterogeneity in sexual behavior, and the explicit modeling of STI co-factors and male circumcision. In addition, the model allows for increasing rates of condom use in the late 90s/early 2000s, consistent with observations [2,3], to replace the prevalence density function used in models A and B. Model C also uses more up-to-date assumptions regarding effectiveness of ART (infectiousness reduction of 90% [21-23] instead of 99.4%, survival twice as high [27]). Model D resembles the full STDSIM model [25,28], including all of the features in model C as well as ART scale-up as observed in South Africa over the period 2004-2010. For the steps between models A, B, and C, we also examined the impact of adding each single component separately through a series of sub-models (figure 3.1). We fitted all models to the HIV prevalence in the South African adult population (aged 15+) as reported by UNAIDS [1]. The most comprehensive model (model D) is also compared with data on demography [29], sexual behavior [30], age-specific HIV prevalence [31], STI prevalence [32], and observed ART treatment coverage [33]. Details on structure, parameterization, and the fit compared to data for all 9 models are described in supplement II: STDSIM and its application to South Africa.

For all 9 models we predicted the impact of a hypothetical UTT intervention with annual screening of the population and immediate ART for those who are HIV positive, as was done by Granich et al: i.e. the intervention is scaled-up linearly to 90% coverage in 7 years time (2012 - 2019), and there is a dropout rate of 8.5% in the first year of treatment and 1.5% in subsequent years [9]. We assume no further scale-up of other prevention interventions (e.g. condom use, circumcision) after 2012 in all models. Following Granich et al we defined the 'elimination phase' of HIV to start when HIV incidence drops below 1 new infection per 1,000 person-years [9]. Furthermore, we calculated the cumulative number of life-years saved and cumulative net costs of UTT compared to continued scale-up of ART at ≤350 cells/μL in model D, the only model that incorporates enough detail to be able to adequately represent the current scale-up at ≤350 cells/μL in South Africa in the baseline of no UTT. Finally, we performed a sensitivity analysis by varying parameters of HIV natural history and heterogeneity in HIV transmission, the state of the HIV epidemic in South Africa, less optimistic UTT interventions, and using alternative assump-

tions on overall cost- and scale-effects. Details on cost-assumptions and the sensitivity analysis can be found in supplement II: STDSIM and its application to South Africa.

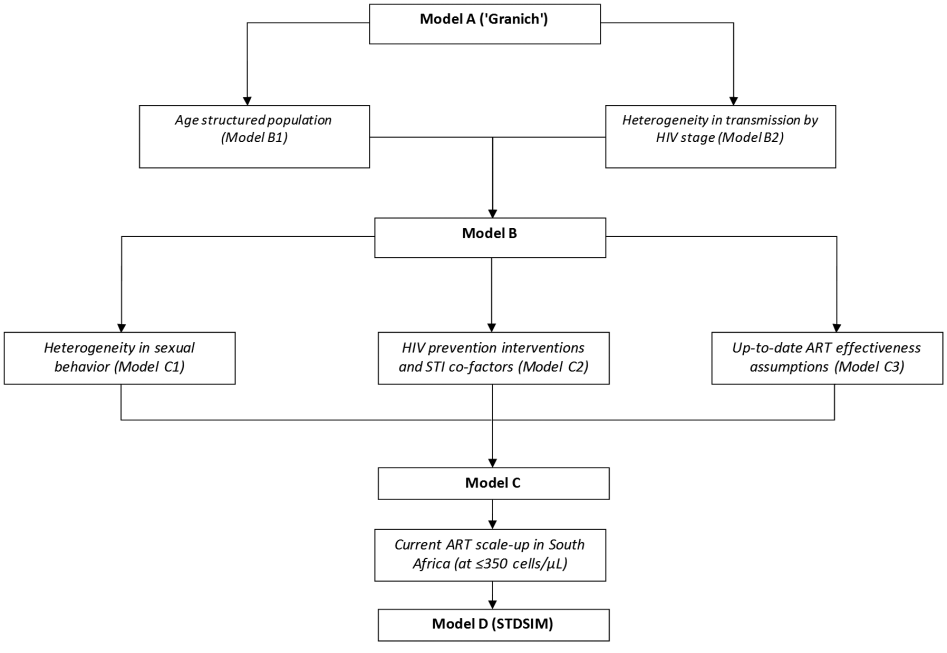

Figure 3.1. Stepwise approach of developing 9 structurally different models through increasing complexity and realism. Model A resembles the deterministic model used by Granich et al [9], now simulated using an event-driven approach. Models A and B are fitted to predict UNAIDS prevalence levels for South Africa by tuning the HIV transmission probabilities and year of HIV introduction. In addition, similar to Granich et al [9], models A and B use a prevalence density function to explain the steady state HIV prevalence observed in South Africa. Models C and D are fitted to represent UNAIDS predicted HIV prevalence by tuning overall partner change rates and the year of HIV introduction. A prevalence density function is no longer used, and scaling-up condom use in the late 90s/early 2000s, introduced in model C2 and consistent with observations [2,3], is now used to explain the steady state HIV prevalence in South Africa. Finally, models C and D allow for more realistic assumptions on ART effectiveness (infectiousness reduction of 90% [21-23] instead of 99.4%, survival twice as high [27]).

3.3 Results

Figure 3.2 (left panels) shows the fit of all models to the HIV prevalence in South Africa as reported by UNAIDS [1], together with the projected impact of annual screening and immediate ART for all HIV infected patients at 90% coverage. All models replicate the HIV prevalence in South Africa in the period 1990 – 2010. However, as a result of the difference in underlying processes in the structurally different models, the corresponding HIV incidence levels are substantially different. For example, the predicted incidence in 2011 for model A was 2/100 person-years, while for model D this was only 1/100 person-years (right panels of figure 3.2). Also, projections regarding the future course of the HIV epidemic in the absence of UTT differ substantially. Future incidence and prevalence in the absence of treatment reach a steady state in models A and B, as indicated by the dashed lines. In model C, the incidence and prevalence of HIV already decline in the no-intervention scenario due to the increase in condom use in the early 2000s. Such a decline is even more profound in model D, where current ART scale-up in South Africa is included.

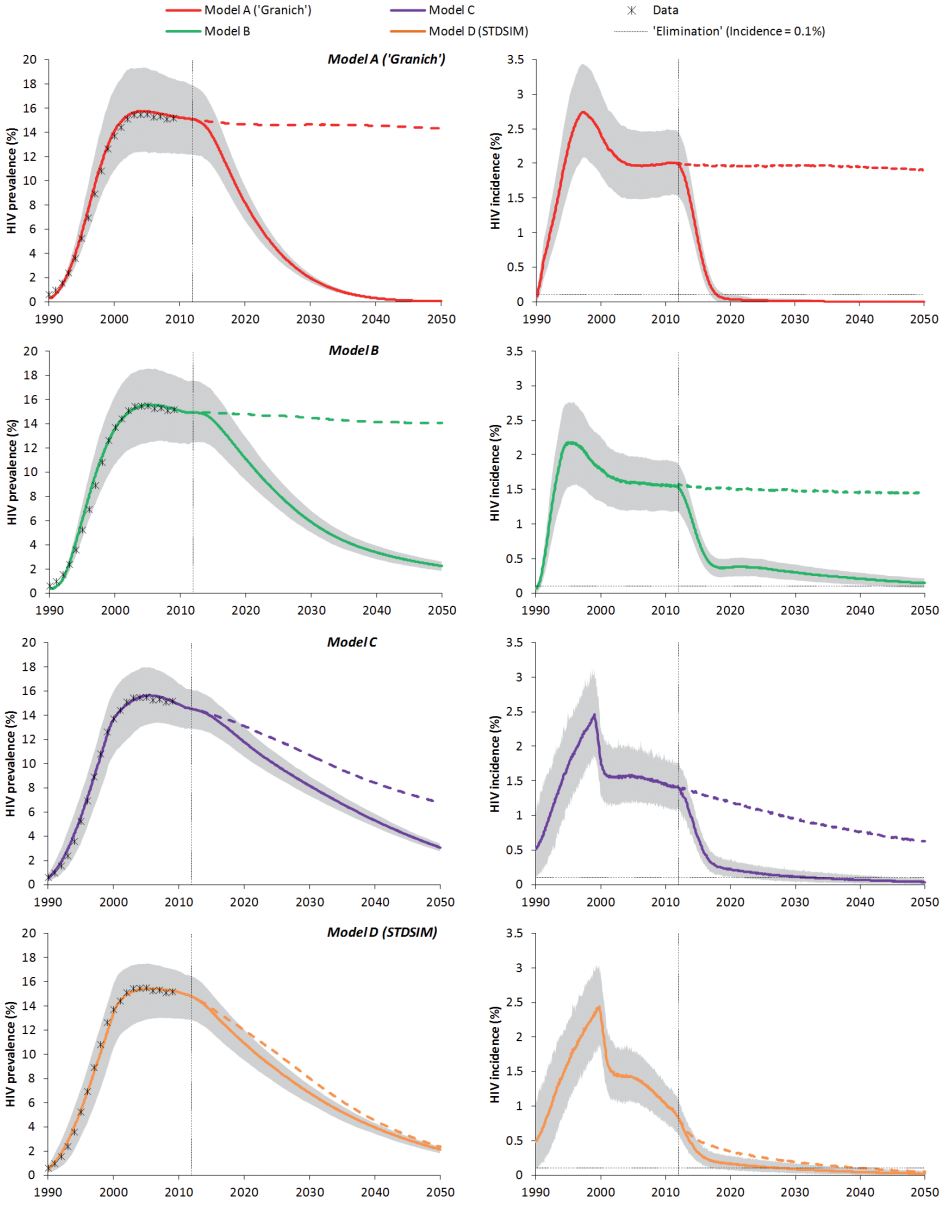

Figure 3.2. Predicted impact of universal testing and immediate ART for all HIV infected patients (UTT) on HIV prevalence (left panels) and incidence (right panels) in adults (aged 15+) for four main models of the South African HIV epidemic over the period 1990-2050. All models are structurally different. Solid lines represent the impact of the UTT intervention; the dashed lines represent the no-UTT counterfactual. Colored lines are the average result of 1,000 simulations, and the gray area represents the 95% confidence interval based on the stochastic variation between individual model runs. UTT is implemented as annual screening of the adult population, and immediate ART for all HIV-infected patients. The intervention is scaled-up linearly, starting in 2012 and reaching 90% coverage in 2019 (similar to Granich et al [9]). The vertical black dashed lines give the timing of the start of the intervention. The horizontal black dotted lines in the right panels indicate the elimination phase, defined as incidence below 1/1,000 person-years. Structures and components of the different models are explained in figure 3.1, and described in detail in the supplementary material.

All models are consistent in predicting that HIV will eventually be eliminated by UTT. However, the timing of elimination significantly differs between the models (figure 3.2, table 3.1). In model A, the HIV epidemic is driven into an elimination phase after 7 years (95% CI: 6; 8), while in models B, C, and D the elimination phase is only reached after 40 (95% CI: 31; 49), 21 (95% CI: 10; 34), and 17 (95% CI: 11; 27) years respectively. For model D, the HIV incidence is even projected to reach the elimination phase in 2041 without the full UTT intervention, due to the impact of the current scale-up of ART at CD4 cell counts of ≤350 cells/μL.

Model Sub-model	Year of elimination*	Life-years saved per ART treatment-year in 2050
Model A ('Granich')	2019	5.7
+ Age structure (B1)	2019	3.8
+ heterogeneity in HIV transmission by disease stage** (B2)	2053	2.6
Model B (B1 and B2 combined)	>2060	3.0
+ Sexual network (C1)	>2060	2.6
+ Background prevention interventions (C2)	2042	2.8
+ Up-to-date ART assumptions (C3)	>2060	2.9
Model C (C1, C2, and C3 combined)	2032	1.8
Model D (STDSIM)	2029	1.7
Model D baseline (ART at ≤350 cells/μL)	2041	N/A

Table 3.1. Year of HIV elimination (incidence <1/1,000 person-years) under universal testing and immediate ART for all HIV infected patients (UTT) and number of life-years saved through UTT compared to the baseline of no UTT. UTT is scaled-up linearly, starting in 2012 and reaching 90% coverage in 2019.

* Incidence below 1/1,000 person-years
** We assumed four different stages: acute, asymptomatic, symptomatic, and AIDS.

The sub-models B2, C1, and C3 do not predict elimination of HIV by 2050 (table 3.1, figure II.4 in supplement II: STDSIM and its application to South Africa). The combination of a high background mortality and heterogeneity in HIV transmission (model B2) results in a disproportionate contribution of acute infection to the overall epidemic (as many HIV infected patients die because of other causes), thereby limiting the potential impact of UTT. Heterogeneity in sexual behavior also prolongs the predicted time to elimination (sub-model C1), as it accounts for high-risk individuals who continue to spread HIV even in the presence of ART. Finally, it is obvious that more up-to-date assumptions on ART effectiveness result in a lower predicted impact of UTT (sub-model C3), as the reduction in infectiousness is lower (90% versus 99.4%) and survival is higher (twice as high compared to Granich et al [9]). On the other hand, explicitly modeling background prevention interventions and STI cofactors (sub-model C2) instead of using a simple prevalence density function shortens the time till elimination as the interventions scaled-up before 2012 affect the dynamics of the epidemic in the long run, reducing incidence even without UTT or further scale-up of other interventions (dashed line model C).

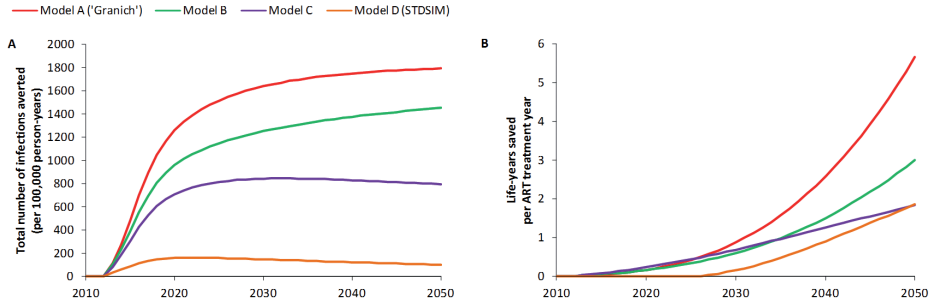

Figure 3.3. Number of infections averted per 100,000 person-years (A) and cumulative number of life-years saved per ART treatment year (B) for universal testing and immediate ART for all HIV infected patients (UTT) in South Africa over the period 2010 - 2050. The intervention consists of annual screening of the adult population (aged 15+), and immediate ART for all HIV-infected patients. Intervention is scaled-up linearly starting in 2012 and reaching 90% coverage in 2019. A: Difference between cumulative numbers of new infections per 100,000 person-years in the intervention scenario versus the baseline without UTT. B: Cumulative number of life-years saved per person-year on ART treatment in the intervention compared to the baseline without the intervention.

There are substantial differences in the impact of UTT compared to the no-UTT baseline in the different models, which has important consequences for the effectiveness of the intervention. By 2050, a cumulative total of 1,800 new infections per 100,000 person-years would be averted in model A, while this is only 200 in model D (figure 3.3A). Consequently, predicted efficiency of ART in saving lives also differs substantially between models (figure 3.3B). Model A predicts about 5.1 cumulative life-years saved per treatment year by 2050, while in model D this is only 1.2, almost five times lower.

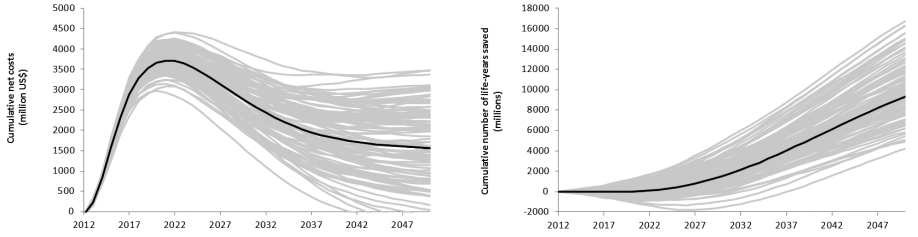

Figure 3.4. Cumulative net costs (A) and cumulative number of life-years saved (B) of universal testing and immediate ART for all HIV infected patients (UTT) compared to the current ART roll-out in South Africa at ≤350 cells/μL, as predicted with model D. Grey lines represent 100 individual model runs, black lines are averages over 1,000 model runs.

Model D shows that cumulative net costs peak at US$ 3.8 billion at around 2020, and will decline thereafter as the impact of UTT on HIV incidence is translated into a lower number of patients on treatment (figure 3.4A). Cumulative net costs reach about US$ 1.8 billion US$ in 2050 (95% CI: 1.4 - 2.2 billion US$). The effects of UTT will only become apparent at around 2020 when the prevented infections will translate into life-years saved (figure 3.4B), and increases linearly to 10.4 million life-years saved by 2050 (95% CI: 10.0 - 10.8 million life-years saved). The resulting incremental cost-effectiveness ratio will be 170 US$/life-year saved (95% CI: 140 - 200 US$ / life-year saved) (table 3.2). All results are robust to alternative assumptions and parameterizations (see sensitivity analysis in supplement II: STDSIM and its application to South Africa).

	Cumulative life-years (millions) (95% CI)	Δ Life-years (millions) (95% CI)	Cumulative costs (million US$) (95% CI)	Δ Cost (million US$) (95% CI)	ICER (US$/LYS) (95% CI)
≤350 cells/μL	1 294 (1 142; 1 454)	-	76 900 (54 300; 104 000)	-	-
UTT	1 304 (1 152; 1 465)	10.4 (10.0; 10.8)	78 600 (55 700; 106 000)	1 780 (1 410; 2 200)	170 (141; 205)

Table 3.2. Effects, cost, and cost-effectiveness of universal test and treat (UTT) versus continued scale-up of ART at ≤350 cells/μL in South Africa over the period 2012 - 2050 (Model D). Costs and effects are discounted at an annual rate of 3%. LYS = Life-year saved. ICER = Incremental cost effectiveness ratio. Life-years concern the total life-years lived in South Africa of the entire population. Of these total life-years, 7% are life-years lived with HIV.

3.4 Discussion

Our study confirms previous reports that an intervention of universal voluntary counseling and testing and immediate ART for all HIV infected individuals (UTT) at 90% coverage will eventually result in the elimination of HIV, even in a high endemic setting such as South Africa and with realistic assumptions on ART effectiveness. However, timing of elimination differs substantially for the different models in our study, and is likely to take 3 times longer than the mere 7 years predicted by Granich et al [9]. In addition, the relative impact of the UTT intervention compared to the baseline differs substantially. Where 1,800 infections were averted per 100,000 person-years in the simplest model, this is only 200 in the most comprehensive model. In fact, the latter model shows that the current scale-up of ART for patients with CD4 cell counts of ≤350 cells/μL already leads to elimination without the additional UTT intervention. However, the considerable number of life-years saved makes UTT at 90% coverage still a highly cost-effective intervention, with an ICER of 170 US$/life-year saved.

Our sub-model analysis shows that choices in model structure and assumptions have an important impact on the predicted impact of UTT. It makes sense that more up-to-date assumptions on the overall efficacy in infectiousness reduction of ART (90% versus 99.4%) lead to delayed elimination. Also, incorporating a high infectiousness during the acute stage results in a less profound impact of UTT since relatively many transmission events will then occur during this short period of high infectiousness, which is difficult to target in UTT interventions [17,34]. Adding heterogeneity in sexual behavior and sexual networks to the model also increases the time till elimination. This is because the relative force of infection of HIV is high in certain high risk groups (e.g. female sex workers) and therefore the impact of UTT is less profound in these subgroups. Finally, adding more realism to the model through the explicit modeling of male circumcision, condom use and STI co-factors, and using increases in condom use to quantify the HIV epidemic in South Africa [2,3] decreases the time till elimination since the counterfactual of no UTT already has a substantial decline in incidence, despite the fact that these interventions are not further scaled-up in the model after 2012. A model that relies on implicit modeling of these interventions to capture the steady state (e.g. through a prevalence density function as was used by Granich et al [9]) will therefore overestimate the impact of UTT. Finally, it appears vital to incorporate the current ART roll-out in the counterfactual scenario. The availability of ART in South Africa and many other African

countries is now a fact-of-life, and the roll-out that generally started in 2003/2004 is already affecting the epidemics through increased survival and decreased transmission [3].

Given that all the model components investigated in this study appear to be important in simulating the interventions, the model that incorporates all these components (model D) gives the most accurate prediction on the impact. In addition, although all models were able to accurately replicate the UNAIDS reported HIV prevalence in South Africa, model D was the only model that was also able to capture the observed decline in incidence over the past decade [2,3]. In model D, incidence in the population aged 15-49 declined from 1.9/100 person-years in 2002 to 1.3/100 person years in 2008, which is nearly the same as the observed reduction from 2.0/100 person-years in 2002-2005 to 1.3/100 person-years in 2005-2008, as reported by Rhele et al [2]. Incidence rates in the other models remained constant over the same period (models A to C). In addition, model D was also able to replicate data on the demographic structure, age-specific HIV prevalence, sexual behavior, STI prevalence, and ART coverage in South Africa (figure II.5 in supplement II: STDSIM and its application to South Africa). Finally, previous studies with STDSIM have shown that the model is capable of reproducing HIV prevalence (overall and age- and sex-specific), incidence, and mortality data from a population-based HIV and demographic surveillance site in KwaZulu-Natal, South Africa [25,35-38].

This is the first study that shows that the current ART treatment roll-out with ART for all HIV infected patients with CD4 cell counts of ≤350 cells/μL will eventually eliminate HIV. This raises questions about the value for money of the required additional investments in UTT. Although we show that the UTT intervention proposed by Granich et al [9] is highly cost-effective, the assumed rates of HIV testing, ART uptake, retention in care, and treatment adherence are rather optimistic [39,40]. Adherence and retention are likely to decrease when treatment is initiated at higher CD4 cell counts [41], while patient-losses are increasingly common when treatment programs are scaled up [42]. Both these issues are especially important in UTT strategies, where patient numbers increase substantially, and many initiate at high CD4 cell counts. In addition, maintaining screening coverage levels at 90% for over 40+ years seems not very plausible. It is likely that test-refusal will be substantially higher [43], increase over time [44], and will be more common among HIV positives [44], resulting in a lower and declining screening coverage over time. Nevertheless, our sensitivity analysis shows that, even with coverage rates of only 60%, UTT would still be a cost-effective strategy.

A recent study on the cost-effectiveness of ART provision in South Africa showed that cost savings will be achieved after just 5 years of UTT at 90% coverage [45], while our study shows that there will be no net savings from this UTT intervention in South Africa. The underlying compartmental transmission model in this paper is essentially the same as previously used by Granich et al [9], and thus resembles our model A. We show that these types of models, which ignore sexual networks and background prevention interventions underlying the current South African epidemic, predict a far more optimistic impact of UTT compared to the baseline. Cost-effectiveness and

economic impact studies based on such models should therefore be interpreted with caution. More research with comprehensive models on the impact of more modest UTT interventions is necessary in order to determine whether universal treatment for HIV really is a cost-effective intervention.

We defined elimination as incidence below 1/1000 person-years. However, real elimination is achieved when both incidence and prevalence reach 0%. Microsimulation allows for such an analysis, and we found that in a model population of about 35,000 people, by 2080, 99% of all model runs predict that HIV prevalence reaches 0% in model A (results not shown). In model D this is only in year 2116 for the UTT scenario, and 2164 for continued scale-up at ≤350 cells/μL.

Both acquired resistance (development of resistance within an individual on treatment) and transmitted resistance (spread of drug-resistant strains) will impact on the effectiveness of treatment programs, and consequently result in a less profound effect of the current ART scale-up or UTT in South Africa. It is currently unclear, however, in how far the fears of rapidly spreading drug resistance expressed at the start of the ART scale-up were justified [46]. The prevalence of drug resistance remains low in South Africa after nearly 10 years of scaling up ART [47,48]. In addition, adherence to treatment is equally high as in many high income countries [49], and survival of patients on treatment in SSA approaches general life-expectancy [50], suggesting that resistance may not become a major problem in South Africa in the near future.

In conclusion, our results from a series of structurally different models support the main message from previous studies that HIV in South Africa can be eliminated through a strategy of annual screening and immediate ART for all HIV infected patients at 90% coverage, but this will occur substantially later. Importantly, the most comprehensive model suggests that HIV incidence in South Africa can even reach the elimination phase if the current treatment scale up of ART at ≤350 cells/μL continues. Results from upcoming community-randomized trials of treatment as prevention will need to be evaluated with models that allow for sufficient detail in assumptions in order to adequately project population level impact and overall cost-effectiveness of the intervention.

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4. Human resources needs for universal access to antiretroviral therapy in South Africa: A time-motion study

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Abstract

Background

Although access to life-saving treatment for HIV infected patients in South Africa has improved significantly since 2004, treating all eligible patients (universal access) remains elusive. As the prices of antiretroviral drugs have dropped over the past years, the availability of human resources may now be the most important barrier to achieving universal access to HIV treatment. We quantify the HIV health workers (HHW) required to be added to the current HIV workforce to achieve universal access to HIV treatment in South Africa, under different eligibility criteria.

Methods

We performed a time-motion study in three HIV clinics in a rural, primary care-based HIV treatment program in KwaZulu-Natal, South Africa, to estimate the average time per patient visit for doctors, nurses, and counsellors. We estimate the additional number of HHW needed for achieving universal access to HIV treatment within one year.

Results

For universal access at CD4 cell count of ≤350 cells/μL an additional 2,200 nurses, 3,800 counsellors, and 300 doctors would be required, at additional annual salary costs of 929 million ZAR (141 million US$). For universal treatment ('treatment-as-prevention'), an additional 6,000 nurses, 11,000 counsellors, and 800 doctors would be required, at additional annual salary costs of 2.6 billion ZAR (400 million US$).

Conclusions

Universal access to HIV treatment for patients with CD4 cell count ≤350 cells/μL in South Africa may be affordable, but the number of HHW available for HIV will need to be substantially increased. Treatment-as-prevention strategies will require considerable additional financial and human resources commitments.

4.1 Background

With about 22.5 million people living with HIV [1], HIV remains one of the most important health problems in sub-Saharan Africa (SSA). Antiretroviral therapy (ART) significantly improves the survival and quality of life of HIV-infected people [2-4]. In June 2011, the United Nations General Assembly High Level Meeting on AIDS adopted a political declaration of achieving "universal access" to HIV treatment by 2015 [5]. In South Africa, access to treatment remains far from universal; under the 2010 WHO ART eligibility criteria [6], ART coverage was estimated to be 55% in the country in 2010 [7]. South Africa is the country with the largest HIV-infected population worldwide (nearly 6 million people) [1]. As the cost of antiretroviral medicines has dropped dramatically over the last decade, the availability of well-trained health workers may now be the most important barrier to providing the life-saving treatment to those in need [8-10]. Based on a review of scientific publications and government documents, George et al concluded that in 2007/2008 there was a total shortage of 79,791 health workers in South Africa's public sector [11].

The current WHO guidelines recommend to initiate ART at CD4 cell count of ≤350 cells/μL [6] to improve the health of both the individual taking ART (by decreasing mortality and morbidity) and in HIV-uninfected community members (by reducing onward transmission of the virus) [12]. South Africa changed its treatment eligibility criteria for adults in 2010 to include those with CD4 cell count between 200 and 350 cells/μL to be eligible when co-infected with tuberculosis or pregnant [13], and further relaxed eligibility criteria to CD4 cell count ≤350 cells/μL for all HIV infected patients in August 2011 [14]. More recently, it has been argued that treatment should be given to all HIV patients, regardless of CD4 cell count, as a treatment-as-prevention strategy to substantially reduce HIV transmission [15,16]. The National Strategic Plan on HIV, STIs and TB for the period 2012 – 2016 states that al HIV treatment in South Africa should be delivered through decentralized, nurse-led primary health care (PHC) HIV clinics [17]. Treatment initiation is performed by doctors who rotate between clinics, while professional nurses and HIV counsellors perform follow-up visits. Recently, the South African government changed its guidelines to also allow nurse-initiated ART [18]. Health care workers are usually employed by the Department of Health on a contract basis, and payment of salaries is based on full time equivalents (FTEs) on a monthly basis.

Here, we use novel data on ART task times obtained in a time-motion study to estimate the additional HIV health workers (HHW) required to achieve to universal ART access in South Africa. We determine the impact of alternative ART delivery models on the additional number of HHW required for universal ART access and the financial resources needed pay the salaries of those health workers.

4.2 Methods

Data collection

We performed a time-motion study - a direct and continuous observation of tasks, using a timekeeping device to record the time taken to accomplish a task [19] - in the Hlabisa HIV Treatment and Care Program in KwaZulu-Natal, South Africa, which is a partnership between the local Department of Health and a Wellcome Trust-funded research centre based in the community, the Africa Centre for Health and Population Studies, University of KwaZulu-Natal [20]. HIV treatment is delivered in the program in 17 PHC HIV clinics and one district hospital. The professional nurses and trained HIV counsellors perform tasks exclusively related to HIV treatment and care. Doctors visit clinics on a scheduled rotation (usually one weekly visit per clinic) to initiate new patients on ART and to review cases of treatment failure, drug toxicity, and other complications. The Hlabisa sub-district has a total population of 228,000 and an adult HIV prevalence of 28% [21]; ART uptake in the area is high, and by June 2011 nearly 17,000 people had been initiated on ART [22].

We randomly selected three PHC HIV clinics (clinics A-C) within the treatment program for observation. We obtained consent for this study from the local Department of Health. A single observer was then randomly assigned to a different HHW (in one of the three categories doctor, nurse, or treatment counselor) on different, randomly assigned calendar days within the observation period. No HHW was observed more than once. Activities were timed and recorded for each separate patient contact and subsequently entered into an Excel spreadsheet. Data were collected by a single observer trained in quantitative and qualitative data collection, and the observer was closely supervised by three doctors and two professional nurses. There were written instruction on how to keep and record time for different types of tasks. The observer was trained in two stages. The initial stage involved observing the workdays of different health care workers without recording any tasks, in order to become familiar with the work routine. Next, a pilot was conducted in which tasks were observed and recorded, and subsequently coded. The pilot data were checked for errors or inconsistencies, and the study protocol was improved based on the pilot findings. During the actual data collection, data were continuously entered and checked by the supervising doctors.

Two investigators independently coded the recorded activities into pre-defined categories: i) direct patient contact (talking to patient; writing; writing and talking; venepuncture; physical examination; dispensing medication); ii) indirect patient contact (discussing clinical or work-related issues with other HHW; performing work-related paperwork or administration, contacting health workers in other health-care facilities, such as hospitals, for patient referral); and iii) other (breaks; idle time; unaccounted time). Categories i and ii are times allocated to perform tasks within the job description of the particular HHW. Category iii contains breaks and idle time. It is important to note that breaks and idled time do not necessarily imply wasted or unproductive time. Breaks may serve an important purpose in resting the HHW in order to maintain productivity when performing tasks in categories i and ii. The final assignment of category codes was determined in discussion between the two investigators and, when conflicting assignments could not be resolved, through discussion with a third investigator.

Data analysis

We calculated time per patient, duration of a workday, and the proportion of the work day spent on direct- and indirect-patient contact, and other activities. We used one-way ANOVA to test differences in average time per patient and average duration of workdays between HHW and clinics. All analyses were done in SAS version 9.0.

Human resources needs and salary costs of scaling-up

Next, we estimated the additional number of HHW and salary costs required for scaling up ART from the current coverage level to universal access within a year, and maintaining these new patients on ART for a period of twelve months after initiation, for the following eligibility criteria: i) ART at CD4 cell count ≤200 cells/μL; ii) ART at CD4 cell count ≤350 cells/μL for patients co-infected with tuberculosis or pregnant; iii) ART at CD4 cell count ≤350 cells/μL for all; iv) ART at CD4 cell count ≤500 cells/μL; and v) ART for all HIV infected individuals. In addition, we considered the impact of the additional salary costs for these HHW on the total HIV sector budget for South Africa. We used estimates from the most recent UNAIDS report on the global HIV epidemic 2010 and the 2010 progress report on universal access to obtain the current number of people living with HIV, on ART, and eligible for ART in South Africa under different treatment thresholds [1,23].

At the time of this study, South African guidelines stated that every initiation-visit should include a contact with a doctor, nurse, and a counselor, and that all ART initiations should be conducted by doctors. Since then, the treatment guidelines in South Africa have changed, allowing ART initiation by ART-trained nurses. A patient on ART should return for a routine clinic visit with a nurse and a counselor every month. When treatment stabilizes, the re-visit frequency can be reduced to once every two months [24]. Here, we assume all recorded doctor-time to represent initiation visits, and recorded nurse- and counselor-time to represent both the time spent during routine clinic visits and initiation-visits. A full-time HHW is assumed to have 20 work-days per month (based on a total of 22 workdays per month, after accounting for holidays and sick leave). The average number of hours in a workday spent on patient contact (direct and indirect) is derived from the time-motion study results. We used the average salary of a given HHW in the local HIV treatment program as of 2010: 38,733 South African Rand (ZAR) (or – at an exchange rate of 6.6 ZAR/US$ [25] – 5,869 US$) per month for doctors; 20,013 ZAR (3032 US$ per month for nurses; and 6,024 ZAR (913 US$) per month for counsellors. The total South African HIV sector budget was 2.1 billion US$ in 2009 [1] (or 14 billion ZAR).

In the baseline scenario, we estimated the total number of doctor-months required for universal coverage by i) measuring the time one initiation takes; ii) multiplying it with the number of required initiations; and iii) dividing this with the number of work-hours in a month. We then translated the total number of doctor-months into the number of full time equivalents (FTEs) on an annual basis needed for initiating all patients in one year, and the number of doctors per 1,000 initiations. In an alternative scenario, we assumed that all initiations were conducted by nurses.

In the baseline scenario, we further assumed all new patients to return on a monthly basis for our study period (one year) for a routine clinic visit with a nurse and a counselor. We estimated the total number of nurse-months and counselor-months needed to initiate and maintain all eligible patients on treatment for 1 year by i) measuring the time one visit takes; ii) multiplying it with the number of newly initiated patients for universal access; and iii) dividing this value by the number of work-hours in a month. We then translated the total number of nurse-months and counselor-months into the number of FTEs needed for universal ART coverage.

Sensitivity and scenario analysis

For our baseline estimate we assume constant returns to scale. However, the efficiency of ART delivery may be a function of scale [26], i.e. efficiency may increase (economies of scale) or decrease (diseconomies of scale) as the total number of patients increases. Although the empirical evidence on the shape of scale function in HIV treatment is overall limited [27,28], Kumaranayake et al find in a review of the evidence that if the number of patients increases by a factor 23, the costs per ART patients will be reduced by 27% - 73% [26]. However, it is also plausible that returns to scale could be decreasing, i.e., that we would find increasing costs per patient as the number of patients grows. For one, at the level of the national South African HIV treatment program the clinics that will need to be added to the ART delivery infrastructure to reach remote and rural populations may operate below their full capacity, because of limited ART patient load due to low population density in remote and rural areas. On the other hand, the clinics in which ART was initially rolled out were more likely to have been located in the more densely populated, urban areas and thus are more likely to operate at capacity. As the program is scaled up the fixed costs per patient may thus increase, implying diseconomies of scale. Running costs per patient may also increase with scale, as the health systems efforts required to motivate patients to initiate and remain on ART may be lower in patients who accessed the ART program at earlier stages of the scale-up than in those who accessed the program at later stages. We thus assessed two scenarios capturing scale effects, one assuming increasing return to scale, the other assuming decreasing return to scale. In both cases, we assumed that the scale effects followed exponential distributions: patients per HHW = EXP(0.03858*F), for economies of scale, and patients per HHW = EXP(-0.03858*F), for diseconomies of scale; where F=constant number of patients per HHW across scale. In addition, we examined the sensitivity of our results to changes in the average 'time per patient' and 'duration of workday' by using the times and durations of either the least efficient or the most efficient clinic in our estimations.

Finally, we performed a scenario analysis on the impact of alternative models of delivering ART on the patient-to-HHW ratio and overall salary costs. Nurse-initiated treatment has been allowed in South Africa recently [24]. Therefore, we performed an additional analysis in which nurses were assumed to perform all initiations, at the same productivity level as doctors [18]. In addition, we assumed the following alternative delivery models: i) decreased frequency of routine clinic visits (once every 2, 3, or 4 months); and ii) decreased frequency of nurse-attended routine clinic visits (once every 2, 3, or 4 months).

Ethical approval

This study received ethics approval from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (ethics certificate BF109/09). Written consent was obtained from all HHW observed.

4.3 Results

Table 4.1 gives an overview of the baseline characteristics of the time-motion data. A total of 13 HHW (6 nurses, 4 counsellors, and 3 doctors) were observed over the period August 12th - September 1st 2009. The total number of patient-visits observed was 334. An average workday lasted 6.3 hours, and the average duration of workdays differed significantly between the busiest and least rural clinic (clinic B) and the least busy and most rural clinic (clinic C) in our sample (7.3 versus 4.9 hours; p=0.01). The observed health worker with the shortest observed duration of a workday was a counselor in clinic C, who spent only 20% of the workday on direct patient contact, while the counselor used 44% of workday time to perform administrative work and 36% on breaks and idle time. This time distribution was likely due to the fact that the patient load in this rural clinic was relatively low. There were no significant differences in the time per patient between the three clinics (p=0.47) or between the different HHW (p=0.24). On average, a nurse-visit took 10 minutes (95% CI 6-13 minutes), a counselor-visit 14 minutes (95% CI 9-19 minutes), and a doctor-visit 13 minutes (95% CI 9-16 minutes).

	Overall	By clinic		
		Clinic A	Clinic B	Clinic C
Number of days observed	13	5	4	4
Period observed	August 12 - September 1	August 19 - August 26	August 12 - August 18	August 27 - September 1
Number of HHWs observed				
Nurse	6	2	2	2
Counselor	4	2	1	1
Doctor	3	1	1	1
Total number of patients observed	334	115	120	99
Average duration of workday (hours)				
Overall	6.3 h	5.2 h	7.3 h	4.9 h
Nurse	7.1 h	5.2 h	7.3 h	5.3 h
Counselor	5.8 h	5.3 h	6.7 h	5.8 h
Doctor	5.4 h	5.1 h	7.7 h	3.4 h
Proportion of time spent on				
Direct patient contact [a]				
Overall	83%	86%	87%	76%
Nurse	83%	84%	83%	82%
Counselor	74%	87%	82%	20%
Doctor	92%	91%	94%	89%
Indirect patient contact [b]				
Overall	9%	7%	9%	10%
Nurse	9%	8%	13%	6%
Counselor	13%	6%	8%	44%
Doctor	4%	8%	4%	3%
Other [c]				
Overall	9%	7%	5%	14%
Nurse	9%	9%	3%	12%
Counselor	13%	7%	10%	36%
Doctor	4%	2%	2%	8%
Average time per patient (minutes) (95% CI)				
Overall	12 (9 - 14)	14 (9 - 18)	11 (8 - 13)	10 (5 - 16)
Nurse	10 (6 - 13)	12 (6 - 18)	12 (7 - 17)	7 (1 - 12)
Counselor	14 (9 - 19)	15 (7 - 23)	8 (5 - 11)	43 (2 - 83)
Doctor	13 (9 - 16)	15 (2 - 27)	15 (11 - 18)	9 (7 - 11)

Table 4.1. Baseline characteristics of time-motion data. HHW = HIV health worker; 95% CI = 95% confidence interval.

a. Direct patient contact consists activities like talking to patients, venepuncture, physical examination, and prescribing medication.

b. Indirect patient contact consists of activities like consultations and meetings with colleagues and administrative work.

c. The other category consists of breaks and idle time between patients

Estimates of ART coverage under different eligibility criteria are shown in table 4.2. As of 2009, nearly 1 million people were on treatment in South Africa [1]. Universal access to ART at CD4 cell count ≤350 cells/μL will require an additional 1.6 million initiations (a total of 2.6 million patients on treatment), while for universal access to ART at CD4 cell count ≤500 cells/μL, 3.1 million additional initiations are needed (a total of 4.1 million patients on treatment). ART for all HIV infected individuals would require 4.6 million additional initiations in order to achieve universal access (to give a total of 5.6 million patients on treatment).

	Coverage indicators South Africa		
	Point estimate	**Low estimate**	**High estimate**
Number receiving ART	971,566	n/a	n/a
Number needing ART			
CD4 ≤200	1,700,000	1,500,000	2,000,000
CD4 ≤350 (TB or pregnant) [a]; CD4 ≤ 200 (all other HIV-positive people)	1,925,000	1,750,000	2,200,000
CD4 ≤350	2,600,000	2,500,000	2,800,000
CD4 ≤500[b]	4,100,000	3,950,000	4,340,000
All HIV-positive people	5,600,000	5,400,000	5,900,000
Coverage			
CD4 ≤200	56%	65%	48%
CD4 ≤350 (TB or pregnant);[a]CD4 ≤ 200 (all other HIV-positive people)	50%	56%	44%
CD4 ≤350	37%	39%	35%
CD4 ≤500b	24%	25%	22%
All HIV-positive people	17%	18%	16%
Number needed to initiate			
CD4 ≤200	728,434	528,434	1,028,434
CD4 ≤350 (TB/pregnant)[a]; CD4 ≤ 200 (all other HIV-positive people)	952,444	778,444	1,228,444
CD4 ≤350	1,628,434	1,528,434	1,828,434
CD4 ≤500[b]	3,128,434	2,978,434	3,368,434
All HIV-positive people	4,628,434	4,428,434	4,928,434

Table 4.2. Coverage indicators South Africa. Source: WHO towards universal access report 2010 [23]. ART= antiretroviral therapy; n/a = not applicable.

CD4 = CD4 cell count (expressed in cells/μL).

a. 25% of those with CD4 cell counts of 200-350 are assumed to be eligible because of co-infection with tuberculosis or pregnancy under the recently abandoned South African guidelines

b. Number estimated to be exactly between those eligible at ≤350 cells/μL and those eligible under ART for all HIV infected patients
CD4 = CD4 cell count (expressed in cells/μL).

Table 4.3 gives an overview of the number of nurse-months, doctor-months, counselor-months, total FTEs, and associated salary costs required for scaling up to universal access under different eligibility criteria. Initiating all patients with CD4 cell count ≤350 cells/μL within one year and maintaining them on treatment for another 12 months would require a net increase of 2,200 nurses, 3,800 counsellors, and 300 doctors, costing 929 million ZAR (141 million US$) in salaries, which is 7% of the current HIV sector budget in South Africa (Table 4.3). ART for all HIV infected individuals will require an additional 6,000 nurses, 11,000 counsellors, and 800 doctors and an additional 2.6 billion ZAR (400 million US$) in salaries to cover all HHW needed to initiate and maintain those who are not yet on treatment, which is a 20% increase of the current total HIV sector budget of South Africa. The HHW-to-patient ratio for all treatment eligibility criteria is 0.2/1,000 for doctors (for performing all initiations), 1.2/1,000 for nurses, and 2.1/1,000 for counsellors (for performing initiations and maintaining all eligible patients on treatment).

	Human resource needs					
	Nurse-months (x 1,000) (95% CI)	**Nurse-FTEs (x 1,000) (95% CI)**	**Counselor-months (x 1,000) (95% CI)**	**Counselor-FTEs (x 1,000) (95% CI)**	**Doctor-months (x 1,000) (95% CI)**	**Doctor-FTEs (x 1,000) (95% CI)**
Point estimate						
CD4 ≤200	12 (8 - 16)	1.0 (0.7 – 1.3)	20 (12 - 28)	1.7 (1.0 – 2.3)	2 (1 - 2)	0.1 (0.1 – 0.2)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	15 (10 - 20)	1.3 (0.9 – 1.7)	27 (16 - 37)	2.2 (1.4 – 3.1)	2 (1 - 3)	0.2 (0.1 – 0.2)
CD4 ≤350	26 (18 - 35)	2.2 (1.5 – 2.9)	45 (28 - 63)	3.8 (2.3 – 5.2)	3 (2 - 4)	0.3 (0.2 – 0.4)
CD4 ≤500b	51 (34 -67)	4.2 (2.8 – 5.6)	87 (53 - 121)	7.3 (4.4 – 10.1)	6 (5 - 8)	0.5 (0.4 – 0.7)
All HIV-positive people	74 (50 - 99)	6.2 (4.2 – 8.2)	129 (79 - 179)	10.7 (6.6 – 14.9)	9 (7 - 12)	0.8 (0.6 – 1.0)
High estimate						
CD4 ≤200	17 (11 -22)	1.4 (0.9 – 1.8)	29 (17 - 40)	2.4 (1.5 – 3.3)	2 (1 - 3)	0.2 (0.1 – 0.2)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	20 (13 - 26)	1.6 (1.1 – 2.2)	34 (21 - 48)	2.8 (1.7 – 4.0)	3 (2 - 3)	0.2 (0.2 – 0.3)
CD4 ≤350	30 (20 - 39)	2.5 (1.7 – 3.3)	51 (31 - 71)	4.2 (2.6 – 5.9)	4 (3 -5)	0.3 (0.2 – 0.4)
CD4 ≤500[b]	54 (37 - 72)	4.5 (3.0 – 6.0)	94 (57 - 130)	7.8 (4.8 – 10.9)	7 (5 - 9)	0.6 (0.4 – 0.7)
All HIV-positive people	80 (54 - 106)	6.6 (4.5 – 8.8)	137 (84 -191)	11.4 (7.0 – 15.9)	10(7 -13)	0.8 (0.6 – 1.1)
Low estimate						
CD4 ≤200	9 (6 - 11)	0.7 (0.5 – 1.0)	15 (9 - 20)	1.2 (0.7 – 1.7)	1 (1 - 1)	0.1 (0.1 – 0.1)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	13 (8 - 17)	1.1 (0.7 – 1.4)	22 (13 - 30)	1.8 (1.1 – 2.5)	2 (2 - 3)	0.1 (0.1 – 0.2)
CD4 ≤350	25 (17 - 33)	2.1 (1.4 – 2.7)	43 (26 - 59)	3.5 (2.2 – 4.9)	3 (2 - 4)	0.3 (0.2 – 0.3)
CD4 ≤500[b]	48 (32 - 64)	4.0 (2.7 – 5.3)	83 (51 - 115)	6.9 (4.2 – 9.6)	6 (4 - 8)	0.5 (0.4 – 0.7)
All HIV-positive people	72 (48 - 95)	6.0 (4.0 – 7.9)	123 (75 - 171)	10.3 (6.2 -14.3)	9 (6 - 12)	0.8 (0.5 – 1.0)

	Costs	
	Total salary costs (million ZAR) (95% CI)	**Proportion of current HIV sector budget (95% CI)** [a]
Point estimate		
CD4 ≤200	12 (8 - 16)	12 (8 - 16)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	15 (10 - 20)	15 (10 - 20)
CD4 ≤350	26 (18 - 35)	26 (18 - 35)
CD4 ≤500b	51 (34 -67)	51 (34 -67)
All HIV-positive people	74 (50 - 99)	74 (50 - 99)
High estimate		
CD4 ≤200	17 (11 -22)	17 (11 -22)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	20 (13 - 26)	20 (13 - 26)
CD4 ≤350	30 (20 - 39)	30 (20 - 39)
CD4 ≤500[b]	54 (37 - 72)	54 (37 - 72)
All HIV-positive people	80 (54 - 106)	80 (54 - 106)
Low estimate		
CD4 ≤200	9 (6 - 11)	9 (6 - 11)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	13 (8 - 17)	13 (8 - 17)
CD4 ≤350	25 (17 - 33)	25 (17 - 33)
CD4 ≤500[b]	48 (32 - 64)	48 (32 - 64)
All HIV-positive people	72 (48 - 95)	72 (48 - 95)

Table 4.3. Human resource needs and salary costs for initiating and maintaining all those eligible on ART for one year, under different treatment strategies. For the calculations of the point, high, and low estimates we used the point, high, and low estimates of the number of people living with HIV in South Africa published in the most recent UNAIDS world AIDS report [66]. FTE = Full time equivalent; 95% CI = 95% confidence interval; ZAR = South African Rand. CD4 = CD4 cell count (expressed in cells/μL). aCurrent total expenditure: estimate of the total amount spent on preventing and treating HIV in South Africa in 2009 (14 billion ZAR) [66].

Different assumptions on scale effects and productivity can affect estimates considerably (Table 4.4). Scale effects become especially important when considering broad eligibility criteria such as ART at CD4 cell count ≤500 cells/μL or for all HIV infected patients. Here, overall costs and HHW needs can vary by 12% and 17% respectively, while under ART at CD4 cell count ≤350 cells/μL economies of scale will only change the cost and HHW needs for universal access by 6%. Regarding productivity, assuming average time per patient and the average duration of workday observed in the most efficient clinic in our sample (clinic B), instead of the overall averages across all three clinics, results in a reduction of the additional number of nurses, counsellors, and doctors required to achieve universal access by 16%, 16%, and 31% respectively, irrespective of the eligibility criteria. On the other hand, assuming the productivity characteristics in our least efficient clinic (clinic C) increases the required additional number of nurses, counsellors, and doctors required by 26%, 36%, and 66%, respectively.

	Human resource needs					
	Nurse-months (x 1,000) (95% CI)	**Nurse-FTEs (x 1,000) (95% CI)**	**Counselor-months (x 1,000) (95% CI)**	**Counselor-FTEs (x 1,000) (95% CI)**	**Doctor-months (x 1,000) (95% CI)**	**Doctor-FTEs (x 1,000) (95% CI)**
Most efficient clinic (Clinic B)						
CD4 ≤200	10 (7 - 13)	0.8 (0.6 -1.1)	17 (10 - 24)	1.4 (0.9 – 2.0)	1 (1 - 1)	0.1 (0.1 – 0.1)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	13 (9 - 17)	1.1 (0.7 – 1.4)	22 (14 - 31)	1.9 (1.1 – 2.6)	1 (1 - 2)	0.1 (0.1 – 0.1)
CD4 ≤350	22 (15 - 29)	1.8 (1.2 – 2.3)	38 (23 - 53)	3.2 (1.9 – 4.4)	2 (2 - 3)	0.2 (0.1 – 0.2)
CD4 ≤500[b]	42 (29 - 56)	3.5 (2.4 – 4.7)	73 (45 - 101)	6.1 (3.7 – 8.4)	4 (3 - 6)	0.4 (0.3 – 0.5)
All HIV-positive people	63 (42 - 84)	5.2 (3.5 – 7.0)	108 (66 - 150)	9.0 (5.5 – 12.5)	6 (5 - 8)	0.5 (0.4 – 0.7)
Least efficient clinic (Clinic C)						
CD4 ≤200	15 (10 - 20)	1.2 (0.8 – 1.6)	28 (17 - 38)	2.3 (1.4 – 3.2)	2 (2 -3)	0.2 (0.2 – 0.3)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	19 (13 - 26)	1.6 (1.1 – 2.2)	36 (22 - 50)	3.0 (1.8 – 4.2)	3 (2 - 4)	0.3 (0.2 – 0.4)
CD4 ≤350	33 (22 - 44)	2.8 (1.9 – 3.7)	62 (38 - 86)	5.1 (3.1 – 7.1)	6 (4 - 7)	0.5 (0.3 – 0.6)
CD4 ≤500[b]	63 (43 - 85)	5.3 (3.6 – 7.1)	118 (72 - 165)	9.9 (6.0 – 13.7)	11 (8 - 14)	0.9 (0.6 – 1.1)
All HIV-positive people	94 (63 - 126)	7.9 (5.3 – 10.5)	175 (107 - 243)	14.6 (8.9 – 20.3)	16 (11 - 20)	1.3 (0.9 – 1.7)
Increasing return to scale						
CD4 ≤200	11 (8 - 15)	1.0 (0.6 – 1.3)	20 (12 - 27)	1.6 (1.0 – 2.3)	1 (1 - 2)	0.1 (0.1 – 0.2)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	15 (10 - 20)	1.2 (0.8 – 1.6)	26 (16 - 36)	2.1 (1.3 – 3.0)	2 (1 - 3)	0.2 (0.1 – 0.2)
CD4 ≤350	25 (17 - 33)	2.1 (1.4 – 2.7)	43 (26 - 59)	3.5 (2.2 – 4.9)	3 (2 - 4)	0.3 (0.2 – 0.3)
CD4 ≤500[b]	45 (30 - 59)	3.7 (2.5 -4.9)	77 (47 - 107)	6.4 (3.9 – 8.9)	6 (4 - 7)	0.5 (0.3 – 0.6)
All HIV-positive people	62 (42 - 82)	5.2 (3.5 – 6.9)	107 (65 - 149)	8.9 (5.5 – 12.4)	8 (6 - 10)	0.7 (0.5 – 0.8)
Decreasing return to scale						
CD4 ≤200	12 (8 - 16)	1.0 (0.6 – 1.3)	21 (13 - 29)	1.7 (1.1 – 2.4)	2 (1 - 2)	0.1 (0.1 – 0.2)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	16 (11 - 21)	1.3 (0.9 – 1.8)	28 (17 - 38)	2.3 (1.4 – 3.2)	2 (1 - 3)	0.2 (0.1 – 0.2)
CD4 ≤350	28 (19 - 37)	2.3 (1.6 – 3.1)	48 (30 - 67)	4.0 (2.5 – 5.6)	4 (3 - 5)	0.3 (0.2 – 0.4)
CD4 ≤500[b]	57 (39 - 76)	4.8 (3.2 – 6.3)	99 (60 - 137)	8.2 (5.0 – 11.4)	7 (5- 9)	0.6 (0.4 – 0.8)
All HIV-positive people	90 (60 - 119)	7.5 (5.0 – 10.0)	155 (95 - 215)	12.9 (7.9 – 17.9)	11 (8 - 15)	0.9 (0.7 – 1.2)

	Costs	
	Total salary costs (million ZAR) (95% CI)	**Proportion of current HIV sector budget (95% CI)[a]**
Most efficient clinic (Clinic B)		
CD4 ≤200	339 (223 - 456)	2% (2% - 3%)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	445 (292 - 597)	3% (2% - 4%)
CD4 ≤350	760 (499 - 1,019)	5% (4% - 7%)
CD4 ≤500[b]	1,459 (959 - 1,959)	10% (7% - 14%)
All HIV-positive people	2,159 (1,419 - 2,899)	15% (10% - 21%)
Least efficient clinic (Clinic C)		
CD4 ≤200	559 (369 - 749)	4% (3% - 5%)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	732 (483 - 981)	5% (3% - 7%)
CD4 ≤350	1,250 (825 - 1,675)	9% (6% - 12%)
CD4 ≤500[b]	2,401 (1,584 - 3,218)	17% (11% - 23%)
All HIV-positive people	3,552 (2,344 - 4,762)	25% (17% - 34%)
Increasing return to scale		
CD4 ≤200	404 (266 - 541)	3% (2% - 4%)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	524 (345 - 702)	4% (2% - 5%)
CD4 ≤350	871 (574 - 1,168)	6% (4% - 8%)
CD4 ≤500[b]	1,576 (1,039 - 2,113)	11% (7% - 15%)
All HIV-positive people	2,196 (1,449 - 2,946)	16% (10% - 21%)
Decreasing return to scale		
CD4 ≤200	427 (282 - 574)	3% (2% - 4%)
CD4 ≤350 (TB or pregnant) ; CD4 ≤ 200 (all other HIV-positive people)	565 (487 - 758)	4% (3% - 5%)
CD4 ≤350	991 (653 - 1,329)	7% (5% - 9%)
CD4 ≤500[b]	2,020 (1,332 - 2,710)	14% (10% - 19%)
All HIV-positive people	3,172 (2,092 - 4,255)	23% (15% - 30%)

Table 4.4. Sensitivity analysis on human resource needs and salary costs for initiating and maintaining all those eligible on ART for one year, under different treatment strategies. The underlying number of patients needing treatment are based on the WHO-reported ART treatment coverage in South Africa [23] and UNAIDS-reported point estimate of the total number of HIV infected people [66], see Table 4.2. FTE = Full time equivalent; 95% CI = 95% confidence interval; ZAR = South African Rand. CD4 = CD4 cell count (expressed in cells/μL)

Alternative models of delivering HIV treatment and care can significantly affect the HHW needs and the costs of scaling up ART to universal access (table 4.5). Nurse-initiated treatment, which has recently become legal in South Africa, will reduce the additional salary costs required by 7% in comparison to the base case. For treatment initiation at CD4 cell count ≤350 cells/μL this change would imply a reduction in salary costs of about 118 million ZAR (929 million ZAR versus 811 million ZAR). For achieving universal access, the additional costs are about 336 million ZAR lower when nurses perform initiations (2,639 million ZAR versus 2,304 million ZAR in salaries). However, the number of additional nurses needed is increased by 13% (from 1.2 to 1.3 per 1,000 patients). Decreasing the frequency of routine clinic visits for new initiations to once every 2 months can save up to 36% of salary costs, and will reduce the number of additional nurses and counsellors required by 42%. Maintaining the frequency of routine clinic visits at once per month, but reducing the frequency of nurse-attended visits has a similar effect on the number of additional nurses required as reducing the overall frequency of clinic visits, but cost savings are less substantial since the same number of counsellors are needed in the two cases.

	Human resource needs (per 1,000 patients) (95% CI)			**Overall salary cost reduction**
	Nurses	**Counsellors**	**Doctors**	
Baseline	1.2 (0.8 - 1.6)	2.1 (1.3 - 2.9)	0.2 (0.1 - 0.2)	n/a
Scenario analysis				
Decrease visit frequency				
Every 2 months	0.7 (0.5 - 0.9)	1.2 (0.7 - 1.6)	0.2 (0.1 - 0.2)	36%
Every 3 months	0.5 (0.3 - 0.6)	0.8 (0.5 - 1.1)	0.2 (0.1 - 0.2)	50%
Every 4 months	0.3 (0.2 - 0.5)	0.6 (0.4 - 0.8)	0.2 (0.1 - 0.2)	57%
Decrease frequency of nurses per visit				
Every 2 months	0.7 (0.5 - 0.9)	2.1 (1.3 - 2.9)	2.0 (1.5 - 2.6)	24%
Every 3 months	0.5 (0.3 - 0.6)	2.1 (1.3 - 2.9)	2.0 (1.5 - 2.6)	33%
Every 4 months	0.3 (0.2 - 0.5)	2.1 (1.3 - 2.9)	2.0 (1.5 - 2.6)	38%
Nurse initiated treatment	1.3 (1.0 - 1.7)	2.1 (1.3 - 2.9)	N.A.	7%

Table 4.5. Impact of alternative models of ART delivery on HHW-to-patient ratio and overall salary costs for universal access to HIV treatment in South Africa. n/a = not applicable; 95% CI = 95% confidence interval.

4.4 Discussion

We estimate for the first time the additional HHW needed to achieve universal access to HIV treatment in South Africa, using data from a time-motion study. We show that universal access to ART at CD4 cell count ≤350 cells/μL will require South Africa to commit a further 2,200 nurses, 3,800 counsellors, and 300 doctors to HIV treatment, costing 929 million ZAR (141 million US$) in salaries. We found an average HHW-to-patient ratio of 0.2 per 1,000 patients for doctors (for performing all ART initiations), and 1.2 per 1,000 patients for nurses and 2.1 per 1,000 patients for counsellors (for performing initiations and maintaining all eligible patients on treatment).

It is interesting to compare our empirical findings from a time-motion study to estimates based on other sources of information. Based on reports of the total numbers of health workers and patients in HIV treatment programs, Hirschhorn et al estimated that in 2004 the number of doctors and nurses required to treat 1,000 HIV patients were 1-2 and 2-7, respectively, across different developing countries [29]. Based on recommendations "by experienced practitioners based on experience at sites in Kenya," a 2004 WHO report estimated that 1 doctor and 2 nurses were needed to treat 1,000 HIV patients [30]. The lower health worker requirements we estimate based on a time-motion study may be due to the fact that more than five years into the public-sector ART scale-up in South Africa [31] the productivity of delivering HIV treatment has increased because of scale effects and learning over time. Of course, it is also possible that the estimates differ because of quality-of-care differentials. The expert opinions elicited in the WHO report may have reflected a higher standard of quality of care than currently found in the real-life, public-sector HIV treatment program in rural KwaZulu-Natal, in which this study took place. Similar to other treatment programs in the region, non-retention and non-adherence in this program are substantial[32]. At the same time, however, the program, in which this study took place, has been very effective in reducing HIV-related mortality [31] and increasing life expectancy [33] in this community, and can therefore be considered an overall successful program delivering relatively high quality-of-care.

Data on the current health workforce specifically devoted to HIV care in South Africa are not available, but WHO estimates show that in 2004 there were about 35,000 doctors and 180,000 nurses in total in the country [34], i.e., South Africa had a health worker-to-population ratio exceeding the threshold of 2.3 doctors and nurses per 1,000 population, which has been proposed by WHO as a critical minimum [35,36]. While our study determines the additional numbers of health workers required for future ART scale-up under different scenarios, it does not enable us to directly evaluate this number in relation to the supply of health workers to establish whether there is a health worker shortage in South Africa, either nationwide or in regions. The number of doctors required to provide universal access to ART is currently one of the most critical capacity constraints in SSA, since only a few thousand doctors graduate from medical schools in the entire subcontinent each year [37,38], and the rates of doctor migration to countries outside the region remains high [11]. However, scaling up treatment to universal access for initiation at CD4 cell count ≤350 cells/μL will require only about 300 additional doctors committed to performing ART initiations, and may thus be feasible without major changes to national health worker production and retention.

On the other hand, recruiting the required additional 2,200 nurses fully devoted to HIV care may prove to be a greater challenge, given that the total of all professional nurses who graduated from nursing schools in South Africa in 2011 was only about 5,600 [39].

It is therefore vital to increase efforts to expand the health worker pool for HIV in South Africa by increasing training and retention, reinstatement of retired health workers, or increasing HHW productivity, in particular to achieve universal coverage at more relaxed eligibility criteria [37]. Currently, public-sector HHW are paid a salary on a monthly basis and, additionally, receive contributions to health and old-age pension insurance, as well as a rural allowance for service in underserved areas. Alternative models of contracting and incentivizing HHW, such as performance-based payment, could improve productivity. On the other hand, such new models may also lead to inefficiencies, such as the transaction costs of monitoring performance, and unintended behavioral consequences, such decreased quantity and quality-of-care of services not included in the performance-based payment scheme [40]. In addition, transferring public-sector ART patients to the private sector for routine follow-up and monitoring – as effectively done in Botswana and Mexico [41,42] – might increase the pool of available HHW. At the same time, of course, this strategy might increase the human resources costs per ART patient, because health worker salaries in the private sector in South Africa are higher than in the public sector. Health-worker interventions, such as shifting task from more to less skilled health workers [43] and integration of ART delivery into the general primary care services [44] should also be considered as means to free up human resources for HIV treatment. Integration might improve productivity, if it either increases capacity utilization (e.g., reducing idle time) or leads to economies of scope, as different health services are combined. Redistribution of HHW from overstaffed to understaffed clinics could further improve HHW productivity by reducing idle time. Finally, a number of interventions could increase the supply of health workers in South Africa, nationally or in regions, including interventions to decrease health worker out-migration and to increase health worker production [45,46]. One recent example is the 2012 agreement between Cuba and South Africa, which is intended to ensure continued placement of Cuban doctors in South African and increased training of South African nationals in Cuban medical schools [47].

There are several options for improving HHW productivity in PHC HIV clinics. We found that the average duration of a workday varied widely across clinics. The number of health care workers required for the treatment of 1,000 ART patients could be reduced by about one third if all clinics achieved the productivity of the most efficient clinic. In addition, the average duration of a workday in our data was 6.3 hours. If we assume a HHW workday to last 8 hours, we find that the total number of nurses, counsellors, and doctors required will be reduced by 23%, 24%, and 37% compared to the baseline in Clinic A, B, and C, respectively. Another way to improve productivity might be to reduce opening hours in selected clinics. We found that in the least busy (and most rural) clinic in our sample, on one particular day only 20% of HHW time was spent on direct patient contact and 36% was spent on breaks and idle time, because only a few patients visited the clinics on that day. Limiting the opening hours of selected PHC HIV clinics might reduce wastage due to idle time.

At the same time, however, such a strategy carries the potential danger of reducing access for particular populations, for instance, the employed or people living in rural areas. Finally, productivity gains might be achieved by cutting the time spent on breaks and idle time between patients. However, we found that on average only 9% of the workday was spent in this category - which translates to 43 minutes of break time on a workday of 8 hours - which is very short considering the demands of the job and the need for the health staff to eat and look after themselves during the work day, likely leaving little room for considerable productivity gains through this approach.

Universal access for all HIV infected patients (i.e. 'treatment-as-prevention') would require an additional 800 doctors, 6,000 nurses, and 11,000 counsellors fully dedicated to HIV treatment. Salary costs to cover all HHW under such a strategy are about 2.6 billion ZAR (394 million US$) per year, which is an increase of 20% compared to the current total HIV sector budget in South Africa. Of course, salaries are only one part of the running costs of added health care workers and expanding HIV treatment. Other expenditures necessary for HIV treatment include running costs for drugs, medical supplies, water and heating as well as investment costs for equipment, facilities, and continuing HHW education [48,49]. In addition, the need for support staff not involved in direct patient contact – such as laboratory technicians, supply-chain workers, general management staff, and trainers – will also grow with increasing treatment coverage. At present, a strategy of ART for all HIV infected patients seems unrealistic for South Africa without large additional financial commitments and substantial increases in HHW training capacity. On the other hand, the future impact of a 'treatment-as-prevention' strategy through reduced transmission has been suggested to be considerable [15,50,51], possibly outweighing the initial investments. Furthermore, the workload of initiating patients with advanced diseases is higher compared to patients with relatively high CD4 cell counts, resulting in a lower HHW-to-patient ratio. Further research is needed into the epidemiological and clinical benefits of a 'treatment-as-prevention' strategy, e.g. through randomized controlled trials in general populations in SSA [52].

Alternative models of ART delivery through task shifting or simplifications might provide a solution for the shortage of HHW. Preliminary studies show that the quality of nurse-initiated treatment is comparable to doctor-initiated treatment [53], and this strategy has recently been implemented in South Africa [13]. Our results suggest that this strategy could reduce overall salary costs by 7%. Also, reducing the required frequency of routine clinic visits could be a useful tool in order to decrease the required number of HHW to maintain patients on ART. Currently, patients are required to come every month until treatment has stabilized, and once every two months thereafter. Up to 50%-60% of total salary costs might be saved if patients only visited a clinic once every three or four months, or if the number of nurse-attended visits is decreased. While these figures suggest substantial potential for resource savings for universal HIV treatment coverage, it is currently not understood how the implementation of these alternative treatment delivery models will affect the quality of care. Already, non-adherence and non-retention are worrisomely high in South Africa's expanding ART program [54], and these problems might worsen when routine-visit frequencies are decreased.

Our study has several limitations. First, the time-motion data used in this study were from three different PHC HIV clinics in a rural area and covered only 13 days of observation. However, time spent per patient did not significantly differ between the clinics. Although the duration of the workday did differ significantly between two of the clinics, this could have been caused by the location of the clinic (rural versus more urban), which is associated with the patient load, rather than differences in work routine or the full potential productivity of the HHW. In the clinic with the shortest effective workday, an average of 14% of the time was spent on breaks and idle time between patients, while in the other clinics this percentage was only 5% and 7%. Second, we extrapolated our data from this specific rural setting to South Africa as a whole. Similar studies in other parts of South Africa are needed to confirm whether this extrapolation is justified.

Third, HHW were aware that they were being observed which might have induced HHW to increase their productivity during observed visits in comparison to unobserved visits. However, such a Hawthorne effect [55] is likely to be limited for a number of reasons. For one, the observer was not involved in the HIV treatment program and was not known to the HHW. Moreover, the observer completely abstained from providing performance feedback to the observed HHW, even if asked for such feedback, to eliminate this underlying cause of the Hawthorne effect [56]. Finally, we did not detect substantial changes in time allocation patterns within one clinic across the different observation days, suggesting that observer bias, which is likely to wane (due to increasing HHW tolerance to being observed) or grow (due to feedback and learning) over time, may not have plaid an important role in this study.

Fourth, the observed activities might not be all encompassing, as some infrequent activities such as continued training and attending workshops or conferences were not observed. However, these activities will take up only a limited proportion of the total number of work-hours over a year [39] and biases due to excluding these activities will thus be limited. Finally, there are several assumptions in our analyses that might affect our results. We assume that the measured doctor-time is only for initiations, and counselor- and nurse-time for both initiation and follow-up. This simplification could have biased our estimates, especially for doctor-time, as doctors also perform tasks other than initiations, such as completing disability grant forms or looking after more complex cases (suspected treatment failure, side effects, adverse events, etc.).

Task time allocation and HHW productivity will likely depend on the model of HIV treatment delivery. The current delivery model may change as South Africa has embarked on a major primary health care (PHC) reform, with the goal of providing universal access to a comprehensive package of health care services in the public sector through a national health insurance scheme [57]. Several initiatives included in the reform may improve the availability of HHW. So-called district specialist teams will be recruited and deployed in all of the 52 districts in the country to improve the standard of care delivered in community-based health care facilities [39]. These teams will consist of four medical specialists and three advanced professional nurses. In addition, each PHC ward will have at least one PHC outreach team consisting of a professional nurse, environmental health and health promotion practitioners, and four to five community health workers. The role of the outreach

team will include health promotion and prevention campaigns, early detection and interventions for selected health problems, as well as support for treatment retention and adherence [39]. These initiatives, which are currently tested in pilot studies, could help to further devolve HIV treatment to communities and homes, freeing up HHW in health care facilities.

We provide a point estimate for the HHW required for one year of treatment in the present time. In the longer run, the current HHW and ART coverage levels may themselves affect HHW requirements for a number of reasons [38]. On the one hand, because ART is effective in reducing mortality, the more patients receive ART in the current period, the more patients will require treatment in future periods, assuming that HIV incidence remains unchanged [58,59]. On the other hand, ART can effectively prevent HIV transmission [15,50,51,60-62], which would lead to a reduction in the number of HHW required in future periods if mortality remained constant. In future studies, dynamic models need to examine the impact of the mortality-reducing and preventive effects of ART on long-term HHW requirements. Those studies should also take into account that ART may change the type of patient needing ART. For one, ART may shift the age composition of ART patients towards older ages [63,64], increasing the average morbidity among ART patients and the average health-worker time required for providing appropriate treatment per patient. Moreover, the case mix of ART patients might change over time due to increasing ART failure and long-term ART toxicities. These changes may increase the average health-worker time required per patient because they necessitate time-consuming counselling, ART switches, and complex treatments of ART side effects [65].

In conclusion, we provide policy-relevant estimates of the number of HHW needed and associated salary costs for scaling up HIV treatment to universal access under different eligibility criteria and delivery models in South Africa. We show that, in terms of HHW required, scaling up to universal access for ART at CD4 cell count ≤350 cells/μL seems achievable in the present context, while universal coverage for all HIV infected patients is likely to be extremely difficult unless substantial additional human and financial resources can be mobilized for ART delivery. Further research is needed to determine how different treatment strategies affect the in- and out-flow of patients into the system through reduced transmission and increased survival, and how quality and productivity of HIV treatment is affected by different ART delivery models.

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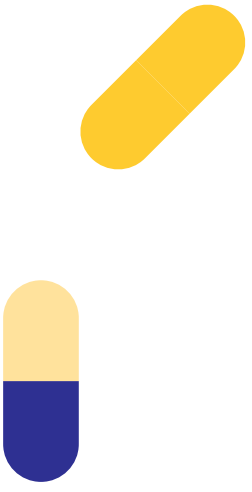

5. The potential impact of RV144-like vaccines in rural South Africa: a study using the STDSIM microsimulation model

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Abstract

Background

The only successful HIV vaccine trial to date is the RV144 trial of the ALVAC/AIDSVAX vaccine in Thailand, which showed an overall incidence reduction of 31%. Most cases were prevented in the first year, suggesting a rapidly waning efficacy. Here, we predict the population level impact and cost-effectiveness of practical implementation of such a vaccine in a setting of a generalized epidemic with high HIV prevalence and incidence.

Methods

We used STDSIM, an established individual-based microsimulation model, tailored to a rural South African area with a well-functioning HIV treatment and care program. We estimated the impact of a single round of mass vaccination for everybody aged 15-49, as well as 5-year and 2-year re-vaccination strategies for young adults (aged 15-29). We calculated proportion of new infections prevented, cost-effectiveness indicators, and budget impact estimates of combined ART and vaccination programs.

Results

A single round of mass vaccination with a RV144-like vaccine will have a limited impact, preventing only 9% or 5% of new infections after 10 years at 60% and 30% coverage levels, respectively. Revaccination strategies are highly cost-effective if vaccine prices can be kept below 150 US$ / vaccine for 2-year revaccination strategies, and below 200 US$/vaccine for 5-year revaccination strategies. Net cost-savings through reduced need for HIV treatment and care occur when vaccine prices are kept below 75 US$/vaccine. These results are sensitive to alternative assumptions on the underlying sexual network, background prevention interventions, and individual's propensity and consistency to participate in the vaccination campaign.

Discussion

A modestly effective vaccine can be a cost-effective intervention in highly endemic settings. To predict the impact of vaccination strategies in other endemic situations, sufficient knowledge of the underlying sexual network, prevention and treatment interventions, and individual propensity and consistency to participate, is key. These issues are all best addressed in an individual-based microsimulation model.

5.1 Background

Despite extensive efforts and billions of dollars invested in attempts to curb the spread of HIV [1], HIV prevalence remains disturbingly high in many endemic countries. Although it has been suggested that HIV incidence may be declining among young adults in countries like South Africa, the total number of prevalent infections at a global level increased again in 2009, with now more than 33.3 million people living with HIV, of whom 22.5 million in Sub-Saharan Africa [2]. Only few biomedical prevention interventions have been proven successful in trials and in the field, while other promising interventions remained ineffective in real world situations [3,4]. In 2009, Rerks-Ngarm et al presented the results of the first and only HIV vaccine randomized controlled trial to date that showed a significantly reduced HIV incidence [5]. In their modified intention-to-treat analysis, the ALVAC and AIDSVAX vaccine combination reduced HIV incidence by 31.2% (95% CI: 1.1% to 52.1%). Although the vaccine efficacy was modest and only borderline significant, some argue that the population level impact of such a vaccine might be comparable to that of male circumcision [6]. With numerous HIV prevention trials showing no effect, the RV144 trial result deserves further attention.

Mathematical modeling can explore the potential effects of HIV prevention interventions in a given population. Many mathematical models have been used to this end [7], including compartmental models [8,9,10] and microsimulation (i.e. 'agent based') models [11,12]. Compartmental models are generally less complex in structure, work with differential equations, and ignore chance. In contrast, microsimulation models simulate individuals ('agents') and therefore allow for more detailed heterogeneity among individuals. These models can also more realistically simulate the many interacting factors that contribute to the spread and control of HIV, including the complexity of sexual networks [13].

Here, we used the established microsimulation model STDSIM to estimate the impact of the ALVAC/AIDSVAX vaccine on the HIV epidemic in a rural South African setting with a high prevalence and incidence with a well-functioning HIV treatment and care program [14,15]. We present base-case results consisting of a single round of mass vaccination, as well as the impact, cost-effectiveness, and budget impact of repeated vaccination (revaccination) strategies in combination with antiretroviral therapy (ART). In addition, we investigate the impact under alternative assumptions for mechanisms that are often highly simplified in other models: sexual mixing patterns, background prevention interventions, and vaccine delivery.

5.2 Methods

Model and vaccine

We used STDSIM, a stochastic microsimulation model for the spread and control of HIV and other STIs [13,16,17]. The model simulates individuals in a dynamic network of sexual contacts, and has been extensively used to evaluate the impact of prevention and treatment interventions on HIV epidemics in sub-Saharan African settings [11,18,19]. Here, we used a quantification,

i.e. parameter settings, for the Hlabisa sub-district in KwaZulu-Natal, South Africa. This area has an HIV prevalence approaching 30% in adults aged 15-49 years in 2010, and a well-developed ART program [14,20]. In the model, based on results from recent observational studies elsewhere in Africa, ART reduces HIV infectiousness by 92% [21,22] and increases the remaining ART-naive HIV survival by a factor of 3 at time of ART initiation [23]. We assume ART to be given at ≤200 cells/μL from 2004, and at ≤350 cells/μL from mid-2010, according to the new WHO treatment guidelines [24]. The coverage of ART in 2009 as a result of the modeled health seeking behavior is about 21% of all HIV infected patients, and 75% of those eligible, which corresponds with local data [20]. The modeled circumcision rate is 25% [25], and condom use during casual sexual contacts or commercial sex is 25% from 2003 onwards [25-27]. A detailed description of the model and this quantification can be found in supplement I: Quantification of STDSIM to rural KwaZulu-Natal. All modeling results in this paper are averages over 1,000 model runs.

The vaccine efficacy is based on the modified intention-to-treat efficacy estimate of 31.2% of Rerks-Ngarm et al [5]. However, most infections were prevented in the first year after vaccination, suggesting a rapidly waning immunity. Consequently, we assumed the following vaccine efficacy (VE, varying between 0 and 1, where 1 is full protection and 0 equals no protection): $VE=0.78 \times \exp(-0.06t)$, where t = time since vaccination in months. Although the vaccine in the trial consisted of several different injections, we assume the vaccine to consist of 1 injection and protection to occur immediately in order to avoid undue complexity in our model.

Vaccination strategies

The base-case scenario consists of a single round of mass vaccination for which the entire population aged 15-49 years is eligible. Two different coverage levels are defined for the base-case scenario: low uptake (30% coverage), and moderate uptake (60% coverage). The mass vaccination campaign is assumed to take place in 2015, and to take a total of 6 months (January 2015 to June 2015). We examined the impact on HIV incidence and prevalence over the period 2015-2025, as well as the proportion of new infections averted over the same period.

A vaccine with such a quickly waning efficacy is unlikely to be introduced in the form of a one-time mass vaccination program. Therefore, we also examined the impact of revaccination strategies for young adults (aged 15-29), assuming two different frequencies of revaccinating, every 2 years and every 5 years, again at coverage levels of 30% and 60%. Here, we consider revaccination as repeated vaccination programs with the same vaccine in the target age-group. We assume that revaccination will boost immunity to the same level and duration of protection as afforded by the initial vaccination, regardless of the remaining level of immunity after a previous vaccination. The propensity to participate in health care and prevention programs varies among individuals, resulting in core groups of participants and non-participants in repeated programs such as repeated vaccination programs. Therefore, modeled participation in the revaccination campaign was random during the first round (when individuals become eligible for the first time based on their age), and individuals participating in the first round are more likely to also participate

in subsequent vaccination rounds. Consistency of participation in revaccination rounds in the model can range from 0% (i.e. fully random participation in each successive round) and 100% (i.e. the same individuals participate in successive re-vaccination rounds). We assumed a consistency of participation of 50%. When individuals age out of the target population (i.e. aged 30+ years), they are no longer eligible for subsequent vaccination rounds. We assume that one vaccination round takes 6 months (January to June).

We calculated the 20-year (2015-2035) impact and efficiency for several revaccination strategies: i) population aged 15-29; ii) population aged 15-49; iii) population aged 15-24; iv) population with highest HIV incidence (i.e. women aged 15-24, men aged 25-34); and v) Population aged 15-49 and with multiple recent partners (2+ partners in the last 6 months). In addition, we explored the impact of risk compensation of those who received the vaccine on the proportion of infections prevented and efficiency of the vaccination program. Individuals who are vaccinated might perceive themselves at a lower risk of acquiring an HIV infection and reduce their condom use [28]. In addition, vaccination might delay the time for an HIV infected patient to seek HIV specific care. Asymptomatic vaccinated HIV infected patients might be less likely to attend voluntary counselling and testing services, while symptomatic vaccinated patients might seek care elsewhere before visiting an HIV clinic due to a lower perceived risk of having HIV. Therefore, we assumed two types of risk compensation: sexual risk compensation (reduced condom use rates from 25% to 15% in casual relations for vaccinated individuals) and healthcare seeking risk compensation (doubling the HIV-stage specific time until a vaccinated and infected person seeks HIV-related care, see supplement I: Quantification of STDSIM to rural KwaZulu-Natal). We calculated the cumulative proportion of new infections prevented over the 20-year period, as well as the number needed to vaccinate (NNV) to prevent one new infection [29].

Cost-effectiveness

HIV infections prevented through vaccination will lead to reductions in costs for HIV treatment and care. Therefore, we estimated the impact of the vaccination program on the total costs of the combined vaccination and treatment and care program. For the annual costs of HIV treatment and care, we used published values from Cape Town [30] (see supplement I: Quantification of STDSIM to rural KwaZulu-Natal and chapter 2 of this thesis). We calculated the cumulative net cost of delivering HIV treatment and care under different vaccination strategies and price levels of the vaccine compared to the cost of HIV treatment and care in the absence of vaccination. Budget impact results were calculated for the 2-year and 5-year revaccination strategies, targeted at the population aged 15-29, and the population with the highest HIV incidence (women aged 15-24, men aged 24-35). Price levels for the vaccine ranged between 10 US$/vaccine and 200 US$/vaccine. All cost results are per vaccine recipient.

International benchmarks suggest that interventions that cost less than three times a country's gross domestic product (GDP) per capita per Disability Adjusted Life Year (DALY) averted can

be considered cost-effective, while interventions that cost less than one time a country's GDP per capita per DALY averted can be considered highly cost-effective [31]. Here, we assumed that life-years gained crudely reflect DALYs averted. By ignoring the disability loss due to living with an infection, we only slightly underestimate the total number of DALYs averted through vaccination, as the WHO estimates show that the years lived with disability only accounts for 9% of the total DALY loss due to HIV in the Africa region [32]. South Africa's GDP per capita was 10,140 US$ in 2009 [33]. We divided the total budget of the vaccination strategies by the associated life years gained, and established the maximum vaccine price level that would still render the vaccination strategy cost-effective (i.e. costing less than 30,420 US$ per life year gained) and highly cost-effective (i.e. costing less than 10,140 US$ per life year gained), respectively. All life-years gained and future costs were discounted at an annual rate of 3% [34].

Scenario analysis

We used the 60% coverage, 2-year revaccination strategy for young adults to determine the importance of the assumptions regarding the underlying sexual network, participation with and implementation of the vaccination program, and the background treatment and prevention interventions.

We first tested the impact of the vaccine in sexual networks with higher and lower levels of concurrency by adjusting the duration of relationships. As these alternative scenarios resulted in a different HIV epidemic than observed, we fine-tuned the HIV epidemic to accurately reflect the observed HIV epidemic of the Hlabisa sub-district by adjusting circumcision and condom use rates, and the effectiveness of STI treatment in reducing HIV transmission (see supplement I: Quantification of STDSIM to rural KwaZulu-Natal for more details). In addition - in order to examine the impact of the vaccine for different levels of endemicity - we made two scenarios in which the overall partner change rates were increased and decreased by 10%, resulting in a proportion of 15-49 year olds with 2+ partners in the last 12 months of 44% and 40% respectively (baseline = 42%). The resulting HIV prevalence in the 10% reduction scenario is comparable to the HIV epidemic in South Africa as a whole [2] (see figure 2.1 in chapter 2).

Since there is heterogeneity in the risk of acquiring and transmitting sexually transmitted infections, the impact of an HIV vaccine will depend especially on the participation rates of high-risk groups [35]. Therefore, we calculated the impact under a scenario where only individuals with multiple recent partners (defined as those having 2 or more partners in the last 6 months) participate (100% participation of men and women with multiple recent partners), and a scenario where only low-risk individuals participate (0% participation of men with multiple recent partners, and 16% participation of women with multiple recent partners), with total population coverage remaining at 60%. In addition, we examined the effect of different durations of a single vaccination round by giving the vaccine to the target population over the course of two year versus delivering it to all participants at once (i.e. over the course of a day), and we looked at how participation consistency affects the impact of the 2-year revaccination strategy by assuming scenarios of 0% consistency and 100% consistency. Finally, we also examined the impact of declining participation rates by assuming

a scenario in which initial coverage is 60% in 2015, but declines by to 40% after 4 revaccination rounds (5% decline every vaccination round).

Furthermore, we analysed the impact of the 2-year revaccination strategy under the following treatment and prevention scenarios: i) no ART, ART at ≤200 cells/μl from 2004 onwards, and ART at ≤500 cells/μl in 2012; ii) circumcision rates of 0% and 100%; iii) no condom use and 50% condom use in casual relationships from 2012 onwards. Although some of these values might be unrealistic, we chose them in order to show the maximum effect these parameters might have on the impact of the vaccine.

5.3 Results

Vaccination strategies

Figure 5.1 shows the 10-year impact of the base-case scenarios on the HIV epidemic in Hlabisa, South Africa. A single round of mass vaccination with the ALVAC/AIDSVAX vaccine in this rural setting of South Africa will initially reduce HIV incidence in mid-2015 by about 40% (1.8/100 person-years to 1.1/100 person-years) under 60% coverage, and about 20% (1.8/100 person-years to 1.4/100 person-years) under 30% coverage. However, due to the short-lived efficacy of the vaccine incidence rates quickly rebound, thus limiting its impact on HIV prevalence (figure 5.1B). The proportion of new infections prevented under coverage levels of 60% and 30% are 9% and 5%, respectively, within the first 10 years after vaccination (figure 5.1C).

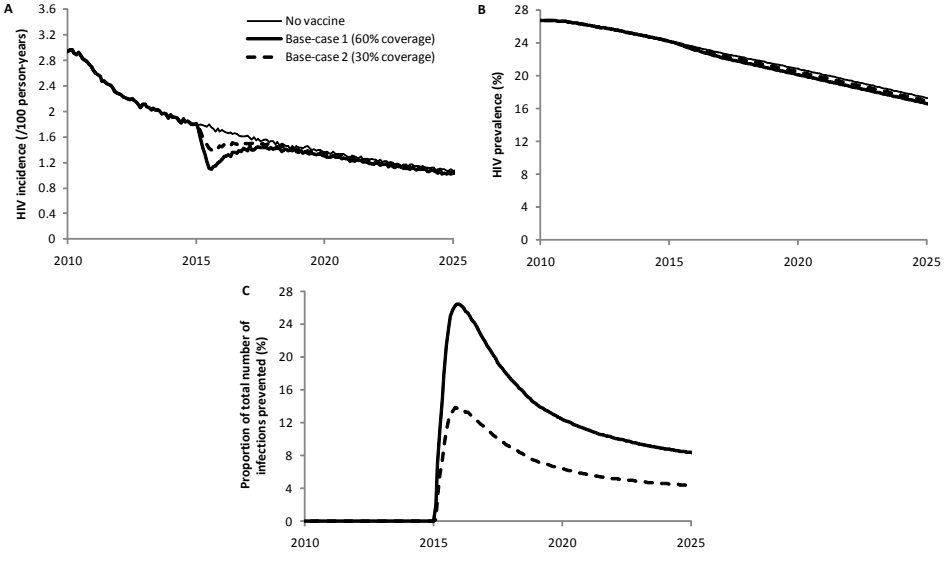

Figure 5.1. Impact of base-case vaccination scenarios on HIV epidemic in Hlabisa over the period 2015-2025. A = HIV prevalence, B = HIV incidence; C = Cumulative proportion of infections prevented.

Revaccination strategies in young adults (aged 15-29) will have a more profound impact on the HIV epidemic (figure 5.2). Revaccinating this population every 2 years at coverage levels of 60% will reduce incidence by 37% (from 0.67% to 0.43%, figure 5.2A) and HIV prevalence by 23% (11.1% to 8.6%, figure 5.2B) by 2035. The cumulative proportion of new infections prevented by this strategy is 23% over a 20-year period (figure 5.2C). Revaccinating every 5 years has a smaller but still substantial impact, reducing incidence by 16% (from 0.67% to 0.57%) and HIV prevalence by 12% (11.1% to 9.8%) by 2035.

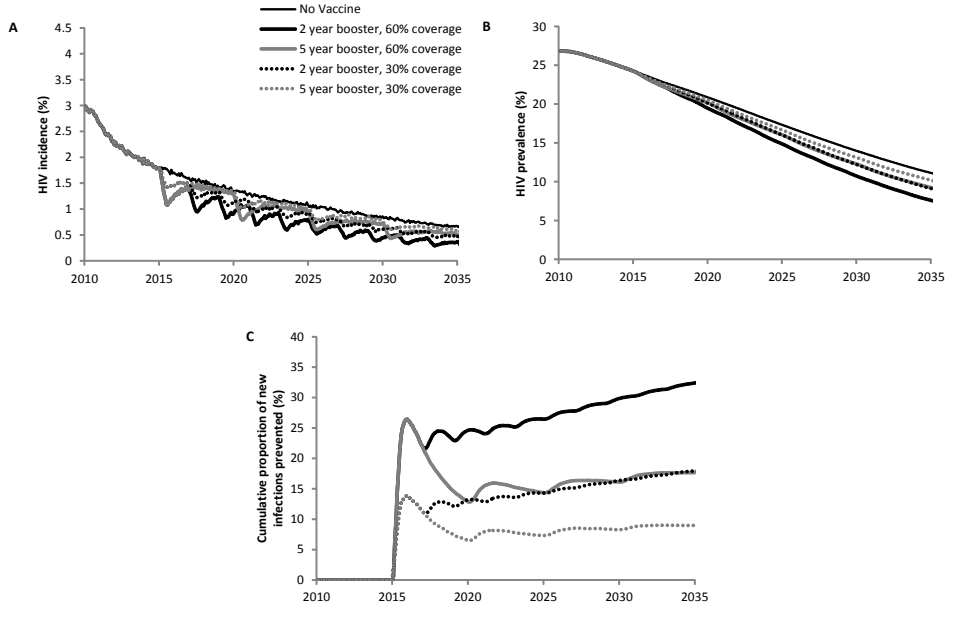

Figure 5.2. Impact of different revaccination strategies on HIV epidemic and proportion of infections prevented in Hlabisa over the period 2015-2040. A = HIV prevalence, B = HIV incidence; C = Cumulative proportion of infections prevented.

Cost-effectiveness

Table 5.1 gives an overview of (cost-) effectiveness indicators for different revaccination strategies. Both 2-year and 5-year revaccination strategies are highly likely to be cost-effective, since the lowest maximum price of delivering a vaccine in order to remain highly cost-effective is 104 US$/vaccine (2-year revaccination for population aged 15-49, 60% coverage). Revaccinating every 5 years is more cost-effective compared to revaccinating every 2 years. The most cost-effective strategy is targeting the age-groups with the highest HIV incidence (NNV = 52 for 2-year revaccination, and 45 for 5-year revaccination), while the biggest impact is achieved by vaccinating the population aged 15-49 (proportion of new infections prevented = 32% for 2-year revaccination, and 18% for 5-year revaccination). Risk compensation both regarding healthcare seeking behavior and sexual behavior can easily nullify the impact of vaccination. The only strategy that still shows a clear positive effect under high levels of risk compensation is the 2-year revaccination strategy, provided that coverage levels are kept at around 60%.

	2-year revaccination				5-year revaccination			
	Infections prevented	NNV	Max costs to be cost-effective (US$)	Max costs to be highly cost-effective (US$)	Infections prevented	NNV	Max costs to be cost-effective (US$)	Max costs to be highly cost-effective (US$)
15-29 years								
30% coverage	13%	64	641 $/vaccine	214 $/vaccine	7%	57	476 $/vaccine	158 $/vaccine
60% coverage	23%	70	505 $/vaccine	168 $/vaccine	12%	60	856 $/vaccine	285 $/vaccine
15-49 years								
30% coverage	18%	80	598 $/vaccine	199 $/vaccine	9%	73	540 $/vaccine	180 $/vaccine
60% coverage	32%	89	312 $/vaccine	104 $/vaccine	18%	72	977 $/vaccine	326 $/vaccine
15-24 years								
30% coverage	8%	64	423 $/vaccine	141 $/vaccine	8%	65	1,518 $/vaccine	506 $/vaccine
60% coverage	15%	72	478 $/vaccine	159 $/vaccine	4%	61	861 $/vaccine	287 $/vaccine
M 25-34 years, F 15-24 years								
30% coverage	11%	47	1,381 $/vaccine	461 $/vaccine	5%	44	1,886 $/vaccine	629 $/vaccine
60% coverage	20%	52	976 $/vaccine	325 $/vaccine	10%	45	1,352 $/vaccine	451 $/vaccine
15-29 years (sexual risk compensation)								
30% coverage	1%	1,507	184 $/vaccine	61 $/vaccine	-7%	n/a	n/a	n/a
60% coverage	12%	82	218 $/vaccine	73 $/vaccine	0%	n/a	n/a	n/a
15-29 years (healthcare seeking risk compensation)								
30% coverage	6%	126	n/a	n/a	-1%	n/a	n/a	n/a
60% coverage	17%	95	264 $/vaccine	88 $/vaccine	6%	123	n/a	n/a
15-49 years (targeting high-risk groups)								
30% coverage	9%	50	234 $/vaccine	2,111 $/vaccine	5%	47	312 $/vaccine	2,807 $/vaccine
60% coverage	18%	53	203 $/vaccine	1,831 $/vaccine	8%	51	177 $/vaccine	1,589 $/vaccine

Table 5.1. (Cost-) effectiveness of different revaccination strategies with the RV 144 vaccine in the Hlabisa sub-district of KwaZulu-Natal, South Africa. Results are cumulative over a period of 20 years. NNV=Number Needed to Vaccinate to prevent one new infection. The maximum costs of a single vaccine in order to be cost-effective is based on a cost-effectiveness threshold of 30,420 US$/life-year gained (3 times South Africa's per capita GDP of 2009 (10,140 US$), cost-effectiveness threshold for highly cost-effective interventions is 10,140 US$/life-year gained. M=Male, F=Female. n/a = not available because no life-years were gained and/or infections prevented

At a price of 75 US$/vaccine, the initial investment of a 2-year revaccination strategy for young adults or high incidence age groups is fully recovered from reductions in HIV treatment and care needs over the 20 years period; and net cost savings will occur (figure 5.3A and 5.3C). For the 5-year revaccination strategy, vaccine prices below 100 US$/vaccine will produce similar effects (figure 5.3B and 5.3D).

Scenario analysis

Table 5.2 gives an overview of the effect of different assumptions concerning background sexual networks, background prevention interventions, and vaccine delivery issues on the proportion of infections prevented and NNV after 20 years of a 2-year revaccination strategy for young adults at 60% coverage. The level of the epidemic clearly affects cost-effectiveness. A 10% reduction in partner change rates, reflecting an HIV epidemic comparable to that of South Africa as a whole, would result in a 40% increase in the NNV. In addition, the prevalence of background prevention interventions already in place substantially affects the impact and cost-effectiveness of vaccination,

with high levels of circumcision and condom use lowering cost-effectiveness (both more than doubling the NNV). In addition, we show that underlying sexual networks affects the impact of vaccination. Higher levels of concurrency imply more overlapping relationships, and thus a relatively higher impact of the vaccine given its short lasting efficacy. On the other hand, the impact of the vaccine is slightly less in more serial monogamous populations.

Parameter	Proportion of infections prevented (Baseline = 23%)	NNV (Baseline = 70)
Different sexual networks [a]		
More serial monogamy	21%	78
More concurrency	26%	62
Overall partner change rates [b]		
+10% (adult HIV prevalence in 2009 = 33%)	23%	63
-10% (adult HIV prevalence in 2009 = 20%)	23%	97
ART use		
No ART	17%	35
≤200 cells/µl	23%	43
≤500 cells/µl	20%	130
Circumcision rates		
0%	24%	63
100% [c]	21%	157
Condom use		
No condoms	24%	37
50% by 2012	17%	152
Heterogeneity of participation		
Individuals with multiple recent partners more likely to participate	25%	59
Individuals with multiple recent partners less likely to participate	19%	90
Duration of vaccination round		
2 years	21%	75
1 day	24%	67
Consistency of participation		
No consistency	24%	63
Full consistency	19%	86
Declining participation rates [d]	19%	89

Table 5.2. Impact of alternative assumptions regarding background sexual network, background prevention and treatment interventions, and vaccine programmatic issues on proportion of new infections prevented and number needed to vaccinate (NNV) over the period 2015-2035. Revaccination strategy is 2-year revaccination for young adults (aged 15-29), at coverage levels of 60%.

5.4 Discussion

We show that one-off vaccination with ALVAC/AIDSVAX-like vaccines will have a limited impact in a generalized HIV epidemic with high HIV incidence and prevalence. However, if immune responses can be restored through revaccination, vaccination might become a highly cost-effective intervention. Due to reduced future costs of HIV treatment and care, HIV vaccines with limited and waning efficacy, might still result in net cost savings within about 20 years if prices can be kept below 100 US$/vaccine for 5-year revaccination strategies, and below 75US$/vaccine for 2-year revaccination strategies.

Although these results are promising, countervailing forces should be considered. Risk compensation through reduced condom use or a reduced propensity to seek HIV treatment and care might counteract the initial impact of vaccination. In addition, participation dynamics affect both the impact and cost-effectiveness of the vaccine. Whether individuals with multiple recent partners are more likely to participate can further alter the cost-effectiveness ratio, as well as the level of consistency of participation for revaccination strategies. Also, the question remains as to whether the ALVAC/AIDSVAX vaccine is effective at all. The modified intention-to-treat analysis presented by Rerks-Ngarm et al was only borderline significant (p=0.04), and there were no immunological effects measured [5]. Moreover, the trial took place in Thailand where subtype B and recombinant subtypes of the HIV-1 virus are dominant, while the HIV-1 subtype C is dominant in Southern Africa [36]. It is unknown whether an unmodified ALVAC/AIDSVAX vaccine will display the same, if any, effect on the transmission of subtype C HIV-1. Finally, whether the immune response can be restored through revaccination or not was not tested by Rerks-Ngarm et al. Therefore, confirmation of our results can only follow from subsequent trials incorporating revaccination strategies, preferably carried out in highly endemic areas.

The implementation of an intervention inevitably entails a trade-off between the cost-effectiveness of different, competing, interventions. In addition, it involves non-financial issues such as equity and feasibility [37]. Although a moderately effective vaccine might be cost-effective, interventions need to be prioritized by their marginal cost-effectiveness, which may still be higher for other interventions, such as scaling up male circumcision [38, 39]. Also, while we considered an international benchmark on the basis of GDP per capita to define interventions as (highly) cost-effective, we realize that this benchmark is poorly grounded in economic theory and therefore somewhat arbitrary. In addition, it might also be ethically moot to let the valuation of human life depend on per capita GDP. Nevertheless, we still consider it convenient in the absence of local comparative cost-effectiveness information. Furthermore, in order to avoid unnecessary complexity, we assumed vaccination only for the HIV negative population. There are indications that a large part of the HIV positive population is aware of their status since 21% is on treatment [20], and 60% of those diagnosed with HIV have a CD4 cell count of >200 cells/μL and are thus ineligible to initiate treatment (figure 2.1G in chapter 2). Since many HIV infected patients are aware of their status and thus unlikely to participate in a vaccination campaign, our assumption that only the HIV negative participates will slightly underestimate the total costs of a vaccination program. On the other hand, DALYs averted are also slightly underestimated by our assumption that life-years gained reflect DALYs averted, as living with an infection is associated with a somewhat lower quality of life, and accounts for about 9% of the total DALY loss due to HIV in Africa [32]. Finally, we did not consider the broader economic and societal impact of preventing HIV infections through vaccination, which might further improve cost-effectiveness ratios [40].

We show that the population level impact of a vaccine in terms of proportion of new infections prevented does not differ much for different levels of endemicity. Nevertheless, the cost-effectiveness of an ALVAC/AIDSVAX-like vaccine depends on absolute numbers averted per vaccination and

will thus be reduced significantly under lower endemicity levels. This implies that population-wide vaccination strategies with such a vaccine may only be cost-effective in highly endemic generalized epidemics. In countries with concentrated epidemics, risk group targeting may be considered.

In our STDSIM model, we were able to explore a wide range of mechanisms such as underlying sexual networks, treatment and prevention interventions, individual based risk compensation, and propensity and consistency of vaccination participation, that could possibly influence the impact of vaccination. We show that simplified assumptions regarding mechanisms might result in conclusions that are not necessarily correct. The complexity of the influence of these different mechanisms therefore merits the use of a model that is capable of simulating the sexual network of a specific settings as well as the interaction between different treatment and prevention interventions that are in place, and an individual based propensity and consistency of participation, i.e. an individual ("agent") based microsimulation model. On the other hand, our finding that these factors influence model predictions also increases the requirement for quality data to quantify the associated model parameters.

Despite the fact that the trial results of Rerks-Ngarm et al were initially labeled as interesting but not useful for implementation [41], our results suggest that a vaccine with limited and waning efficacy might be a cost-effective intervention in generalized HIV epidemics and can even lead to net cost savings, however provided that the immune response can be restored through revaccination and no risk-compensation takes place. A single round of mass vaccination will indeed only have a limited and short-lived impact. Since the trial results are borderline significant and took place in Thailand, subsequent trials of ALVAC/AIDSVAX-like vaccines in high endemic countries are needed. Furthermore, we present clear advantages of individual-based modeling in evaluating HIV prevention interventions, since the impact of the vaccine is dependent on the background sexual network, combination of prevention interventions, and individuals' propensity and consistency to participate in vaccination campaigns.

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6. Ageing with HIV in South Africa

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Supplementary material at: Supplement I: Quantification of STDSIM to rural KwaZulu-Natal

Abstract

We used an established microsimulation model, quantified to a rural South African setting with a well-developed antiretroviral treatment program, to predict the impact of antiretroviral therapy on the HIV epidemic in the population aged 50+. We show that the HIV prevalence in patients aged 50+ will nearly double in the next 30 years, while the fraction of HIV infected patients aged over 50 will triple in the same period. This ageing epidemic has important consequences for the South African health-care system, as older HIV patients require specialized care.

6.1 Background

Antiretroviral therapy (ART) is changing the character of the HIV epidemic in sub-Saharan Africa. At the individual level, ART has increased survival of those infected. At the population level, widespread availability of ART could result in the overall ageing of the infected population. ART use in sub-Saharan Africa is expanding rapidly, with an estimated 3.9 million patients on treatment in 2009 [1]. Estimates show that there are already about 3 million people over 50 years living with HIV in sub-Saharan Africa [2]. Recently, Mills et al argue for more attention to be paid to HIV infected older people in terms of prevention and care [3]. In the United States, estimates from the CDC show that about 29% of the entire population living with HIV was aged over 50 years in 2008 [4], and projections show that in about 5 years time, more than half of all HIV infected patients will be aged over 50 years [5]. Although it is clear that the number of HIV infected elderly (aged over 50) in sub-Saharan Africa will rise as a result of the ART roll-out, the magnitude of this phenomenon has not yet been quantified. One of the countries most likely to be confronted with this shifting epidemic is South Africa, where nearly 6 million people are estimated to be HIV infected, of whom 970,000 were on ART in 2009 [6]. HIV prevalence in the population aged over 50 in South Africa is estimated at about 9% [2, 7].

6.2 Methods

To predict the impact of the current ART roll-out on age- and sex-specific HIV prevalences in South Africa up to 2040, we used an established mathematical model (STDSIM) that simulates individuals in a dynamic network of sexual contacts [8, 9]. The model is tailored to the Hlabisa sub-district in KwaZulu-Natal, South Africa (supplement I: Quantification of STDSIM to rural KwaZulu-Natal). This area has a high HIV prevalence [10] and a well-developed ART program [11, 12]. In the model, the survival of ART-naïve HIV infected patients is on average 10 years. We assumed ART to increase survival from start of treatment by a factor 3 and decrease infectivity by 92%, as observed in recent studies [13, 14]. We assumed ART to be initiated at CD4 cell counts of ≤200 cells/μL in the period 2004 - 2010, and ≤350 cells/μL in 2011, according to the new WHO guidelines [15]. The model contains an age-specific partner change rate, and frequency of intercourse within a sexual relationship. In previous applications of our model [9] decreasing trends of sexual activity by age in the population aged 15-49 were simply extrapolated to the over-50 group because of lack of available data on sexual behavior in the population aged 50+. This resulted in a negligible level of risk behavior and HIV-incidence in the over-50 group, which is inconsistent with recent local data in terms of HIV prevalence in this group [7]. Therefore, we now assumed partner acquisition rates to remain at the same level from age 45 onwards, while the frequency of sexual contacts within a relationship is reduced by 25% for those aged over 50. The ART roll-out in Hlabisa is part of the South African national ART roll-out aimed at achieving universal coverage. Therefore, we assume that the impact of ART on the course of the epidemic is not affected by migration.

6.3 Results

Figure 6.1A shows the projected trends in HIV prevalence in the population aged 15-49 and 50+ in Hlabisa. While HIV prevalence in the 15-49 group would more than halve in the period 2010-2040 from 28% to 9%, the HIV prevalence in the population aged 50 years and older is estimated to nearly double in the same period, from about 9% (8% in women; 11% in men) to 17% (16% in women; 17% in men). The total number of HIV infections in those aged over 50 is expected to have increased by 51% in 2025 (49% for men; 53% for women), after which the number of HIV infections in this age group remains relatively stable (figure 6.1B). The absolute number of HIV infections in the elderly is estimated to even have doubled by 2025 when comparing to 2004, the year the ART roll-out in the area started. As a result, the age distribution of HIV infected patients would change considerably (figure 6.1C). This is especially true for men, where currently less than 1 in 12 HIV infected people is aged over 50; in 2040 this would be 1 in 4.

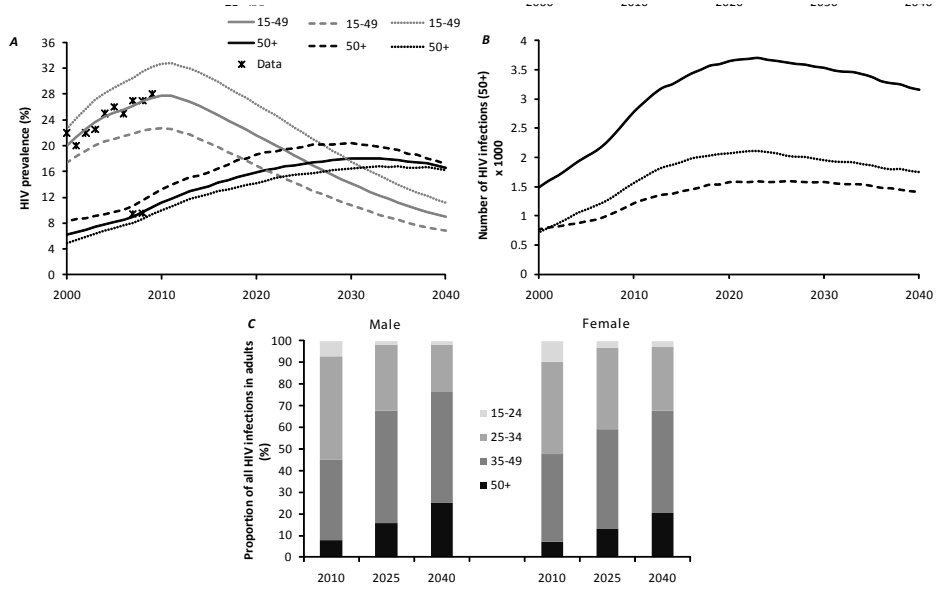

Figure 6.1. HIV prevalence (in the 15-49 and 50+ age groups), total number of infections, and age distribution of HIV infected patients over the period 2000-2040 in the Hlabisa sub-district of KwaZulu-Natal, South Africa, predicted with the STDSIM model. A = HIV prevalence in those aged 15-49 and 50+ years. Data points from HIV surveillance in Hlabisa [5, 7], B = Absolute number of HIV infections among the population aged 50+ in the Hlabisa sub-district (total population size approximately 280,000 in 2009), C = Age distribution of HIV infected men and women in 2010, 2025 and 2040.

6.4 Discussion

We show that the number of HIV infected elderly will increase substantially over the coming decades. This will further complicate an ongoing epidemiological transition in South Africa, where projections show that, despite the excess mortality due to HIV, the population aged over 60 years is estimated to more than double by 2030 due to lower all-cause mortality rates [16]. Cardiovascular risk factors are already prevalent among South African adults, with high levels of obesity, hypertension, and cigarette smoking [17]. In addition, HIV infection and ART have been found to be further

independent risk factors for cardiovascular diseases and other age-related chronic conditions [18]. The ageing of the HIV epidemic will also have important consequences for the organization of HIV care and prevention. Treated HIV is a chronic condition interacting with and accelerating ageing. Co-morbidities, interactions with other drugs, and drug toxicity complicate antiretroviral treatment in the elderly, who often require individualized regimens and careful monitoring [18]. Furthermore, disease progression increases with age at acquiring HIV, and effectiveness of ART is lower in people initiated at an older age than at younger age [18]

The above-mentioned processes are not accounted for in the model, however, it is unlikely that they will severely affect our results. A reduced effectiveness of ART and thus increased transmission probability of HIV, coupled with the expected lower all-cause mortality [16], may result in an even more substantial increase in the number of HIV infected elderly compared to our model predictions. On the other hand, our assumption that the full WHO treatment guidelines will be implemented in 2011 will result in a slight overestimation of the number of HIV infected elderly, since under the current South African ART policy only pregnant women and TB infected patients are eligible for ART at ≤350 cells/μL, while for others the ≤200 cells/μL threshold remains for the time being. Furthermore, disease progression is generally faster in the elderly [18], but this is likely to have a limited impact on our predictions since these patients often die of other causes. Finally, we did not consider the impact of ART and HIV on the population growth in the area because long-term projections on population size and structure would require additional assumptions regarding future changes in fertility and background mortality rates which are not only influenced by HIV and ART, but also other processes such as economic growth, and political and economic stability.

We used a 92% reduction in infectivity due to ART and a factor 3 increase in ART naive based on the best available estimates, but some argue that this might be overly optimistic [19]. If we assume an 80% reduction instead, HIV prevalence in the population aged over 50 will increase even further to about 26% in 2040, and the total number of HIV infected individuals aged over 50 will have doubled by 2040 (results not shown). Also, increased survival benefits [20] will result in a further increase in the HIV prevalence (to 25% in 2040) and the total number of HIV infected elderly (a 90% increase in 2040 compared to 2010). The proportion of HIV infected patients aged over 50 only changes slightly under these alternative assumptions (results not shown).

In conclusion, we show that the HIV epidemic in South Africa is at a critical turning point. While the number of infections among young people will continue to decline [6], the number of HIV infections in the elderly can be expected to increase by about 50% in the next fifteen years. In the near future this group will need to be an important focus of attention, and creative solutions need to be found to alleviate further stress placed on an already overburdened health system through the increased need for specialized care.

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7. The impact of antiretroviral treatment on the age composition of the HIV epidemic in sub-Saharan Africa

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Supplementary material at: Supplement III: Quantification of 43 countries in sub-Saharan Africa

Abstract

Background

Antiretroviral treatment (ART) coverage is rapidly expanding in sub-Saharan Africa (SSA). Based on the effect of ART on survival of HIV-infected people and HIV transmission the age composition of the HIV epidemic in the region is expected to change in the coming decades. We quantify the change of the age composition of HIV-infected people in all countries in SSA.

Methods

We used STDSIM, a stochastic microsimulation model, and developed an approach to represent HIV prevalence and treatment coverage in 43 countries in SSA, using publicly available data. We predict future trends in HIV prevalence and total number of infections among the populations aged 15-49 and 50 years and older (50+) for different ART coverage levels.

Results

We show that, if treatment coverage continues to increase at present rates, the total number of HIV-infected patients aged 50+ will nearly triple over the coming years: from 3.1 million in 2011 to 9.1 million in 2040, dramatically changing the age composition of the HIV epidemic in SSA. In 2011, about 1 in 7 HIV-infected people was aged 50 years or older; in 2040, this ratio will be larger than 1 in 4.

Conclusions

The HIV epidemic in SSA is rapidly ageing, implying changing needs and demands in many social sectors, including health, social care, and old-age pension systems. Health policymakers need to anticipate the impact of the changing HIV age composition in their planning for future capacity in these systems.

7.1 Background

The rapid and large scale-up of antiretroviral treatment (ART) for HIV in sub-Saharan Africa (SSA) constitutes an unprecedented global public health effort, resulting in great improvements in length and quality of life of those infected. The expansion of ART coverage since the early 2000s has led to a substantial increase in the number of HIV-infected patients on ART, with nearly 4 million people initiated in SSA as of late 2009 [1]. In June 2011, the United Nations General Assembly High Level Meeting on AIDS renewed its commitment to achieving universal ART coverage, calling for a doubling in scale-up efforts to initiate another 10 million people, to achieve universal coverage of those in need by 2015 [2]. Yet, while "[t]he UN meeting was tasked with charting the future course of the global HIV response, (…) [it] failed to mention the ageing of the pandemic" [3].

Effective ART increases survival [4-6] and can decrease HIV transmission probabilities [7-10]. Mills and colleagues estimated that life-expectancy of HIV-infected patients in SSA can approach life-expectancy of the uninfected population if treatment is initiated early (at CD4 cell counts of >250 cells/μL) [5]. The results of the HIV Prevention Trials Network (HPTN) 052 trial show that HIV transmission rates can be reduced by as much as 96% in HIV-discordant stable partnerships [8], and results from observational studies show reductions of about 90% in transmission rates [7,9]. Thus, as with expanding ART coverage HIV-infected people will live into older ages, and HIV incidence in the young and middle aged population is likely to decrease, a shift of the age composition of the HIV epidemic towards older ages might be expected. Such a shift has already occurred in developed countries. About 29% of HIV-infected patients in the United States was aged over 50 years in 2008, while this proportion was only 17% in 2001 [11]. A previous study quantified the ageing of the HIV epidemic for the South African province of KwaZulu-Natal, estimating that the number of HIV-infected adults aged 50 and older (50+) will double from 2004 to 2025 [12]. Similar projections for other parts of SSA are currently missing, and it is unlikely that the South African results can be generalized to countries with different demographic and behavioral characteristics as well as distinct HIV treatment and prevention efforts. Already, an estimated 3 million people aged 50+ live with HIV in SSA [13], and with a further 7 million HIV-infected people in SSA eligible for HIV treatment [14], there is a large pool of currently untreated HIV-infected adults that will be able to survive to older ages as treatment coverage expands.

Here, we predict age-specific HIV prevalence trends in 43 countries in SSA under different trajectories of ART coverage expansion. We used STDSIM, a stochastic microsimulation model that simulates individuals in a dynamic network of sexual contacts [15-17]. We developed an approach that can be applied to quantify all national HIV epidemics in 43 sub Saharan African countries in the period 2000-2009 by using country-specific data on demographic composition [18-20], data on country-specific ART coverage [1], and country specific circumcision prevalence rates [14,21], as well as epidemic specific sexual behavior profiles.

7.2 Methods

Model

In the model, HIV is represented by 4 consecutive stages: early infection (0.25 years); asymptomatic infection (5.5 years); symptomatic infection (4 years); and AIDS (0.7 years). Median survival of an untreated HIV infection is about 10 years (95% confidence interval: 5 - 19 years) [22]. People on ART are assumed to have a 90% reduction in infectiousness [7,9], and their life-expectancy at the moment of treatment initiation is four times the remaining untreated life-expectancy (figure III.1 – see supplement III: Quantification of 43 countries in sub-Saharan Africa) [6]. More details about the model structure can be found in supplement III: Quantification of 43 countries in sub-Saharan Africa and in three previous publications [15,23,24].

Model quantification

Demographics

Background mortality rates (mortality in the absence of HIV) were calculated using country-specific life tables [19], and burden of disease estimates published by the World Health Organization (WHO) [20]. For each country, we first calculated the proportion of deaths attributed to HIV through comparison of the age- and sex-specific burden of disease estimates [20], and the all-cause mortality rates in the WHO life tables [19]. We then used the ratio between these two mortality estimates (HIV-specific and all-cause) to compute background mortality rates for all causes except for HIV. Figure III.2A and III.S2B in supplement III: Quantification of 43 countries in sub-Saharan Africa present the country-specific HIV-corrected background mortality rates for men and women, respectively. Age- and period-specific fertility rates for each country were obtained from the 2008 United Nations (UN) World Fertility Data [18]. We assumed that fertility rates remained constant after 2011.

ART scale-up

We fitted antiretroviral treatment coverage until 2009 to the coverage levels reported by WHO [1], using two sub-models. The first sub-model represents an individual's demand for ART as a function of HIV-disease stage; the second sub-model describes the capacity of the health system to meet this demand. ART coverage in our model is the ART demand met by the capacity of the health system. To fit the modeled ART coverage to the annual coverage data reported by WHO (for the period 2004-2009) [1], we used a quadratic ($\alpha x2$), linear (αx), or square-root ($\alpha x1/2$) of scale-up of ART capacity in the health system, while assuming the ART demand function to be the same as previously estimated for South Africa [15]. For each of the three scale-up functions, we calculated the annual ART coverage of those eligible (at CD4 counts of ≤200 cells/μL) for all countries in SSA using the country-specific starting years of the ART scale-up (the scale-up started in all countries in the period 2001 - 2005). We choose the multiplication factors (α) in the different functions to maximize the model fit by minimizing the Mean Squared Error (MSE) of the model predictions compared to the country-specific ART coverage estimates reported by WHO [1].

We assumed all countries to provide ART at CD4 counts of ≤200 cells/μL up to 2009, with three exceptions: (i) Botswana offered ART at CD4 counts of ≤250 cells/μL for all HIV-infected individuals since the start of its ART scale-up in 2003 [25]; (ii) Rwanda switched to ART at CD4 counts of ≤350 cells/μL for all HIV-infected individuals in 2007 [26]; and (iii) Namibia has offered lifelong ART at CD4 counts of ≤350 cells/μL for all pregnant women since 2007 (about 20% of all HIV-infected women aged 15-49 and with CD4 cell counts of 200-350 cells/μL seeking care) [27]. We assumed a baseline annual rate of stopping treatment of 5% [28], and that people who stopped will never re-initiate treatment. Since, retention in care varies with the capacity of the health system to deliver ART [29] , we assumed that the annual rate of stopping treatment is reduced to 2.5% when the health-systems capacity to provide ART reaches 80%, and to further reduce to 1% when the capacity is 100%.

HIV epidemic and sexual-behavior profiles

To represent to the HIV epidemics in SSA, we defined five sexual-behavior profiles that differ in their age- and sex-specific rates of forming – and condom use during – three different types of sexual partnerships (table III.1 – see supplement III: Quantification of 43 countries in sub-Saharan Africa): stable relationships (lasting on average 25 years); casual relationship (lasting on average 6 months); and commercial sex (a once-off contact) [23,24].

We named the sexual behavior profiles according to the epidemics they have produced: (i) concentrated risk profile (high risk of HIV among commercial sex workers (CSWs) and clients; low risk in the general population); (ii) mixed risk profile (high risk of HIV among CSWs and clients; medium risk in the general population), and (iii) generalized risk profile (high risk in the general population). Three of the four parameter settings of the 'four cities study' fitted these three profiles, and were chosen accordingly: Cotonou, Benin (concentrated risk profile); Yaoundé, Cameroon (mixed risk profile); and Kisumu, Kenya (generalized risk profile) [24]. High levels of condom use among CSWs introduced in the early nineties in the concentrated risk profile and mixed risk profile resulted in declining HIV prevalence. To capture this distinction, we added two extra profiles: (iv) concentrated risk profile (low condom use) and (v) mixed risk profile (low condom use), both with reduced condom use rates during commercial sex.

In the 'four cities study' [24] sexual behavior parameters for the population aged 15-49 were stratified by 5-year age groups and fitted to represent age-specific reported numbers of sex partners from behavioral surveys from the original 'four cities study' [30].. In order to derive parameter values for sexual behavior for the age group 50+, for which measured data was not available in the study, we assumed that partner change rates and CSW-visiting behavior remained the same for all age groups 45+. Within each partnership we assumed a 25% reduction in the frequency of sexual contacts in the age group 50+ relative to the age group 45-49. This assumption fitted closely to the data from a HIV and sexual behavior surveillance in the population aged 50+ in KwaZulu-Natal, South Africa [12,31].

For each country, we ran the model with all five sexual-behavior profiles and the country-specific circumcision prevalence [14,21], and ART scale-up function (see above). We then selected the profile that best described the HIV epidemic in a given county in the period 2000-2009. In order to do so, we constructed a 'fit score' that captures the development of the HIV prevalence over time. The score is the sum of the MSE of HIV prevalence predictions over 2000-2009 (for fitting prevalence levels), and the squared error (SE) over the difference between prevalence in 2000 to 2004, and 2005 to 2009 to fit the observed trend in HIV prevalence. We used UNAIDS estimates of the country-specific HIV prevalence in adults aged 15-49 over the period 2000-2009 in order to assess fit [14].

Finally, we fine-tuned the model quantifications for each country by choosing the best-fitting combination of overall partner change rates (range +/- 25%; see table III.1 – see supplement III: Quantification of 43 countries in sub-Saharan Africa) and year of HIV introduction that produced the lowest MSE on the HIV prevalence estimates in adults aged 15-49, as compared to UNAIDS estimates for the period 2000-2009. For the concentrated risk and mixed risk profiles we allowed for a maximum of 25% reduction in CSW visit rates to further fine-tune predicted HIV epidemics, because the epidemics produced by these profiles are largely driven by commercial sex.

Simulations

We predicted trends in HIV prevalence in the population aged 15-49 and 50+ over the period 2011 - 2040 in 43 countries in SSA. In our baseline estimate, we assumed ART to be scaled-up continuously after 2009 according to the country-specific scale-up function of the health system capacity (see above), until capacity reaches 100%. By October 2010, 7 countries in SSA had adopted the 2010 WHO treatment guidelines that recommend ART initiation at CD4 counts of ≤350 cells/μL into their national policy (Kenya, Lesotho, Malawi, Rwanda, Tanzania, Zambia, and Zimbabwe) [1], while South Africa adopted the guidelines in August 2011 [32]. We assumed that all other countries will have adopted the new guidelines by January 2013.

We calculated country-specific trends in HIV prevalence and total number of HIV infections in the population aged 15-49 and 50+. We assumed three alternative scenarios of scale-up of health-systems capacity to provide ART: (i) decline (reduction in capacity by 20% in 2012 and constant capacity levels thereafter); (ii) no further scale-up (capacity remains constant at 2011 levels); (iii) rapid scale-up (capacity increase to 100% for all countries by 2015).

7.3 Results

Using five predefined sexual-behavior profiles (figure 7.1), our model was able to accurately replicate the ART coverage scale-up (figure 7.2A) and HIV epidemics (figure 7.2B and 7.2C) of all 43 sub-Saharan African countries. For only 9 countries, HIV prevalence projections differed more than 10% compared to UNAIDS estimates at some point during the period 2000-2009. The absolute number of HIV infections in older adults (2.6 million) and the population aged

15-49 (17.8 million) in 2007 are very similar to the estimates that Negin et al derived using a different methodological approach (2.9 million and 17.9 million, respectively) [13]. In addition, our model predictions regarding population growth over the period 2000 - 2040 are very similar to those provided by the United Nations Population Prospects (figure III.3 -- see supplement III: Quantification of 43 countries in sub-Saharan Africa) [33]. A detailed description of the parameters for individual countries can be found in table III.2 (see supplement III: Quantification of 43 countries in sub-Saharan Africa).

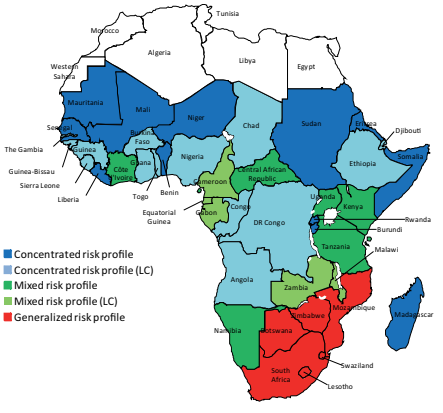

Figure 7.1. Geographical distribution of sexual-behavior profiles. The color of each country represents the best fitting sexual-behavior profile given country-specific circumcision levels (table III.2 – see supplement III: Quantification of 43 countries in sub-Saharan Africa) and ART roll out (figure 7.2A). A detailed description of the profiles is given in table III.1 (see supplement III: Quantification of 43 countries in sub-Saharan Africa).

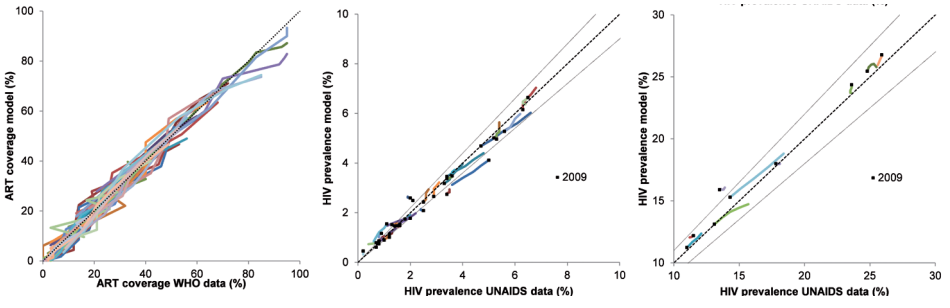

Figure 7.2. Model fit compared to data. A. Predicted ART coverage of those eligible at ≤200 cells/μL in the model compared to WHO data over the period 2004-2009. The dashed line represents a perfect fit (e.g. predicted coverage in model = WHO data). B. Predicted HIV prevalence for low and medium endemic countries in the model compared to UNAIDS prevalence estimates over the period 2004-2009. The dashed line represents a perfect fit (e.g. predicted prevalence in the model = UNAIDS data), the dotted line represents a 10% difference between model predictions and data. C. Predicted HIV prevalence for high endemic countries in the model compared to UNAIDS prevalence estimates over the period 2004-2009. The dashed line represents a perfect fit (eg predicted prevalence in the model = UNAIDS data), the dotted line represents a 10% difference between model predictions and data. Full country-specific parameter settings are given in table III.2 (see supplement III: Quantification of 43 countries in sub-Saharan Africa).

Figure 7.3 shows the HIV prevalence in the population aged 15-49 and 50+ for the years 2011, 2025, and 2040 under the baseline scenario of continued scale-up of ART. Overall, prevalence in the population aged 15-49 will decline from 5% in 2011 to 3% in 2040, while prevalence in the

population aged 50+ will increase from 3% to 4% over the same period. The number of countries with an HIV prevalence of <1% in the population aged 15-49 will increase from 6 in 2011 to 17 in 2040, while the number of countries in this prevalence category for the population aged 50+ will halve in the same period, from 12 to 6. HIV prevalence in older adults will be 2% or higher in 22 countries in SSA in 2040, while this is the case for only 11 countries regarding adult HIV prevalence. In countries with currently very high HIV prevalence rates in both younger and older adults, HIV prevalence in the population aged 50+ will increase dramatically (table 7.1). For instance, in Botswana, HIV prevalence in the population aged 50+ was 15% in 2011, and will increase to 24% in 2040. Similar trends are predicted for South Africa (an increase of HIV prevalence in the population aged 50+ from 10% to 16%), Swaziland (15% to 27%) and Lesotho (13% to 25%) (figure 7.3).

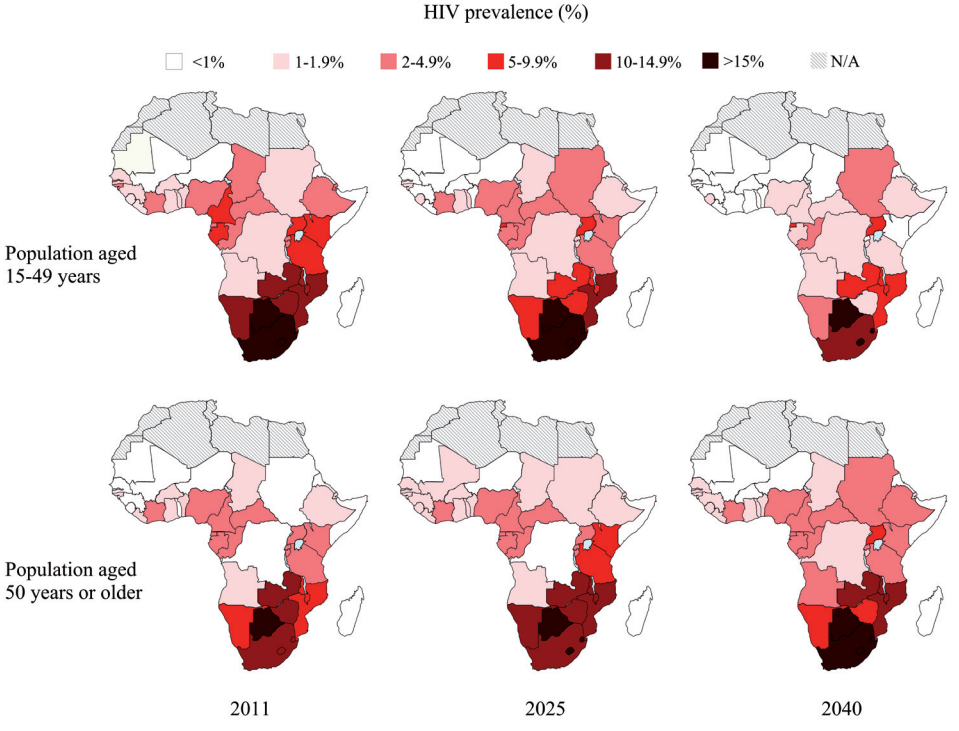

Figure 7.3. HIV prevalence in the population age 15-49 and 50+ in sub-Saharan Africa for the years 2011, 2025 and 2040, under continuous scale up of antiretroviral therapy. N/A = Not Applicable

	HIV prevalence					
	Population aged 15-49			Population aged 50+		
	2011	2025	2040	2011	2025	2040
Sub-Saharan Africa	**5%**	**3%**	**2%**	**3%**	**4%**	**4%**
Central Africa	**2%**	**2%**	**1%**	**2%**	**2%**	**2%**
Angola	2%	2%	2%	1%	2%	2%
Cameroon	5%	3%	1%	4%	4%	4%
Central African Rep.	5%	3%	1%	4%	4%	3%
Chad	3%	1%	1%	2%	2%	1%
Dem. Rep. Congo	1%	1%	1%	1%	1%	1%
The Congo	5%	3%	2%	4%	4%	4%
Equatorial Guinea	4%	8%	7%	3%	6%	7%
Gabon	3%	3%	2%	2%	4%	4%
Eastern Africa	**4%**	**3%**	**2%**	**3%**	**3%**	**3%**
Burundi	3%	1%	1%	3%	2%	2%
Djibouti	2%	1%	1%	2%	1%	1%
Eritrea	1%	<0.5%	<0.5%	1%	1%	1%
Ethiopia	2%	2%	2%	2%	2%	2%
Kenya	6%	3%	1%	5%	6%	4%
Madagascar	<0.5%	<0.5%	<0.5%	<0.5%	<0.5%	1%
Mozambique	12%	11%	9%	8%	12%	14%
Rwanda	3%	1%	1%	3%	3%	2%
Somalia	1%	1%	1%	1%	1%	1%
Sudan	1%	2%	2%	1%	2%	2%
Tanzania	5%	3%	1%	4%	5%	4%
Uganda	7%	5%	5%	4%	4%	6%
Southern Africa	**16%**	**12%**	**9%**	**10%**	**13%**	**13%**
Botswana	25%	18%	16%	17%	23%	25%
Lesotho	25%	24%	21%	14%	19%	25%
Malawi	11%	8%	8%	9%	10%	12%
Namibia	13%	8%	4%	10%	10%	9%
South Africa	18%	15%	11%	11%	14%	16%
Swaziland	25%	21%	20%	16%	23%	27%
Zambia	14%	8%	9%	8%	11%	12%
Zimbabwe	14%	6%	2%	12%	13%	8%
Western Africa	**2%**	**2%**	**1%**	**2%**	**2%**	**2%**
Benin	2%	1%	<0.5%	1%	1%	1%
Burkina Faso	1%	1%	<0.5%	1%	1%	1%
Côte D'Ivoire	4%	2%	1%	3%	3%	2%
The Gambia	2%	2%	2%	1%	2%	2%
Ghana	2%	1%	1%	1%	2%	2%
Guinea	2%	1%	1%	1%	1%	1%
Guinea-Bissau	2%	1%	1%	1%	2%	2%
Liberia	1%	1%	<0.5%	1%	1%	1%
Mali	1%	1%	<0.5%	1%	1%	1%
Mauritania	1%	1%	<0.5%	<0.5%	1%	1%
Niger	1%	<0.5%	<0.5%	1%	1%	1%
Nigeria	4%	2%	2%	2%	3%	3%
Senegal	1%	1%	1%	1%	1%	1%
Sierra Leone	1%	1%	1%	1%	1%	1%
Togo	2%	1%	1%	1%	1%	2%

Table 7.1. HIV prevalence in the population aged 15-49 years and 50 years or older in 2011, 2025 and 2040 for all 43 countries of sub-Saharan Africa, assuming continued scale-up of ART.

The total number of HIV-infected patients aged 50+ in SSA will increase rapidly over the coming decades, from 3.1 million in 2011 to 9.1 million in 2040, an increase of 190% (figure 7.4, table 7.2). At the same time, the number of HIV infections among young adults (aged 15-34) will rapidly decline: from 12.1 million in 2011 to 9.1 million in 2030 (a 25% reduction). As prevalence levels stabilize in 2030, the total number of infections will increase again to 10.8 million in 2040. Overall, the total number of HIV-infected people aged 15 years and older (15+) will increase over the next three decades, from 22.4 million in 2011 to 32.4 million in 2040, an increase of 44%.

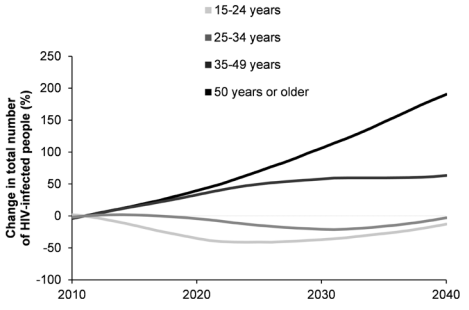

Figure 7.4. Projected trends of total number of infections and in sub-Saharan Africa over the period 2010-2040 under continuous scale up of antiretroviral therapy. The change is relative to the total number of HIV infected patients per age category in 2011.

As a result of the disproportionate increase in the number of HIV-infected older adults (figure 7.4), the age composition of the HIV-infected population will change (table 7.2). In 2011, about 13% of all HIV-infected people were aged 50+; by 2040 this proportion will have more than doubled, to 27% (table 7.2). In contrast, young adults (aged 15-34) will contribute decreasing proportions of infections to the total number, from 52% in 2011 to 33% in 2040 (figure 7.5). Countries that have both a high ART coverage and declining HIV prevalence among the population aged 15-49 will be faced with an especially dramatic shift in age composition of the HIV epidemic. The most extreme shift is observed in Zimbabwe, where the proportion of HIV-infected people being aged 50+ will increase from 16% in 2011 to 62% in 2040. Countries like Kenya (13% to 51%), Tanzania (14% to 48%), Namibia (12% to 38%), and South Africa (14% to 36%) show similar trends. In contrast, countries with low and slowly expanding ART coverage show less rapid changes in age composition. In Sierra Leone, the proportion of HIV-infected people being aged 50+ increases from 11% in 2011 to 18% in 2040, and similar trends are found in Democratic Republic of Congo (13% to 15%), The Gambia (9% to 15%), Somalia (14% to 21%), and Burundi (16% to 22%) (table 7.2).

	HIV infections in population aged 15-49			HIV infections in population aged 50+					
	Absolute number (x 1000)			Absolute number (x 1000)			As proportion of all infections		
	2011	2025	2040	2011	2025	2040	2011	2025	2040
Sub-Saharan Africa	**19 325**	**20 244**	**23 358**	**3 119**	**5 307**	**9 059**	**13%**	**20%**	**27%**
Central Africa	**1 308**	**1 450**	**1 774**	**211**	**349**	**547**	**14%**	**19%**	**23%**
Angola	150	205	339	21	40	82	12%	16%	20%
Cameroon	450	431	303	75	135	200	14%	24%	40%
Central African Rep.	110	82	46	21	31	37	16%	27%	44%
Chad	83	86	115	14	22	26	14%	20%	19%
Dem. Rep. Congo	378	500	792	55	86	141	13%	15%	15%
The Congo	54	65	97	9	16	33	14%	20%	25%
Equatorial Guinea	21	38	51	3	6	11	11%	14%	18%
Gabon	49	44	31	8	13	17	14%	23%	35%
Eastern Africa	**6 147**	**6 956**	**9 138**	**955**	**1 769**	**3 067**	**13%**	**20%**	**24%**
Burundi	115	95	133	22	26	38	16%	22%	22%
Djibouti	10	8	8	2	2	3	14%	22%	27%
Eritrea	21	19	20	3	7	11	14%	26%	34%
Ethiopia	817	1 234	2 016	135	263	583	14%	18%	22%
Kenya	1 101	728	341	172	319	357	13%	30%	51%
Madagascar	26	50	78	7	18	40	20%	27%	34%
Mozambique	1 533	1 888	2 366	215	397	752	12%	17%	24%
Rwanda	140	90	83	30	56	62	19%	38%	43%
Somalia	31	54	80	5	11	21	14%	17%	21%
Sudan	339	631	1 054	44	140	318	12%	18%	23%
Tanzania	1 126	846	458	189	342	426	14%	29%	48%
Uganda	751	1 314	2 501	84	188	456	10%	13%	15%
Southern Africa	**8 443**	**8 211**	**8 196**	**1 356**	**2 202**	**3 706**	**13%**	**19%**	**29%**
Botswana	286	310	425	43	91	175	15%	23%	29%
Lesotho	298	375	450	34	55	105	10%	13%	19%
Malawi	773	909	1 602	112	209	429	13%	19%	21%
Namibia	185	132	76	26	35	47	12%	21%	38%
South Africa	5 120	4 902	3 733	822	1 293	2 065	14%	21%	36%
Swaziland	147	201	289	20	43	84	12%	18%	22%
Zambia	692	763	1 326	89	185	361	11%	20%	21%
Zimbabwe	798	618	295	158	291	440	16%	32%	60%
Western Africa	**3 428**	**3 626**	**4 249**	**594**	**987**	**1 739**	**15%**	**21%**	**29%**
Benin	47	36	35	10	16	22	17%	31%	38%
Burkina Faso	74	61	62	14	22	27	16%	26%	30%
Côte D'Ivoire	370	288	176	77	122	170	17%	30%	49%
The Gambia	15	26	38	1	3	7	9%	12%	15%
Ghana	225	256	257	38	82	153	15%	24%	37%
Guinea	66	70	88	11	22	35	14%	24%	28%
Guinea-Bissau	11	13	16	2	4	7	15%	24%	29%
Liberia	24	18	17	5	7	11	16%	28%	39%
Mali	77	57	56	13	20	27	14%	26%	33%
Mauritania	12	12	11	2	5	8	15%	28%	41%
Niger	48	46	53	9	20	31	17%	30%	37%
Nigeria	2 299	2 542	3 188	373	620	1 158	14%	20%	27%
Senegal	54	76	100	7	18	35	12%	19%	26%
Sierra Leone	38	62	82	5	101	18	11%	14%	18%
Togo	47	62	69	7	15	31	13%	20%	31%

Table 7.2. Impact of continued ART scale-up on absolute number of HIV infections and proportion of all HIV-infected patients aged 50+ in 43 countries of sub-Saharan Africa

In the decline scenario, with 20% decrease in ART capacity in 2012, we predict that the number of HIV-infected older adults will reach 6.9 million in 2040, or 22% of all HIV-infected patients (figure 7.5). If, on the other hand, treatment capacity remained at the level of 2011 (i.e., in the no further scale-up scenario), the total number of HIV-infected older adults would be 7.4 million in 2040, which is 24% of all HIV-infected adults. Under the rapid scale-up scenario the number of HIV-infected older adults in 2040 would be 9.3 million in 2040, which is 28% of all HIV infections.

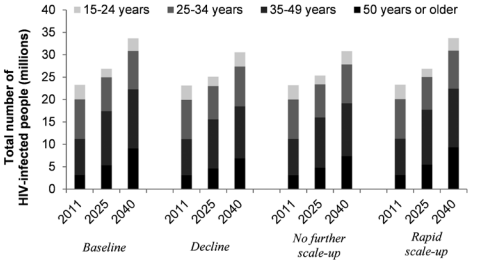

Figure 7.5 Predicted age composition of the HIV-infected population by ART scale-up scenario. Baseline = baseline scenario of continued scale-up of ART coverage; decline = scenario in which health-system capacity to deliver ART is reduced by 20% in 2012; no further scale-up = scenario in which health-system capacity to deliver ART remains at the same level as in 2011; Rapid scale-up = scenario in which health-system capacity to deliver ART is scaled-up to 100% for all countries by 2015.

7.4 Discussion

We estimate that the total number of HIV-infected older adults (aged 50+) will nearly triple from about 3.1 million in 2011 to 9.1 million in 2040, assuming that ART scale-up continues at the current speed. In 2011, about 1 in 7 HIV-infected patients were aged 50 years or older in SSA, while in 2040 this ratio will be more than 1 in 4. Due to an overall increase in the number of people aged 50+ in SSA, the increase in prevalence is relatively modest, from 3% in 2011 to 4% in 2040. In contrast, HIV prevalence among the population aged 15-49 will decline over the coming decades, from 5% in 2011 to 3% in 2040.

This ageing of the HIV epidemic is likely to have broad and important consequences for the organization of health care services in SSA, as has been pointed out in a commentary on the results we present in this study [33].Due to the increase in life-expectancy due to the ART scale-up, populations will age, "unmasking" the burden of non-communicable diseases (NCDs) previously hidden due to high rates of HIV-related mortality [34]. Already, NCDs are becoming more important in low- and middle income settings, where prevalence of risk factors is high and prevention efforts are limited [35-39]. In South Africa, 55% of all middle-aged women were found to be obese in a cross sectional survey [40,41]. Smoking prevalence in SSA is high and increasing, and meals generally contain high levels of calories and salt [40,41]. Consequently, hypertension and diabetes are becoming more common in SSA [42,43]. As the contribution of these risk factors to the overall risk of NCDs accumulates over age, they become particularly important as the HIV epidemic ages. In addition, HIV infections in older adults are often complicated by preexisting or developing non-AIDS related co-morbidities such as cardiovascular and metabolic diseases, which in turn

might aggravate HIV disease progression [44]. Finally, HIV infection and ART are independent risk factors of many NCDs such as non-AIDS related malignancies, cardiovascular diseases (CVDs), kidney and liver failure, and osteoporosis [45-47]. Therefore, quantitative estimates on the impact of the ageing HIV epidemic on the overall disease burden in SSA are needed.

The predicted ageing of the HIV epidemic will also affect social sectors other than the health sector, in particular in countries where HIV prevalence in older adults will substantially increase over the coming decades. Currently, many countries in SSA have no, or very limited, pension programs [48], and support for elderly generally falls under the responsibility of the family [49]. As the numbers of HIV-infected adults who live into old ages increases due to ART, the need for financial and social support of older adults will increase as well. Policy makers need to consider how this need can be met in the specific contexts of their countries' existing old-age pension and social care systems. At the same time, the increasing presence of older adults in the hyperendemic communities in SSA may bring important benefits to families and communities in the region, including improved child care and social cohesion, and greater flexibility of middle-aged family members to temporarily migrate in search for work opportunities. Future empirical research needs to establish how the presence of older HIV-infected adults in sub-Saharan African households affects households' social and economic well-being, and which interventions can strengthen positive effects and mitigate negative ones.

Our results show that the total number of HIV-infected adults (aged 15+) will increase by 44% over the next three decades, creating a continuously growing need for financial and human resources to provide ART. Already, financial and human resources to provide ART in SSA are stretched [50,51], emphasizing the need for continued scale-up of cost-effective prevention interventions alongside treatment in order to reduce incidence and thus future treatment needs [52-54]. In addition, it might be necessary to more closely integrate the delivery of treatment and care for different chronic diseases, in order to reduce the financial and time burdens that older patients on ART bear in regularly utilizing healthcare for several conditions.. Economies of scope might increase the efficiency of the healthcare delivery, and general health systems might be strengthened as vertical health systems structures are integrated [55].

Our study has several limitations. We modeled countries as a homogenous mix of people, assuming country averages to apply to the entire population. However, in reality there may be important differences in HIV epidemics within countries [56]. In addition, we assumed HIV survival and transmission probabilities to be universally applicable, while in reality there may be differences in these parameter by strains of HIV virus in different parts of Africa [57]. The HIV-2 virus, which is only prevalent in some Western-African countries, is known to have a lower virulence and transmission potential compared to the more common HIV-1 strain [57]. Also, our model does not include mother-to-child transmission of HIV. As HIV-infected children can be treated effectively with ART [58], they may now live into young adulthood, increasing the number of HIV-infected people in this age category.

Both acquired resistance (development of resistance within an individual on treatment) and transmitted resistance (spread of drug-resistant strains) may impact on the effectiveness of treatment programs, and consequently result in a less profound effect of the ART scale-up on the population age composition. Patients who develop resistance might fail to suppress viral replication while on treatment, resulting in shorter survival times and higher infectiousness. While second- or third-line therapies can be prescribed to treat those with resistance to first-line ART, many treatment programs in SSA are currently not well-equipped to deal with drug resistance, as both monitoring for treatment resistance and providing second- and third-line ART regimens is expensive and requires specialized expertise [59]. Therefore, if the prevalence of resistance increases, effective treatment coverage will decline. In our sensitivity analysis, we explore the effect of declining treatment coverage on the changes in age-composition. We find that the changes in age composition are similar but somewhat reduced in magnitude if effective coverage is reduced substantially (e.g., by one fifth compared to the baseline case). It is currently unclear, however, in how far the fears of rapidly spreading drug resistance expressed at the start of the ART scale-up [60] were justified. The prevalence of drug resistance remains low in most countries in SSA after nearly 10 years of scaling up ART [61,62]. In addition, adherence to treatment in SSA is comparable to many high income countries [63], and survival of patients on treatment in SSA approaches general life-expectancy [5], suggesting that resistance may not become a major problem in the region in the near future.

In this study, we assumed that risk behavior remained the same after age 45. While detailed data on sexual risk taking in older age for SSA is lacking, it is plausible that the frequency of sexual activity declines to some extent in older adults [64].On the other hand, there is evidence that older people are at increased risk for HIV through both biological mechanisms and increased increasing riskiness in behavior during sex. Post-menopausal women might be more susceptible to HIV because of the thinning of the vaginal wall [65], and data from the Demographic and Health Surveys (DHS) show that condom use and knowledge about condoms is particularly low in older adults [13]. In the United States, condom use among older adults with known risk factors for HIV was about six times lower compared to adults aged 15-49 [66]. Yet, despite the considerable and increasing burden of HIV in older adults in SSA, our understanding of sexual behavior in this group remains limited. With increasing prevalence of HIV in older adults, HIV incidence in this age-group is also likely to increase, warranting the need for age-appropriate prevention interventions.

It is important to note that our model accurately replicated the HIV epidemic in all the 43 SSA countries (figure 7.2), suggesting that the theoretical limitations we describe above do not substantially matter for our estimations. This claim is further supported by comparison of our estimates of a total of 2.6 million HIV-infected older adults in 2007 to the number published by Negin et al. (which is 2.9 million) [13].

In conclusion, we show that the HIV epidemic in sub-Saharan Africa will rapidly age over the coming decades. This has important consequences for both the organization of health care services and the general organization of societies in the sub-continent, as older HIV-infected patients require specialized treatment and care, as well as social and financial support. In addition,

expanded treatment coverage is likely to increase the burdens of other diseases in SSA, in particular NCDs. Health policymakers need to anticipate the impact of the ageing HIV epidemic in their planning for the future capacity of health systems to prevent and treat diseases of old age in HIV-infected individuals.

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Supplement I: Quantification of STDSIM to rural KwaZulu-Natal

General model structure

We used STDSIM, a stochastic microsimulation model of the transmission and control of HIV and other STIs [1-3]. The model simulates the life course of individuals in a dynamic network of sexual contacts. Events like partnership formation or the acquisition of infections are the result of random processes, determined by probability distributions. Therefore, the results of the model are subject to stochastic variation. It is necessary to perform multiple runs and average the results to diminish the stochasticity in predictions.

The model consists of four modules: demography, sexual behavior, transmission and natural history, and interventions. The demography module implements the processes of birth, death, and migration. Processes for initiation and dissolution of sexual relationships, for mixing according to age preference, for sexual contacts within relationships and for sexual contacts between clients and sex workers are defined in the sexual behavior module. In the transmission and natural history module, transmission probabilities per sexual contact are specified for HIV and other simulated STIs. Finally, the interventions module specifies the timing and effectiveness of control measures in curbing transmission or enhancing survival. More details about the general model structure can be found in Supplements I - STDSIM and its application to South Africa in this thesis, and also in previous publications: van der Ploeg et al [1], Korenromp et al [2], and Orroth et al [3]. The modeling of antiretroviral therapy (ART) is new with regard to these papers, and will be explained below.

Modeling ART

HIV stages and CD4 cell counts

HIV infection is modeled in 6 consecutive stages: an acute stage (10 weeks), 2 asymptomatic stages (125 weeks each), 2 symptomatic stages (120 weeks and 80 weeks respectively), and an AIDS stage (40 weeks) (figure I.1). The resulting survival time after infection, in the absence of treatment, is on average 10 years. This is consistent with observed data [4] the same as in previous STDSIM studies [3, 5], and nearly equal to the 11 years recently assumed in the modeling study by Granich et al [6]. Transmission probabilities are increased by a factor of 15 during the acute stage, 3 during the symptomatic stages and 7.5 during the AIDS stage, relative to the asymptomatic stages [3, 5]. The durations of the acute, asymptomatic and symptomatic stages are assumed to be exponentially distributed, whereas a Weibull distribution with a shape parameter 2 is used to describe the AIDS stage [3].

Initial CD4 cell counts of HIV negatives are randomly drawn from a lognormal distribution with median 7.02 (equivalent to 1116 cells/μL) and a standard deviation of 0.303, which has previously been used by Granich et al and Williams et al [6, 7]. For each individual, this initial value is multiplied by x, the relative CD4 cell count, which starts at 1 and continuously decreases during HIV progression (red line in figure I.1). Analogous to Granich et al [6] and Williams et al [7], we assumed a rapid decline of x to 0.75 during the acute stage, followed by a linear decrease during the remaining stages until x = 0.005, after which the individual dies of AIDS [6, 7].

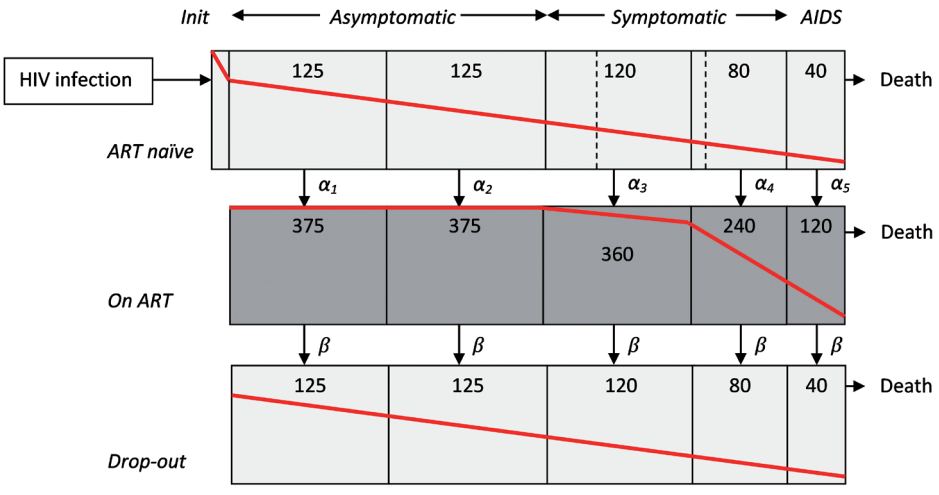

Figure I.1. Model representation of HIV stages, CD4 cell counts and ART. Each box represents an HIV stage with corresponding average duration in weeks. The red line in the boxes represents the relative CD4 cell count x, which overall declines from 1 (top of the box) to 0.005 (close to bottom of the box). After infection patients enter in the acute phase of the ART naïve HIV infection and progress through five stages after which they die (Death). Parameters rh (1) to rh (5) are rates of successful health seeking behavior of HIV infected individuals in the corresponding ART-naïve stages. Health seeking behavior rates are assumed to increase linearly with stage number. Patients initiate ART when their CD4 cell count is below a certain threshold (i.e. 200 cells/μL or 350 cells/μL). Parameter rd is the dropout rate of patients on ART. The dashed vertical lines in the ART naïve boxes represent the average duration until HIV infected individuals reach CD4 cell counts of 350 cells/μL (left) and 200 cells/μL (right), respectively.

ART

At a rate rh (i), patients can visit a clinic and get a CD4 cell count test. These health seeking rates can be varied per HIV stage (figure I.1). When the CD4 cell count is equal to or below a given threshold (200 or 350 cells/μL), ART is initiated, and the patient moves to the corresponding ART stage (figure I.1). The durations of the HIV stages on ART are three times that of the ART-naïve HIV-infected, based on a study by Walensky et al, who used randomized trials and observational cohorts to assess the survival of HIV-patients on ART [8]. ART is assumed to decrease infectivity of HIV by 92%, based on a meta-analysis by Attia et al [9]. This value was also used in a recent modeling study by Dodd et al [10] and is the same as recently found by Donnell et al [11]. Patients stop treatment permanently at a rate rd (annual dropout rate).

Baseline quantification of STDSIM

The model parameters were quantified to represent the Hlabisa sub-district of the Umkhanyakunde District in KwaZulu-Natal (KZN), South Africa [12, 13].

Demography

We used location-specific fertility- and migration-rates in order to fit the demographic structure of the Hlabisa sub-district [14]. In recent years, fertility rates in the area have been declining [15, 16]. Therefore, we adjusted fertility rates in accordance with published values: 4.4 until 1992; 3.9 in 1992-1996; 3.3 in 1997-2001; and 2.8 from 2002 onwards [16].

We used age- and sex-specific in- and out-migration rates as published by the Africa Centre [14]. Background mortality rates (i.e. excluding HIV-related death) were based on Coale-Demeney life tables (table: South 55) [17].

Sexual risk behavior

We assumed an average age of sexual debut of 18 years for women and 20 for men, based on observational data [18]. The study area is characterized by significant amounts of circular migration with about 60% of the adult male population spending most nights away in urban areas, where they frequently have additional sexual partners, often including sex workers [14, 19, 20]. We therefore adopted rates of visits to sex workers used in the STDSIM quantification for Kisumu (Kenya) [3], which has an HIV prevalence similar to that in our study population: ANC prevalence 34% in Kisumu [3] versus 36% in KZN [21] in 2000. The overall partner change rate ('promiscuity factor'), which reflects the tendency of individuals to become available to form new sexual relationships [2], was calibrated such that the model accurately reflects the trend in HIV prevalence as available from antenatal clinic (ANC) data (1990-2004) [21] and ACDIS sero-surveillance data (2004-2009) [4]. In 2004, the population prevalence in the ACDIS cohort was 0.6 (25%/41%) that of the ANC prevalence in KZN, and we therefore multiplied the ANC prevalences by this factor. The resulting fit of the HIV prevalence is illustrated in figure 2.1D in chapter 2, which also shows the predicted prevalence for a 10% increase and 10% decrease in the best-fitting overall partner change rate.

Transmission and natural history

We modeled the following STIs: HIV, Chancroid, Gonorrhea, Chlamydia, Syphilis, and HSV-2.

All biological parameters (transmission probabilities, co-factor effects, and natural history) are the same as in the recent STDSIM application for the Four cities study [3, 22], and can be found in table 1 of Orroth et al [3]

Interventions

We assumed a linear increase in the rate rh (i) of seeking and receiving voluntary counseling and testing for HIV, as a function of stage number i (i = 1 to 5), not including the acute stage (figure I.1). We estimated an intercept and slope by fitting the predicted distribution of CD4 cell counts during the patient's first test to that recorded in the Hlabisa Treatment and Care Program [13] (intercept = 0.1 tests/year, slope = 1.1). In the model we phased in ART in accordance with the timeline of the actual rollout among the 17 clinics in Hlabisa sub-district. Whenever a new health facility started distributing ART, we increased the number of patients seeking care by 1/17th. Furthermore, we assumed that clinics start at 50% capacity, and run at full capacity after 1 year. After 4 years of the ART program, 5% of the population that initiated ART was observed to be lost to follow-up [13]. Therefore, in the model we assumed an annual dropout rate rd of 1.27% and we further assumed that these patients do not initiate ART again.

We assumed an increase in condom use in casual (non-marital) and sex worker contacts in 1998 (from 0% to 10%) and 2003 (from 10% to 20%), according to KZN data [23-25]. For the whole study period, we assumed that condoms were not used in steady (marital) relationships. In addition, we incorporated a slight improvement in STI treatment coverage based on the introduction of syndromic treatment guidelines in 1995 [26, 27] (Men: coverage of treatment for chlamydia- and gonorrhea-symptoms from 20% to 50%, syphilis- and chancroid-symptoms from 20% to 60%; Women: coverage of treatment for chlamydia- and gonorrhea-symptoms from 15% to 40%, syphilis- and chancroid-symptoms from 15% to 50%). We used the best available estimate of the KZN circumcision rate (26% in 2003) [25].

Additional assumptions to represent the current South African policy

We did not explicitly model the current South African policy of putting pregnant and TB co-infected HIV patients earlier on ART, as this would lead to an undue increase of complexity in the model. However, to roughly compare the new WHO strategy to the current South African strategy, we also assumed a scenario that a fraction of the patients with CD4 cell counts of 201-350 cells/μl is eligible for treatment. The Hlabisa Treatment and Care Program did not record TB or pregnancy status of patients with CD4 cell counts of >200 cells/μl. However, the proportion of pregnant women among those initiating treatment at ≤200 cells/μl was about 4%. It is likely that the proportion of pregnant women in the group with CD4 cell counts of 201-350 cells/μl is considerably higher [28], say 10%. The prevalence of TB among HIV patients in this area is high (25%), but these mainly concern patients with low CD4 cell counts [29]. When assuming 10% of HIV patients testing with CD4 cell counts of 201-350 having TB, this results in 19% of the 201-350 group being eligible for ART under the current South African policy, either for being pregnant or having TB co-infection.

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Supplement II: STDSIM and its application to South Africa

II.1 General model structure

We used STDSIM, a stochastic event-driven microsimulation model of the transmission and control of HIV and other sexually transmitted diseases (STDs) [1-4]. The model simulates the life course of individuals in a dynamic network of sexual contacts. Events like partnership formation and the acquisition of infection are the result of random processes, determined by probability distributions. Therefore, the results of the model are subject to stochastic variation. It is necessary to perform multiple runs and average the results to diminish the stochasticity in predictions.

The model consists of four modules: demography, sexual behavior, transmission and natural history, and interventions. The demography module implements the processes of birth, death, and migration (see model B1). Processes for initiation and dissolution of sexual relationships, for mixing according to age preference, for sexual contacts within relationships and for sexual contacts between female sex workers and their male clients are defined in the sexual behavior module (see model C1). In the transmission and natural history module, transmission probabilities per sexual contact are specified for HIV and 5 other STDs: chancroid, chlamydia, gonorrhea, syphilis and HSV-2 (see model B2 and C2). Finally, the interventions module specifies the timing and effectiveness of control measures in curbing transmission (e.g. condom use, circumcision, STD treatment, lower partner change rates) or enhancing survival (e.g. antiretroviral therapy). Model runs start in the year 1910 with a predefined initial population composition.

More details justifications on the chosen structures and parameters in STDSIM can be found in van der Ploeg et al [4], Korenromp et al [3], and Orroth et al [2]. The modeling of antiretroviral therapy (ART) using STDSIM is described by Hontelez et al [1,5].

Below, we describe the 4 modules used in STDISM, and their application to the 9 different models used in chapter 3 of this thesis (see fig 3.1). In model A, we stripped the STDSIM model, and then add, in a stepwise approach, parameters of the STDSIM model. The resulting Model D is the full STDSIM model. For some parameters in the models the values were derived in earlier STDSIM studies through fitting against data. Below, we describe all model mechanisms and parameter values; for justification of some parameter values we refer to earlier papers where applicable. In all models, we examine the impact of universal testing and immediate treatment (UTT) for all HIV infected patients in the same manner as done by Granich et al: annual screening of the adult population at 90% coverage (scaled up linearly from 2012 to 2019), and immediate ART for all HIV infected patients [6].

II.2 Model structures and parameterization

Model A ('Granich')

We reproduced the deterministic transmission model by Granich et al [6] using the STDSIM model. We assume all individuals in the model constitute a homogeneous mixture of people in which HIV spreads from person-to-person. Individuals are assumed to have a one-off sexual contact with a random individual of the opposite sex every 8.5 days. We simulate a population aged 15-65

with a constant background mortality rate of 0.025/year. HIV is modeled in 4 consecutive stages with equal duration (30 months) and transmission probabilities, and is introduced in the model by randomly 'infecting' 10 men and 10 women in 1989. ART is assumed to decrease infectiousness by 99%, and the duration of the ART stages is twice the duration of the ART-naïve stages [6]. In addition, like the Granich model, transmission rates are further reduced by 40% because of simultaneous scale-up of other prevention interventions [6]. In accordance with Granich et al, we adjust transmission rates according to HIV prevalence (e-xP) to capture heterogeneity in transmission and the observed steady state in HIV prevalence [6], where p = HIV prevalence while x and the overall HIV transmission probabilities were tuned in order to fit the predicted HIV prevalence to the data reported by UNAIDS. Figure 3.2 in chapter 3 (upper left panel) shows that the model reproduces the observed HIV prevalence in South Africa, and that the impact of the intervention is exactly the same as reported by Granich et al [6].

Model B

To arrive at model B, we extended model A by adding background demographic processes specific of South Africa, and steps in the HIV natural history as used in STDSIM.

Demographics (model B1)

In the model, births are assigned randomly to sexually active women between the ages 15 and 49. The probability of having a child depends on the age of the women. We used UN reported data on age-specific fertility rates for South Africa (table II.1) [7]. The resulting initial total fertility rate (defined as the expected life-time number of births per women) equals 4.9 births per woman. Overall fertility rates over time can be adjusted in order to capture (declining) trends in fertility rates by multiplying all values in table II.1 with the same factor. We assumed total fertility rates to decline according to UN reported trends in fertility total fertility rates for South Africa (figure II.1A) [7].

At birth, the age at (non-HIV) death of each individual is drawn from pre-defined, sex-specific survival curves. In order to obtain background mortality rates in the absence of HIV for South Africa, we corrected the age- and sex-specific mortality rates for South Africa reported by WHO [8] using the cause-specific mortality estimates from WHO burden of disease estimates [9]. The resulting survival curve is shown in figure II.1B.

Age group	Annual probability of getting a child
15-19	0.08
20-24	0.21
25-29	0.23
30-34	0.21
35-39	0.16
40-44	0.06
45-49	0.04

Table II.1. Annual probability for a woman to have a child, by age group. Distribution over age groups according to UN data [10].

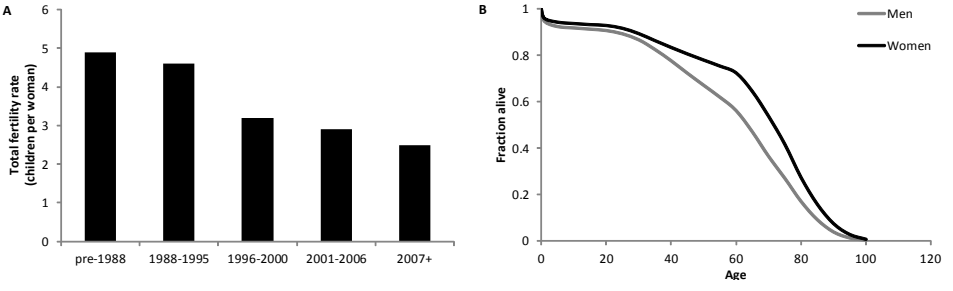

Figure II.1. Demographic input parameters. (A) Total fertility rates (life-time number of births/woman) over time. Data obtained from UN World Fertility Data [7]. (B) Background mortality (mortality in the absence of AIDS) obtained from WHO [8]. All cause mortality rates were corrected using Burden of Disease estimates of HIV mortality rates in South Africa [9] in order to obtain estimates on non-AIDS related mortality rates in South Africa.

Natural history and heterogeneity in transmission (model B2)

For model B2, we added HIV natural history dynamics to capture differences in transmissibility by stage. We assumed the following HIV diseases progression: (i) early/acute infection with a median duration of 3 months; (ii) asymptomatic infection with a median duration of 5 years; (iii) symptomatic infection with a median duration of 4 years; and (iv) AIDS, with a median duration of 8 months. All stages are exponentially distributed, and the total median HIV survival equals 10 years [IQR 8 - 13] [11,12]. Transmission probabilities are highest during the acute stages and lowest during the asymptomatic stages; we allow transmission probabilities to increase again during the symptomatic- and AIDS-stages [2,13]. Relative to asymptomatic infection (2nd stage), transmission probabilities are increased by a factor 15 during early/acute infection, a factor 3 during symptomatic infection, and a factor 7.5 during AIDS [2]. In addition, we assumed sexual activity of HIV-infected patients in the AIDS stage (last 40 weeks of life) to reduce by 50% because of ill health [14]. We used HIV transmission probabilities in the asymptomatic stage to fit the HIV prevalence to the data. Again, as in model A, we adjusted transmission rates according to HIV prevalence (e-xP) in order to capture heterogeneity in transmission and the observed steady state in HIV prevalence.

Model C

Next, we expanded model B by adding: (i) heterogeneity in sexual behavior (model C1); (ii) background prevention interventions and STD co-factors (model C2); and (iii) more conservative and up-to-date ART assumptions (model C3).

Heterogeneity in sexual behavior (model C1)

We added a dynamic sexual network to the model that describes age- and sex-specific risk behavior by 5-year age groups. We use the same patterns of mixing as recently used by Hontelez et al for a rural South African setting (Hlabisa sub district of KwaZulu-Natal) [1,5]. The model contains three types of sexual relationships: steady relationships, casual relationships, and commercial sex. The formation of partnerships occurs according to a supply- and demand-based mechanism. People become available for a sexual relationship at an age of sexual debut, which is randomly drawn at birth from a uniform distribution (table II.2). Each time the partnership status of a person changes (e.g. a partnership is formed or ended), a new duration until the person becomes available for a new relationship (time until availability) is drawn from a predefined exponential distribution with μ being the mean time until availability defined as: $\mu = \tau_{s,r}/(r_{s,a} \times p)$

With: $\tau_{s,r}$ = time interval by person's sex (s) and relationship status (r)
$r_{s,a}$ = specific promiscuity factor by sex (s) and age (a)
p = personal promiscuity level

The personal promiscuity factor (p) reflects the heterogeneity in the tendency to form partnerships between individuals, and is given by a gamma distribution with an average value (pm) of 1.0, and a shape parameter of 1.5.

The duration of the availability period of an individual is given by an exponential distribution, with mean time to find (ϰ) defined as: $\frac{\delta}{r_{s,a} \times p}$, where the value of δ is 0.25 years for men and 2.25 years for women (table II.2) [3]. $r_{s,a}$ and p are explained above. When a person is available for a new relationship, he/she can be selected by an individual of the opposite sex who has ended his/her availability period. If a person is not selected at the end of the availability period, he/she will select a partner from the pool of available persons of the opposite sex. The type of relationship (steady or casual) that is formed when a partner is selected depends on the age of the male partner, and is defined as a probability of a steady relationship (table II.2). The probability of a new relationship being a casual relationship is given by 1 - probability of a steady relationship. A relationship starts with a sexual contact. After each contact, the time until a new sexual contact within the relationship is drawn from an exponential distribution with a mean frequency of sexual contact depending on relationship type and the age of the male partner (table II.2). Finally, the duration of a new relationship is drawn from an exponential distribution, where the average relationship duration is depends on the relationship type (table II.2).

	Women	Men	Distribution
Age of sexual debut	17 [Range: 15 - 19]	17 [Range: 15 - 19]	Uniform
Average time till availability ($\tau_{s,r}$)			
Single	0.5 years	0.5 years	Exponential
Steady relationship	25 years	10 years	Exponential
Casual relationship	3.5 years	2 years	Exponential
Time to find (δ)	0.25 years	2.25 years	Exponential
			Gamma
Mean personal promiscuity (pm)	1.0	1.0	
			(shape = 1.5)
Age specific promiscuity ($r_{s,a}$)			
15-19	7.8	1.9	Fixed value
20-24	7.8	3.9	Fixed value
25-29	4.9	5.8	Fixed value
30-34	2.9	7.8	Fixed value
35-39	1.9	4.9	Fixed value
40-44	1.9	1.9	Fixed value
45-49	1.9	1.9	Fixed value
50+	1.9	1.9	Fixed value
Probability of steady relationship by age group			
15-19	N/A*	0.05	Fixed value
20-24	N/A*	0.1	Fixed value
25-29	N/A*	0.3	Fixed value
30-34	N/A*	0.5	Fixed value
35-39	N/A*	0.7	Fixed value
40-44	N/A*	0.9	Fixed value
45-49	N/A*	0.9	Fixed value
50+	N/A*	0.9	Fixed value
Frequency of sexual contact			
Steady relation			
15-34	N/A*	6.5 times/month	Exponential
35-49	N/A*	4.4 times/month	Exponential
50+	N/A*	3.7 times/month	Exponential
Casual relation			
15-34	N/A*	3.3 times/month	Exponential
35-49	N/A*	2.2 times/month	Exponential
50+	N/A*	1.7 times/month	Exponential
Average relationship duration			
Casual relationship	0.5 years	0.5 years	Exponential
Steady relationship	25 years	25 years	Exponential

Table II.2. Sexual behavior parameters. Justification for the age distribution in promiscuity, frequency of contact, and duration of partnerships can be found in Orroth et al [2] and Korenromp et al [3]. All age specific promiscuity values (i.e. overall partner change rates) were adjusted with the same factor in order to represent the HIV epidemic observed in South Africa.* determined by the age of the male partner

Partner selection at the end of the time to find is guided through an age preference matrix (table II.3), which defines the probability of selecting a partner from a certain age class. When there is no partner available in the preferred age class, immediate re-sampling is done of a new preferred age-class using the remaining age groups with a probability larger than 0.0. If no partner can be found in any of the age-classes, a new time to find is drawn from the above described equation. Probabilities in the age-preference matrix are chosen to have men prefer slightly younger women. Preference matrices for both sexes are given in table II.3.

Male age (y)	Female age (y)								
	<15	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50+
<15	0.95	0.05	0.0	0.0	0.0	0.0	0.0	0.0	0.0
15-19	0.9	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
20-24	0.7	0.25	0.05	0.0	0.0	0.0	0.0	0.0	0.0
25-29	0.5	0.25	0.2	0.05	0.0	0.0	0.0	0.0	0.0
30-34	0.3	0.25	0.2	0.2	0.05	0.0	0.0	0.0	0.0
35-39	0.1	0.2	0.25	0.2	0.2	0.05	0.0	0.0	0.0
40-44	0.0	0.1	0.2	0.25	0.2	0.2	0.05	0.0	0.0
45-49	0.0	0.0	0.1	0.2	0.25	0.2	0.2	0.05	0.0
50+	0.0	0.0	0.0	0.1	0.2	0.25	0.2	0.2	0.05
Female age (y)	**Male age (y)**								
	<15	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50+
<15	0.1	0.3	0.3	0.25	0.05	0.0	0.0	0.0	0.0
15-19	0.0	0.15	0.4	0.3	0.1	0.05	0.0	0.0	0.0
20-24	0.0	0.0	0.15	0.4	0.3	0.1	0.05	0.0	0.0
25-29	0.0	0.0	0.0	0.15	0.4	0.3	0.1	0.05	0.0
30-34	0.0	0.0	0.0	0.0	0.15	0.4	0.3	0.15	0.0
35-39	0.0	0.0	0.0	0.0	0.0	0.15	0.4	0.4	0.05
40-44	0.0	0.0	0.0	0.0	0.0	0.0	0.15	0.7	0.15
45-49	0.0	0.0	0.0	0.0	0.0	0.0	0.05	0.8	0.15
50+	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.05	0.95

Table II.3. Age preference matrix for men and women. Same as in previous STDSIM studies[1-3]. Justification for the values can be found in Korenromp et al [3]

Figure II.2 gives distribution in number of recent partners (last 12 months) by age and sex, which follows from the above described input parameters on sexual behavior. Although it is hard to compare these trends to data as reliable estimates are scarce, predicted distributions are close to those observed by Johnson et al [15]. Their estimates show that 41% of all men aged 15-49 report more than 1 partner in the last twelve months, and 25% of all women aged 15-49 report more than 1 recent partner. In our model, these figures are 42% and 34%. It is likely that women underreport their sexual behavior [16-18], explaining the slightly higher proportion of women with multiple partners in our model.

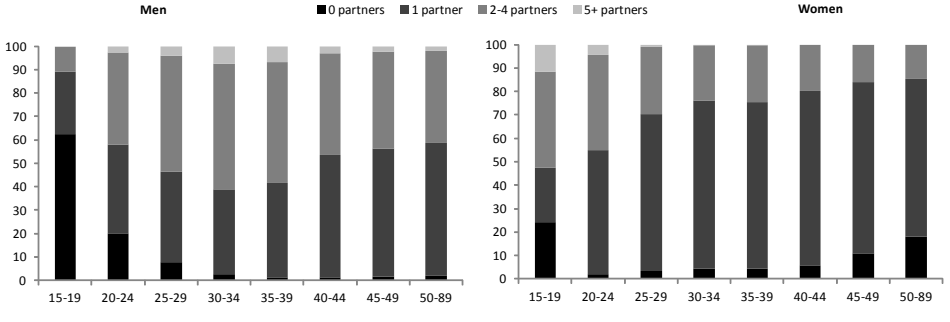

Figure II.2. Distribution of number of partners (steady + casual) in the last 12 months by age and sex. Results follow from parameter settings described in tables II.1 to II.4

Commercial sex

In the model, male clients can visit female sex workers (FSW). A males' frequency of FSW visit is determined by defining frequency classes (in this study 0, 1, and 12 times per year [1,2]). For each class, the proportion of men with and without a steady relationship falling in that category can be specified. A personal prostitute visiting inclination, assigned to each male at birth, determines which individual males are assigned to which frequency classes. At sexual debut and at each FSW visit, the next FSW visit is scheduled according to an exponential distribution with the mean duration until next visit is based on the FSW visit frequency of the individual.

The number of FSWs in the model results from the male demand. New FSWs are recruited from sexually active females with a defined age range. The number of available FSWs and their predefined number of clients per week is checked each year and matched with the number of visitors. If the number FSWs is too low, new FSWs are recruited. If the number is too high, a random selection terminates their career. For this study, we used the same values as previously used for KwaZulu-Natal, South Africa [1] (table II.4).

Female sex workers	
Start age	17-30 years
Max. stop age	35 years
Minimum career length	1 year
Clients	
Proportion of men by frequency	
Married	
0 visits/year	67%
1 visit/year	28%
12 visits/year	5%
Unmarried	
0 visits/year	34%
1 visit/year	55%
12 visits/year	11%

Table II.4. Parameter settings for commercial sex. Same as in previous STDSIM studies [1,2]. Justification can be found in Orroth et al [2].

Model C1 describes the South African HIV epidemic in an age-structured model that includes sexual networks (model B + above described sexual network). We used the HIV transmission probabilities in the asymptomatic phase to fit the HIV prevalence according to UNAIDS estimates. We assume the observed steady state in the HIV prevalence to result from behavior change. Therefore, we multiply all values of $r_{s,a}$ (sex and age specific promiscuity -- see above) by 0.95 in 1994, 0.75 in 1996, and 0.55 in 1998. The resulting sexual behavior pattern by sex and age in the year 1990 (start of the epidemic) is given in figure II.2, and for the year 2003 (after above described reduction in risk behavior) in figure II.3.

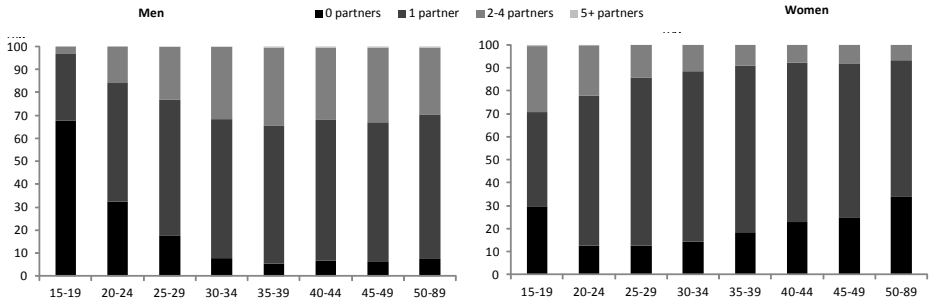

Figure II.3. Distribution of number of partners in the last 12 months (steady + casual) by age and sex in 2003 (after change in overall partner change rates). Results follow form parameter settings described in tables II.1 to II.4 and above described adjustment in overall partner change rates.

Co-factor effects and other STDs (model C2)

In order to adequately capture co-factor effects and background preventive interventions we added the following STDs to the model: chlamydia, syphilis, gonorrhea, chancroid, and HSV-2. Details about their natural history and effect on HIV transmission can be found in table II.5. The justification for chosen values is described elsewhere[1,2]. We assumed HIV transmission rates to vary by sex (male-to-female transmission being twice as efficient as female-to-male transmission) and circumcision status (uncircumcised men are twice as likely to be infected with HIV during an unprotected sex act with an infected partner). Condom use rates in South Africa have increased over time [19], which has been suggested to cause the observed steady state HIV prevalence over the past few years [20]. We assumed a stepwise increase in condom use rates to capture the observed steady state in HIV prevalence: from 0% to 10% in 1998, and from 10% to 25% in 2000. We assumed a circumcision prevalence of 35% [21]. We fitted the HIV prevalence to the data using the transmission probability in asymptomatic HIV.

	Duration	Transmission probabilities		Cofactor effect on HIV transmission	'Lack of circumcision' effect
		M-->F	F-->M		
Chancroid	11 weeks	0.23	0.115	25	2
Gonorrhea	14 weeks	0.26	0.13	3	1
Chlamydia	14 weeks(M); 52 weeks (F)	0.252	0.126	3	1
Syphilis					2
Primary	6 months	0.175	0.088	7.5	
Early latent	1 year	0.018	0.009	1	
Latent	2.5 years	0	0	1	
Late latent	12.5 years	0	0	1	
HSV-2					2
Primary	3 weeks	0.3	0.15	25	
Early latent (with recurrent ulcer)	2 years	0.01	0.005	1	
Late latent (with recurrent ulcer)	10 years	0.005	0.003	1	
Late latent	Lifelong	0	0	1	
Recurrent ulcer1	1 week	0.2	0.1	10	

Table II.5. Parameter settings for natural history of simulated STDs. Same as previously used in other studies [1,2]. 'Lack of circumcision' effect represents factor increase in susceptibility to the STD for men who are not circumcised, i.e. uncircumcised men are twice as likely to get infected during an unprotected sex-act with an infected partner. Justification can be found in Orroth et al [2]. 1Recurrent ulcers occur during the late latent stage of HSV-2. Average duration between recurrent ulcers is 3 months in early-latent, and 8 months in late-latent.

Up to date assumptions on ART effectiveness (model C3)

Granich et al assumed ART to reduce infectiousness by 99% [6]. However, recent observational studies and a randomized controlled trial showed that this is likely to be lower [22-24]. A meta-analysis of observational studies resulted in an average reduction of 92% [22], which was later also reported by Donnell et al [23]. The HPTN052 trial showed a reduction of 96% [25], however, the participants in the trial were completely adherent to treatment, which is unlikely in large-scale interventions. A Cochrane review including all observational studies and the above described trial reported a reduction in transmission as a result of ART of about 86% [24]. Here, we assume a 90% efficacy in reducing transmission implicitly allowing for imperfect adherence. In addition, Granich et al assumed that ART increases survival of HIV infected patients by a factor of 2 relative to their remaining untreated HIV life-expectancy. We assume the survival benefit of ART to be twice as high as assumed by Granich et al (i.e. a factor 4 increase), consistent with observations [26].

Quantifying HIV prevalence in model C

The full model C is a combination of model B, and sub models C1, C2, and C3. To fine-tune the predicted HIV prevalence, we adjusted the following parameters compared to the sub models: (i) HIV is introduced in 1989 in 6 FSWs rather than the general population (as occurred in models A and B) (ii) HIV transmission probabilities in the asymptomatic phase are fixed at 0.001 per act for men and 0.0005 per act for women [13]; (iii) there is no change in overall promiscuity level over time (as occurs in model C1) and partner change rates remains constant at the 1990 level

(see figure II.2; section2.3.1); (iv) the fraction of men that consistently use condoms during non-marital sex acts (Cm) is increased to 10% in 1998 and 25% in 2000, consistent with observations of increased condom use in South Africa [19,20]. In addition, we assumed that 25% of all FSWs will use a condom during a contact with a client (Cfsw). Therefore, the total condom use rates regarding FSW visits equals 44% (1-(1- Cm) x (1- Cfsw)).

Model D (STDSIM)

CD4 cell counts and ART roll-out

Model D includes all of the above models but with 2 important additions: CD4 cell count decline during disease progression and the ART roll-out in South Africa for the period 2004-2011. Based on data from Orange Farm, South Africa, we assumed the initial (HIV-negative) CD4 cell count in the population to follow a lognormal distribution with median 7.02 (equivalent to 1116 cells/μL) [27]. We assumed CD4 cell counts to decline by 25% during acute infection, and decline linearly over the other stages until the CD4 cell count reaches 0.5% of its initial value, after which an individual dies of AIDS[1,6,27]. Therefore, based on the average HIV-negative CD4 cell counts and duration of HIV infection, an individual will on average reach a CD4 cell count of ≤350 cells/μL after about 6 years following infection, and at that point will have a remaining life expectancy of about 4 years.

In the model, ART coverage is the result of two components: (i) an individual's demand for ART as a function of HIV-disease stage, and (ii) the capacity of the health system to meet this demand. ART coverage in our model is the ART demand met by the capacity of the health system. We assumed the ART demand function to be the same as previously estimated for the Hlabisa sub district of KwaZulu-Natal, South Africa [1], in which about 30% of all infected individuals start to seek care for HIV well after their CD4 cell counts drop below 200 cells/μL. We assumed the capacity of the health system to meet the demand to increase following a simple quadratic distribution ($\alpha X2$), and we optimized α by calculating the Mean Squared Error of predicted ART coverage in the model compared to coverage data reported by WHO [28]. We assumed eligibility criteria to change from ART at ≤200 cells/μL to ≤350 cells/μL in mid-2011, and the ART scale-up to continue according to the estimated scale-up pattern for the years 2012 - 2050 in the baseline. We assumed a baseline annual rate of stopping treatment of 5% [29], and these patients will not initiate treatment again. However, retention in care varies with ART capacity of the health system [30]. Therefore, we assumed the annual rate of stopping treatment to reduce to 2.5% when the health-systems capacity to provide ART reaches 80%, and to further reduce to 1% when capacity is 100%. The rates of stopping treatment during the UTT intervention are kept as they were (8.5% stop treatment in the first year, 1.5% annual rate of stopping treatment thereafter)

Finally, increased survival of HIV-infected patient due to ART would result in a rise in prevalence in the period 2004-2010, which is inconsistent with data reported by the UNAIDS. Therefore, we assumed condom use to further increase to 30% in 2004 in order to correct for the

increase in prevalence. The 30% condom use is a little more consistent with data compared to the 25% assumed in model C. Hargreaves et al showed that reported condom use during last non-spousal sexual contact in a rural South African cohort increased between 2001 and 2004 from 33% to 39% for men, and from 27% to 32% for women [31].

Model fit to data

HIV prevalence fit (all models)

For all main models (A to D) the fit to UNAIDS reported HIV prevalence in South Africa is given in figure 3.2 in chapter 3. In addition, figure II.4 gives the fit of all sub-models compared to data, and the predicted impact of UTT on HIV incidence and prevalence (see also table 3.1 in chapter 3).

Model fit to other data (model D)

Figure II.5 shows the predicted demographic structure, sexual behavior, age-specific HIV prevalence, STD prevalence, ART roll-out, and CD4 cell count distributions, and survival of those on treatment by CD4 cell count at initiation in model D compared to data. Figure II.5A shows that the projected demographic structure of the population matches closely to the data reported by the United Nations Population Division [10]. Figure II.5B shows that the age-specific HIV prevalence in women matches closely to data from the national HIV surveillance [32]. Age specific distribution in numbers of partners for men and women is given in figures II.5C and II.5D respectively. Although it is hard to compare these trends to data as reliable estimates are scarce, predicted distributions are close to those observed by Johnson et al [15]. Their estimates show that 41% of all men aged 15-49 report more than 1 partner in the last twelve months, and 25% of all women aged 15-49 report more than 1 recent partner. In our model, these figures are 42% and 34%. It is not unlikely that women underreport their sexual behavior [16-18], explaining the slightly higher proportion of women with multiple partners in our model. In addition, our projected trends in STDs (figure II.5E and II.5F) are comparable to those reported by Johnson et al [33], who performed a Bayesian analysis of all sentinel surveillance data to estimate the national South African trends in STD prevalence. Prevalence levels for gonorrhea and chlamydia are higher and lower respectively compared to the estimates form Johnson et al [33], yet these data are broad estimates with considerable uncertainty and our estimates still fall within their 95% confidence interval [33]. In addition, our model was able to accurately replicate STD prevalence levels of a rural South African area in KwaZulu-Natal [1]. Both in terms of coverage (figure II.5G) and total numbers of people on treatment (figure II.5H) over the period 2006-2011, our model predictions match closely to data from WHO [28]. The CD4 cell count distributions in those coming to a clinic for the first time matches closely to observed data (figure II.5I) from a large treatment cohort in rural Africa [1,34], indicating a nearly perfect fit for health seeking behavior and ART roll-out in South Africa. Finally, average life-expectancy of those on treatment by CD4 cell count at initiation matches closely to data from a large treatment cohort in KwaZulu-Natal (figure II.5J) [26].

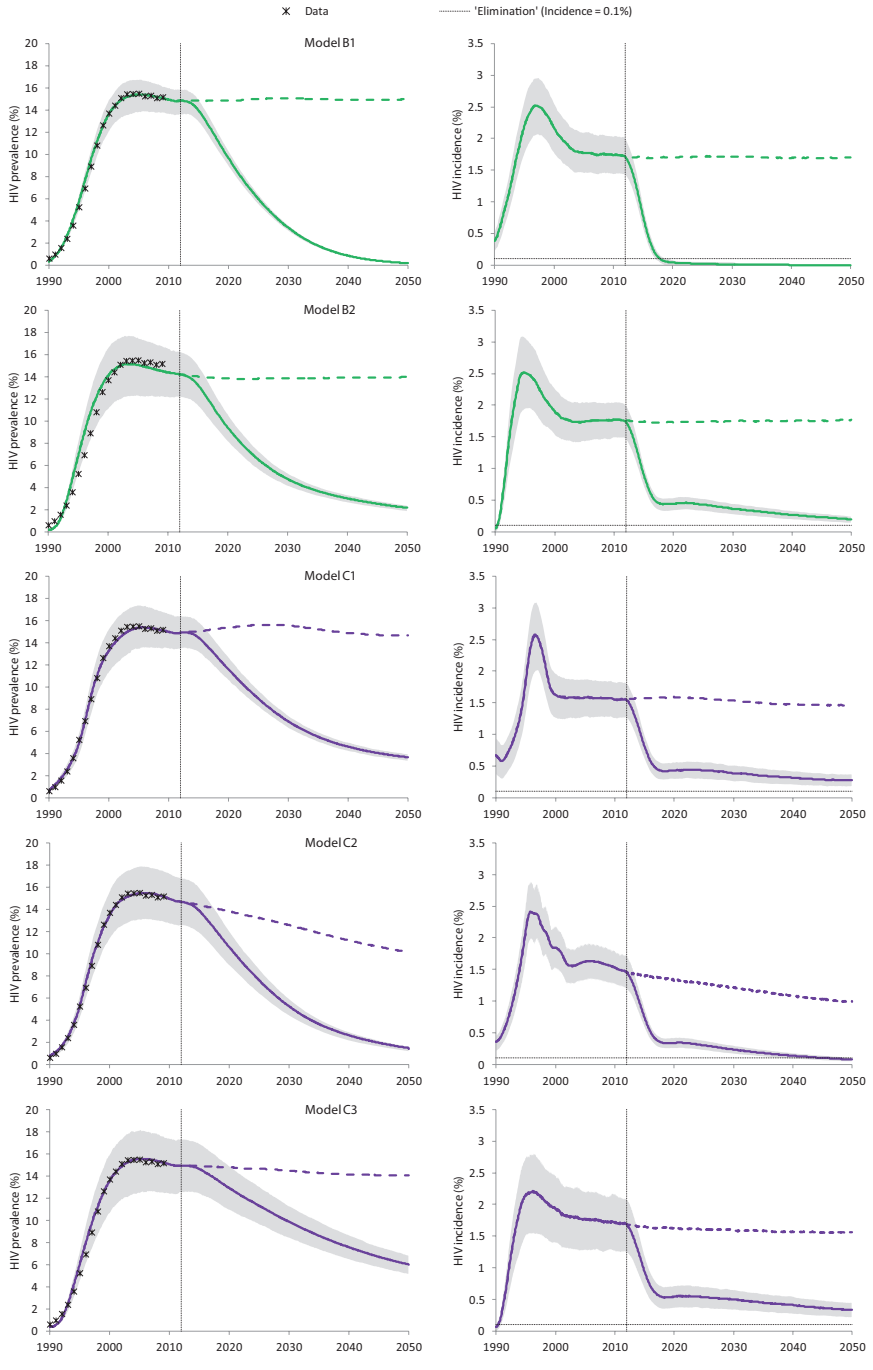

Figure II.4. Predicted impact of universal testing and immediate ART for all HIV infected patients (UTT) on HIV prevalence (left panels) and incidence (right panels) in adults (aged 15+) for five sub models of the South African HIV epidemic over the period 1990-2050. Colored lines are the average result of 1,000 simulations, and the gray area represents the 95% confidence interval based on the stochastic variation between individual model runs.UTT is implemented as annual screening of the adult population, and immediate ART for all HIV-infected patients. The intervention is scaled-up linearly, starting in 2012 and reaching 90% coverage in 2019 (similar to Granich et al (9)). The vertical black dashed lines give the timing of the start of the intervention. The horizontal black dotted lines in the right panels indicate the elimination phase, defined as incidence below 1/1,000 person-years. Same figures for the four main models are given in figure 3.2 in chapter 2.

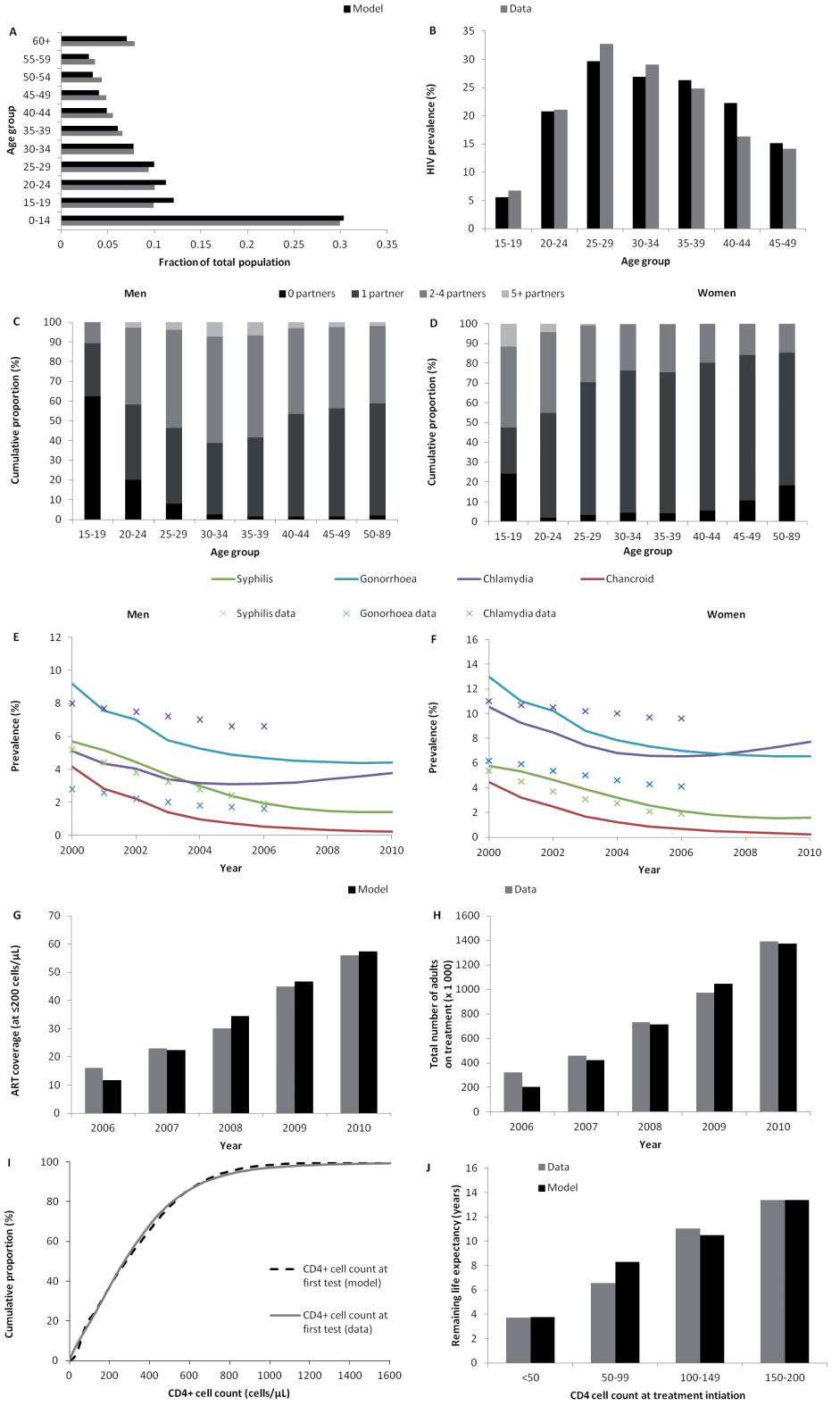
A
Model
Age group
60+
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
15-19
0-14
0 0.05 0.1 0.15 0.2 0.25 0.3 0.35
Fraction of total population
B
Data
HIV prevalence (%)
0 5 10 15 20 25 30 35
15-19 20-24 25-29 30-34 35-39 40-44 45-49
Age group
Men
0 partners
1 partner
2-4 partners
5+ partners
Women
C
Cumulative proportion (%)
0 10 20 30 40 50 60 70 80 90 100
15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-89
Age group
D
Cumulative proportion (%)
0 10 20 30 40 50 60 70 80 90 100
15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-89
Age group
Syphilis
Gonorrhoea
Chlamydia
Chancroid
Men
Syphilis data
Gonorhoea data
Chlamydia data
Women
E
Prevalence (%)
0 2 4 6 8 10 12
2000 2002 2004 2006 2008 2010
Year
F
Prevalence (%)
0 2 4 6 8 10 12 14 16
2000 2002 2004 2006 2008 2010
Year
Model
Data
G
ART coverage (at ≤200 cells/μL)
0 10 20 30 40 50 60 70
2006 2007 2008 2009 2010
Year
H
Total number of adults on treatment (x 1 000)
0 200 400 600 800 1000 1200 1400 1600
2006 2007 2008 2009 2010
Year
I
Cumulative proportion (%)
0 20 40 60 80 100
0 200 400 600 800 1000 1200 1400 1600
CD4+ cell count (cells/μL)
CD4+ cell count at first test (model)
CD4+ cell count at first test (data)
J
Data
Model
Remaining life expectancy (years)
0 2 4 6 8 10 12 14 16
<50 50-99 100-149 150-200
CD4 cell count at treatment intiation

Figure II.5. Model fit compared to data (model D). A. Projected demographic structure of South Africa in 2011, model compared to UN data [10]. B. Age specific HIV prevalence (model compared to data) in 2008. C. Age-specific distribution in number of partners in the last twelve months for men D. Age-specific distribution in number of partners in the last twelve months for women . E. Trend in prevalence of STDs in men, model compared to estimates from Johnson et al [33]. F. Trend in prevalence of STDs in women, model compared to estimates from Johnson et al [33]. G. Projected ART coverage in South Africa, model versus WHO data [28]. H. Projected total number of people on ART in South Africa, model versus WHO data [28]. I. Cumulative distribution of CD4 cell counts at first HIV test, model compared to data from KwaZulu-Natal, South Africa [1,34]. J. Average remaining life-expectancy at treatment initiation by CD4 cell count at treatment initiation, model compared to data [26].

II.3 Cost assumptions (Model D)

We calculate cumulative number of life-years saved and cumulative net costs of UTT compared to continued scale-up of ART at ≤350 cells/μL in model D (the only model that incorporates the current scale-up at ≤350 cells/μL in South Africa). We analyzed costs from the health care sector perspective, and assumed ART costs similar as in Hontelez et al, where annual ART costs were stratified by CD4 cell count at initiation and the number of years on treatment (table II.6) [1], which were derived from ART programs in Cape Town, South Africa [35,36]. Costs include costs for ART provision, treatment of opportunistic infections, outpatient visits, and inpatient days. Costs were stratified by CD4 cell count at initiation since those initiating treatment at late stages (low CD4 cell count) are more likely to have opportunistic infections and other complications thus require more additional care. This difference disappears after subsequent years of successful treatment. We assumed annual ART costs for those initiating at CD4 cell counts of >350 cells/μL to be similar to the costs for those who initiated at 200-350 cells/μL and were on treatment for more than 2 years. For the UTT scenario, in which treatment initiation is not guided by CD4 cell counts, we lowered all cost input values by 104 US$ to reflect the cost of a CD4 cell count test [1]. We discounted future costs and life-years saved by 3% annually [37].

CD4+ count (cells/μl) at ART initiation	**Per patient annual ART costs (US$)**		
	First year	Second and third year	Subsequent years
0-100	3,664	1,435	1,095
101-200	3,060	1,284	1,095
201-350	2,304	1,095	1,095
>350	1,095	1,095	1,095

Table II.6. Cost input values used in this study. Costs are stratified by CD4+ count at antiretroviral therapy (ART) initiation, and include costs of diagnostic testing, ART provision, treatment of opportunistic infections, outpatient visits, and inpatient days.

II.4 Sensitivity analysis

We performed a sensitivity analysis on the predicted year of HIV elimination under UTT and continued scale-up of ART at ≤350 cells/μL (figure 3.2 in chapter 2), and the cost-effectiveness of UTT compared to continued scale-up of ART at ≤350 cells/μL (table 3.2 in chapter 3) in model D. We varied parameters on HIV natural history and transmission dynamics, the course of the HIV epidemic in South Africa, and economics of ART. For each alternative setting (except when assuming a different course of the HIV epidemic), we fine-tuned model predictions in order to make the predicted HIV prevalence comparable to the baseline (model D - see figure 3.2 in chapter 2).

Parameter settings

HIV natural history and transmission dynamics

First, we increase and decrease the HIV negative CD4 cell count distribution through multiplication by a factor 3/2nd (median HIV negative CD4 cell count of 1674) and 2/3rd (median CD4 cell count of 744) respectively. Second, the contribution of different stages of the HIV infection (e.g. early infection versus late infection) to the overall HIV transmission is uncertain and under intense debate [38-40]. Therefore, we assume the following alternative parameterizations of HIV disease progression and transmission: (i) 'Powers' parameterization (assumptions based on Powers et al [38]); (ii) 'Williams' parameterization (assumptions based on Williams et al [39]); (iii) no increase in transmission probabilities in the symptomatic infection stage; and (iv) co-cofactor effects of the STDs decrease by a factor 2/3. The predicted HIV prevalence will change due to these alternative assumptions. Therefore, we used the infectiousness in the asymptomatic stage, year of HIV introduction, and condom use rates to fine-tune the predicted HIV prevalence to again represent UNAIDS reported data (figure II.6). Table II.7 gives all parameter values for each of the 4 scenarios and the baseline.

	Model D (STDSIM)	'Powers' parameterization	'Williams' parameterization	Model D (STDSIM) - No transmission increase during symptomatic infection	Model D (STDSIM) - Reduce co-factor effects of other STIs by 2/3
Infectiousness relative to asymptomatic stage					
Acute	15	30.3	3.2	15	15
Asymptomatic	1	1	1	1	1
Symptomatic	3	3	3	1	3
AIDS	7.5*	7.5**	7.5*	7.5*	7.5*
Average duration					
Acute	3 months	4.8 months	2 weeks	3 months	3 months
Asymptomatic	5 years	5.7 years	5 years	5 years	5 years
Symptomatic	4 years	1.1 year	4 years	4 years	4 years
AIDS	8 months	1.1 year	8 months	8 months	8 months
Infectiousness asymptomatic stage	0.00095	0.00065	0.0013	0.0011	0.0014
Condom use					
1999	10%	5%	10%	10%	10%
2000	20%	10%	20%	20%	20%
2002 onward	30%	15%	30%	30%	30%
Year of HIV introduction	1988	1992	1979	1988	1988

Table II.7. Alternative assumptions on HIV natural history and transmission probabilities for sensitivity analyses. Infectiousness in the asymptomatic stage, condom use, and the year of HIV introduction are used to fine tune predicted HIV prevalence to the UNAIDS data [41].

* Frequency of sexual contact within a relationship is reduced by 50% due to ill health
** Frequency of sexual contact within a relationship is reduced by 100% due to ill health

Course of the epidemic

UNAIDS reported HIV prevalence and incidence data depend on model based extrapolations from cross-sectional surveys, and some argue that their reported decline in incidence and thus reported steady state in HIV prevalence might not be true given observations in population based cohorts [42], while others say that the decline in incidence is the result of a combination of an increase in condom use together with a reduction in number of partners. Therefore, we have also performed a sensitivity analysis on the predicted trend in the HIV epidemic by: (i) reducing condom use uptake by half, thus resulting in an increasing rather than a stabilizing HIV epidemic in 2000-2010; and (ii) the reduction in incidence is achieved through a combination of increased condom use and decreased partner change rates. We decrease partner change rates by proportionally reducing all age- and sex-specific promiscuity levels (see 2.3.1 heterogeneity in sexual behavior). Parameter assumptions and the resulting change in sexual behavior are given in table II.8. Figure II.6 gives the fit compared to the UNAIDS reported data.

	Model D (STDSIM)	Increasing prevalence in 2000s	Alternative behavior change assumptions
Condom use			
1999	10%	5%	5%
2000	20%	10%	10%
2002 onward	30%	15%	15%
Reduction in promiscuity[1]			
1999	N/A	N/A	90%
2000	N/A	N/A	75%
Proportion of men (aged 15-49) with 2+ partners [2]			
1998	41%	41%	41%
2012	41%	41%	35%

Table II.8. Input parameters for sensitivity analysis on the course of the epidemic
1 Level of age- and sex-specific promiscuity relative to the baseline. Baseline values are given in table II.2 and explained in section heterogeneity in sexual behavior in these supplements.
2 Over the last 12 months. To illustrate the effect of the adjustment in the age- and sex-specific promiscuity

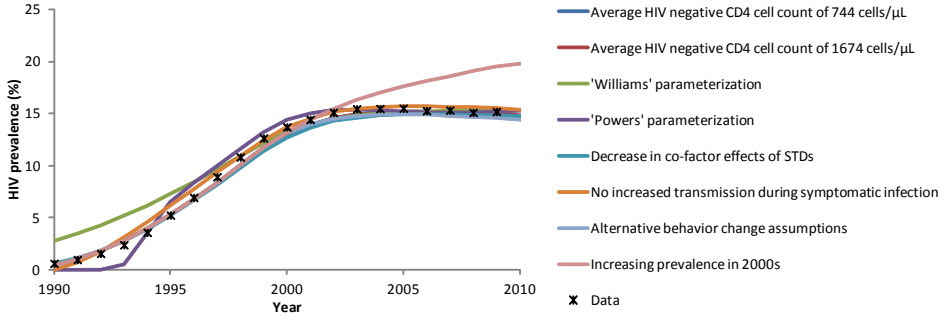

Figure II.6. Predicted HIV prevalence for all sensitivity analyses (except for alternative economic and UTT performance assumptions) compared to UNAIDS reported HIV prevalence in South Africa [41].Parameter assumptions are given in table II.7 and II.8.

Alternative economic assumptions

Finally, we addressed alternative economic assumptions: (i) higher and lower discount rates (10% and 1% respectively); (ii) economies and diseconomies of scale (exponentially increase or decrease in per-patient costs respectively when patient loads increase [43]); (iii) a 20% increase in total costs reflecting infrastructural expansion in the 'test-and-treat' scenario; and (iv) no differentiation of annual ART costs by CD4 cell count at initiation and number of years on treatment.

Less optimistic programmatic assumptions

The assumed UTT intervention of 90% coverage and 1.5% dropout is very optimistic. It is likely that screening coverage will be lower and dropout rates will be higher. Therefore, we add two additional UTT scenarios to our sensitivity analysis: (i) annual screening coverage of 60% instead of 90%; and (ii) dropout rates of 5% annually instead of 1.5% (and still an initial dropout rate of 8.5% in the first year of treatment).

II.5 Supplementary results (sensitivity analysis)

Table II.9 shows the results of the sensitivity analysis. Elimination of HIV (incidence <1/1,000 person-years) is achieved in all of the scenarios, except when assuming high proportions of transmissions due to acute infection. The time until elimination is especially affected by the course of the epidemic. If HIV prevalence in South Africa in the 2000s would continue to rise rather than stabilize, elimination will only be achieved in 2062 (for UTT) and at around 2100 (for ART at ≤350 cells/μL). For all other scenarios, timing of elimination remains relatively unchanged. UTT is highly cost-effective in all of the scenarios in our sensitivity analysis.

	Stage of infection of the index case[1]		Year of HIV 'elimination'		ICER for UTT
	Early infection	≤350 cells/μL	≤350 cells/μL	UTT	
Model D (STDSIM)	23%	52%	2041	2029	170 US$/LYS
Average HIV-negative CD_4 cell count (baseline = 1116 cells/μL)					
1674 cells/μL	23%	40%	2050	2030	350 US$/LYS
744 cells/μL	23%	65%	2035	2028	Dominant
Course of the epidemic in South Africa					
Increasing prevalence in 2000s	23%	51%	>2075	2062	Dominant
Alternative behavior change assumptions	23%	51%	2039	2027	220 US$/LYS
Alternative HIV transmission parameterization					
'Powers' parameterization	47%	38%	No elimination	No elimination	Dominant
'Williams' parameterization	2%	62%	2047	2032	Dominant
No transmission increase during symptomatic infection	31%	39%	2050	2031	20 US$/LYS
Reduce co-factor effects of other STIs by 2/3	22%	55%	2043	2032	200 US$/LYS
Alternative economic assumptions					
Discount rate (baseline = 3%)					
10%	23%	52%	2041	2029	1 200 US$/LYS
1%	23%	52%	2041	2029	53 US$/LYS
Scale effects					
Economies of scale	23%	52%	2041	2029	850 US$/LYS
Diseconomies of scale	23%	52%	2041	2029	1 100 US$/LYS
Costs for Infrastructural expansion	23%	52%	2041	2029	624 US$/LYS
No differentiation by CD_4 at initiation and years on treatment	23%	52%	2041	2029	960 US$/LYS
Less optimistic programmatic assumptions					
60% annual screening coverage	23%	52%	2041	2031	132 US$/LYS
5% annual rate of stopping treatment, 8.5% in first year	23%	52%	2041	2048	Dominated

Table II.9. Results of the sensitivity analysis. The year of elimination is defined as the first year HIV incidence drops below 1/1,000 person-years. UTT = universal testing and immediate treatment for all HIV infected patients, starting in 2012 and scaled up to 90% coverage in 2019.
1 Stage of the HIV infection in the index case of an HIV transmission event in the year 2003 (year prior to introduction of ART in the model)

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Supplement III: Quantification of 43 countries in sub-Saharan Africa

III.1 General model structure

We used STDSIM, a stochastic microsimulation model of the transmission and control of HIV and other sexually transmitted infections (STIs) [1-4]. The model simulates the life course of individuals in a dynamic network of sexual contacts. Events like partnership formation or the acquisition of infections are the result of random processes, determined by probability distributions. Therefore, the results of the model are subject to stochastic variation. It is necessary to perform multiple runs and average the results to diminish the stochasticity in predictions.

The model consists of four modules: demography, sexual behavior, transmission and natural history, and interventions. The demography module implements the processes of birth, death, and migration. Processes for initiation and dissolution of sexual relationships, for mixing according to age preference, for sexual contacts within relationships and for sexual contacts between clients and sex workers are defined in the sexual behavior module. In the transmission and natural history module, transmission probabilities per sexual contact are specified for HIV and other simulated STIs. Finally, the interventions module specifies the timing and effectiveness of control measures in curbing transmission or enhancing survival. Model runs start in the year 1910 with a fixed population size. The country-specific background age-specific fertility and mortality rates create a population of about 20,000 to 50,000 in 2010. This modeled population size needs to be extrapolated to observed population sizes. In order to do this, we divide the population size in 2010 as reported by the United Nations World Population Prospects (2010 revision) [5] by the modeled population size in 2010, and apply the obtained ratio to all years. Figure III.3 shows that the resulting population projections of the model compared to the UN world population prospects are highly similar.

Further details about the general model structure can be found in van der Ploeg et al [4], Korenromp et al [2], and Orroth et al [3]. The modeling of antiretroviral therapy (ART) is described by Hontelez et al [1,6]. This document contains tables III.1 and III.2, and figures III.1 to III.3.

III.2 Supplementary tables

	Sexual behavior Profile				
	Concentrated	**Concentrated (low condom use)**	**Mixed**	**Mixed (low condom use)**	**Generalized**
Age at sexual debut (range)					
Men	18 yrs (±3 yrs)	18 yrs (±3 yrs)	17 yrs (±3 yrs)	17 yrs (±3 yrs)	17 yrs (±3 yrs)
Women	18 yrs (±4 yrs)	18 yrs (±4 yrs)	17 yrs (±4 yrs)	17 yrs (±4 yrs)	15 yrs (±4 yrs)
Proportion in a stable relationship					
Men (aged 15-49)	40%	40%	44%	44%	53%
Women (aged 15-49)	43%	43%	34%	34%	66%
Portion of men with 2+ partners in last 12 months					
Baseline	36%	36%	50%	50%	55%
+25% partner change rates	39%	39%	53%	53%	58%
-25% partner change rates	33%	33%	46%	46%	51%
Commercial sex					
Number of clients per week	4	4	2	2	1.6
Proportion of men visiting sex workers (no. visits/year)					
Married	24% 2/year; 0.5% 24/year	24% 2/year; 0.5% 24/year	29% 4/year; 5% 24/year	29% 4/year; 5% 24/year	28% 4/year; 6% 24/year
Unmarried	48% 2/year; 10% 24/year	48% 2/year; 10% 24/year	60% 4 /year; 11% 24/year	60% 4 /year; 11% 24/year	55% 4 /year; 11% 24/year
Proportion of women being sex worker	0.3%	0.3%	0.7%	0.7%	2 %
Condom use					
Commercial sex					
1990	10%	0%	10%	0%	10%
1993	25%	10%	25%	10%	20%
1995	50%	25%	50%	25%	30%
Casual partnerships					
1990	10%	10%	10%	10%	10%
1995	20%	20%	20%	20%	25%

Table III.1. Sexual behavior profiles. Profiles based on Orroth et al. [3], with modifications explained in the main text.

	Profile[1]	Circumcision prevalence[2]	ART roll-out		Year of HIV introduction[3]	Fine-tune[4]	
			Start year	Function (MF)		Partner change rates	CSW visit rates
Angola	Concentrated (LC)	66%	2002	Q (0.004)	1990	-20%	-20%
Benin	Concentrated	84%	2004	L (0.167)	1989	0%	0%
Botswana	Generalized	25%	2001	Linear (0.5)	1989	+10%	n/a
Burkina Faso	Concentrated (LC)	89%	2004	Linear (0.1)	1985	0%	0%
Burundi	Concentrated	2%	2004	Sqrt (0.003)	1985	+20%	0%
Cameroon	Mixed (LC)	93%	2001	Q (0.004)	1989	-10%	n/a
CAR	Mixed	67%	2003	Q (0.004)	1989	-5%	n/a
The Congo	Concentrated (LC)	70%	2004	L (0.05)	1983	-20%	-5%
Côte D'Ivoire	Mixed	93%	2003	L (0.033)	1988	-25%	n/a
Chad	Concentrated (LC)	64%	2004	Q (0.014)	1984	+25%	0%
Djibouti	Concentrated (LC)	94%	2003	Sqrt (0.0017)	1990	0%	0%
DR Congo	Concentrated (LC)	70%	2004	Sqrt (0.0013)	1989	-20%	-20%
Equatorial-G	Mixed (LC)	86%	2005	Sqrt (0.001)	1995	+40%	n/a
Eritrea	Concentrated	95%	2005	Q (0.03)	1990	-10%	0%
Ethiopia	Concentrated (LC)	76%	2004	L (0.083)	1991	-20%	-10%
Gabon	Mixed (LC)	93%	2001	Q (0.01)	1990	0%	n/a
Gambia	Concentrated (LC)	90%	2003	Sqrt (0.0033)	1996	+13%	0%
Ghana	Concentrated (LC)	95%	2003	Q (0.006)	1990	-20%	-15%
Guinea	Concentrated (LC)	83%	2003	Q (0.01)	1990	-20%	-20%
Guinea-B	Concentrated (LC)	91%	2005	Q (0.02)	1990	+25%	0%
Kenya	Mixed	84%	2003	Q (0.015)	1985	+10%	n/a
Lesotho	Generalized	0%	2004	Q (0.025)	1989	-5%	n/a
Liberia	Concentrated	70%	2003	Q (0.003)	1986	+20%	0%
Madagascar	Concentrated	100%	2005	Q (0.003)	1996	-25%	-25%
Malawi	Mixed (LC)	27%	2003	Q (0.015)	1990	-35%	n/a
Mali	Concentrated	95%	2004	L (0.125)	1989	0%	0%
Mauritania	Concentrated	100%	2005	L (0.071)	1994	0%	0%
Mozambique	Generalized	56%	2005	L (0.0833)	1991	+5%	n/a
Namibia	Mixed	15%	2004	L (0.5)	1990	+5%	n/a
Niger	Concentrated	92%	2005	Q (0.011)	1991	-20%	-5%
Nigeria	Concentrated (LC)	81%	2004	L (0.033)	1983	+20%	0%
Rwanda	Concentrated	10%	2004	L (0.333)	1981	+20%	0%
Senegal	Concentrated	89%	2003	L (0.125)	1995	-20%	-20%
Sierra Leone	Concentrated (LC)	90%	2001	L (0.0167)	1995	-7%	0%
Somalia	Concentrated	93%	2005	L (0.0125)	1995	-20%	-20%
South Africa	Generalized	35%	2003	Q (0.014)	1990	0%	n/a
Sudan	Concentrated	47%	2004	Q (0.003)	1999	-35%	-35%
Swaziland	Generalized	8%	2002	Q (0.02)	1990	+5%	n/a
Togo	Concentrated (LC)	93%	2001	Q (0.004)	1994	-20%	-20%
Tanzania	Mixed	70%	2004	L (0.0833)	1986	+25%	n/a
Uganda	Concentrated (LC)	25%	2001	Q (0.006)	1981	+13%	0%
Zambia	Mixed (LC)	12%	2004	Q (0.056)	1990	-30%	n/a
Zimbabwe	Generalized	10%	2004	Q (0.014)	1987	+15%	n/a

Table III.2. Country specific HIV prevalence and ART roll-out fits. All countries included in the analyses are listed with their corresponding sexual behavior profile, circumcision prevalence, ART scale-up function, HIV introduction year, change in overall partner-change rates, and change in overall CSW visit rates.

1. Figure 7.1 in chapter 7 gives geographical representation of the chosen profiles;

2. Source: Williams BG et al [7] except for Madagascar, Mauritania, and Swaziland, where data comes from UNAIDS database [8]. Year of circumcision prevalence is 2006, except for CAR (1995); Eritrea (2003); Gabon (2001); Madagascar (2010); Mauritania (2001); Sudan (1991); Swaziland (2008); and Togo (1999).

3. Year of HIV introduction does not necessarily represent the year first HIV case(s) were identified in a country. The year is chosen to fit the country specific development of the HIV epidemic in our model.

4. Change in overall partner change rates and CSW visit rates compared to original profile. Effects of change on number of partners in the last 12 months is shown in table III.1 CSW=Commercial Sex Worker; CAR = Central Africa Republic; Guinea-B = Guinea-Bissau; Equatorial-G = Equatorial Guinea; DR Congo = Democratic Republic of Congo n/a = Not applicable; MF = Multiplication Factor; Q = Quadratic; L = Linear; Sqrt = Square-Root; LC = low condom use.

III.3 Supplementary figures

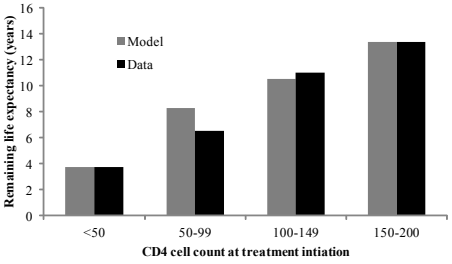

Figure III.1. Life-expectancy remaining at ART initiation by CD4 cell count, model prediction versus data. Source for data: Mutevedzi et al [9]

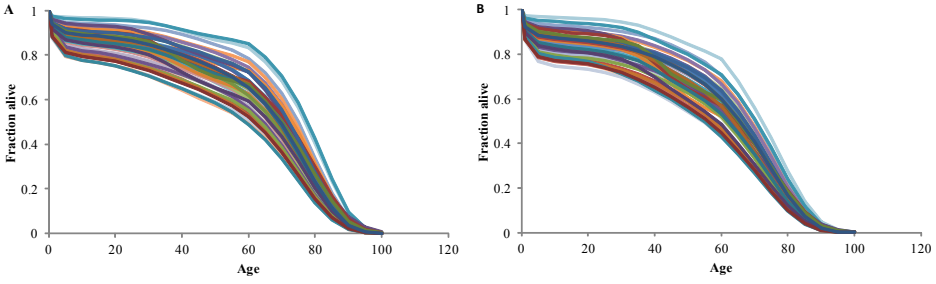

Figure III.2. Country specific survival corrected for HIV mortality. A. Women; B. Men. Each line represents a country.

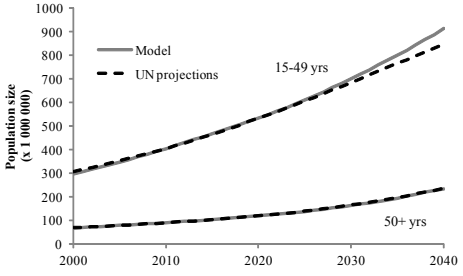

Figure III.3. Trends in population size for the population aged 15-49 and 50+ in sub-Saharan Africa, model predictions versus UN projections. UN projections represent the UN population prospects 2010 update. We used the 'medium' variant population projections for comparison [10].

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8. General discussion

8.1 Answering the research questions

1. When should treatment with ART for HIV infected individuals be initiated in order to optimize public health benefits and resource allocation?

Treatment should be initiated for HIV infected people with a CD4 cell count below 350 cells/μL, according to current WHO treatment guidelines. Treatment initiation for all HIV infected individuals, regardless of CD4 cell count, might have a more profound impact of the HIV epidemic, yet whether such an intervention is cost-effective is unclear.

We show that, for the Hlabisa sub district of KwaZulu-Natal, South Africa, initiating treatment according to the new WHO treatment guidelines of ART at ≤350 cells/μL compared to continued initiation at ≤200 cells/μL will not only save many additional lives, but will also lead to net cost savings within about 16 years (chapter 2). This positive finding is the result of a combination of two processes: 1) people who initiate treatment at an earlier stage (e.g. CD4 cell count between 200 and 350) are healthier and require less additional care for opportunistic infections, and thus incur less health care costs compared to those who initiate treatment late; and 2) treatment effectively reduces transmission probabilities, resulting in a lower future burden of people requiring treatment due to a lower HIV incidence under the new WHO treatment guidelines. In our sensitivity analysis, we also show that this positive result is likely to hold for South Africa as a whole.

Although cost savings may occur in the future, changing the eligibility criteria to treatment for all HIV infected individuals with a CD4 cell count of ≤350 cells/μL will require substantial investments that need to be available. Next to the required financial investments, an increasing number of people on treatment will require an improved health care infrastructure. More health facilities may need to be constructed and the demand for more health workers will increase, along with the required costs for training and retaining these health workers in the South African public health care system (see also research question 2 and chapter 4).

It is still unclear whether initiation at higher CD4 cell counts, or even regardless of CD4 cell counts, is more cost-effective compared to initiating treatment at ≤350 cells/μL. We show that a universal test and treat (UTT) intervention might be a highly cost-effective intervention if coverage levels of 90% can be achieved and maintained over time (chapter 3), yet the assumed programmatic effectiveness of the intervention is likely to be too optimistic. We primarily chose to calculate the intervention with these optimistic participation levels in order to compare our results to those by Granich et al [1], but population based surveys in South Africa show that participation rates of about 50% of annual screening for HIV may be more realistic [2-4]. In addition, it is likely that HIV infected people are relatively less likely to participate in these screening interventions, further limiting its effectiveness [2-4]. Furthermore, high annual screening rates are unlikely be maintained for several decades, as screening fatigue will lower participation after a few years. Finally, people with a high CD4 cell count are often asymptomatic, and thus have a lower incentive to take drugs. Consequently, their acceptability for ART will be lower, and dropout rates will be higher.

Therefore, it is questionable whether, under realistic assumptions, a UTT intervention might still be cost-effective.

The financial implications of a UTT intervention are also not clear. Commonly used linear cost functions that simply multiply the number of people on treatment with the annual cost of treatment are not sufficient, as the organization of health care systems becomes an increasingly important driver of health care costs with expanding eligibility criteria [5-7]. The size and scope of clinics providing ART is an important driver of per patient costs, yet empirically sound estimates on scale and scope functions are currently missing [5,6]. In addition, outreach programs for annual screening will involve large, community based or even home based screening, counseling, and testing for HIV, which will require a large influx of new health care worker.

In conclusion, we advise that South Africa should expand their treatment eligibility to treatment for all HIV infected people with CD4 cell counts ≤350 cells/μL. The current knowledge base on the costs and effects of providing treatment for all HIV infected people is too limited to expand treatment eligibility criteria further.

2. What financial and human resources are needed for universal access to treatment under different ART treatment strategies in South Africa?

Scaling up to universal access for all patients with a CD4 cell count of ≤350 cells/μL is possible in the current context, with only a slight increase in the current health work force. Universal coverage for all HIV infected patients is likely to be extremely difficult unless substantial additional human and financial resources are committed to ART delivery

We show that scaling up to universal access of ART for HIV infected people with a CD4 cell count of ≤350 cells/μL is achievable in South Africa, as only a slight increase in terms of health care workers (HCWs) (chapter 4) and financial resources (chapter 2) is required. Further scale-up of ART to universal access for all HIV infected individuals ('treatment as prevention') is not likely to be feasible in the near future because of the required increase in available HCWs (chapter 4). In addition, we show that alternative models of health care delivery, such as nurse-initiated treatment and reducing the number of consultancies per year might help close the gap between the supply of and the demand for HCWs for ART.

Nevertheless - regardless of treatment eligibility criteria - scaling up to universal access in South Africa will require the health worker pool for HIV in South Africa to be expanded in order to provide treatment and care for all eligible HIV infected people. Innovative interventions to increasing training and retention, or increasing HCW efficiency, will need to be considered to increase the pool of available health workers [8]. Initiatives like task-shifting in other health care services [9] and integration of health services [10] in South Africa should be considered to free up human resources for HIV care. Economies of scope (i.e. the total costs of offering multiple services at one location are lower than the sum of the costs of proving individual services at different locations)

in successful integration will improve health service efficiency, and will also improve access for patients as different services are combined. Also, outsourcing patients for monitoring to the private sector – as effectively done in Botswana and Mexico [11,12] – might increase the pool of available HCWs, yet the costs of the program might increase because salaries in the private sector are higher. International initiatives – like the Cuban initiative to train and exchange health care workers with South Africa [13]– may also increase the pool of trained HCWs in South Africa.

There are several options for improving day-to-day efficiency in primary health care clinics in order to reduce the required number of HCWs. From our time-motion study (chapter 4), we found that the mean duration of a workday between the different clinics in our sample differed substantially (range: 4.9 hours to 7.3 hours), and that the number of HCWs required might reduce by about 30% if we assume all clinics to achieve the same productivity as the most productive clinic in our sample. If we would further assume a workday for all HCWs to last 8 hours, we find that the total number of nurses, counselors, and physicians required for universal access is reduced by 23%, 24%, and 37% respectively, compared to the baseline. Productivity gains may also be achieved by closely observing time spent on breaks and idle time between patients. However, we found that on average 9% of the workday was spent in this category – i.e. 43 minutes of break time on a workday of 8 hours - which is already very short considering the demands of the job, thus leaving little room for improvement in productivity. Finally, HCWs are currently paid on a monthly basis, and alternative models of incentivizing HCWs such as payment by output could improve efficiency and productivity. On the other hand, these kinds of initiatives might be detrimental to the delivered quality in the long run, as HCWs might be more concerned with quantity than with quality. Also, working conditions might suffer, resulting in outmigration of HCWs to other countries.

Productivity of a health clinic does not solely depend on the number of hours in a workday, but is also largely determined by the number of patients that visit the clinic. Therefore, the geographical distribution of HCWs across HIV clinics in South Africa should be compared to the HIV care needs in geographical areas in order to determine whether some clinics are over- or understaffed. Redistribution of HCWs from overstaffed to understaffed clinics will improve productivity of HCWs by reducing idle time. Another way to improve productivity and efficiency in less busy clinics is to reduce opening hours. We found in our least busy clinic that on a particular day only 20% of the day was spent on direct patient contact and 36% on breaks/idle time, simply because there were not many patients coming to the clinic that particular day. Reducing the opening hours of the HIV clinic while ensuring that this does not preclude those who are working or at school, would prevent the unnecessary time spent waiting for patients.

We provide a point estimate for the current HCW needs over one year of treatment and do not account for the influx of newly eligible patients into the system, since - over the period of one year - the effect of the current number of HCWs on the future number required for universal coverage is likely negligible. However, in the longer run these effects are likely to become increasingly important.

Because ART is effective in reducing mortality, the more patients receive ART in the current period, the more patients will require treatment in future periods, assuming all other factors remain unchanged [8,14]. However, other factors may not remain unchanged. For instance, ART is likely to effectively reduce transmission [1,15,16], reducing the number of HCWs needed in future periods. Future dynamic models need to examine the impact of the ART effects on mortality and transmission on HCW requirements in the long-run. Those studies should also take into account that ART may change the type of patient needing ART. For one, ART may shift the age composition of ART patients towards older ages [17,18], increasing the average morbidity among ART patients and the average health-worker time required for providing appropriate treatment per patient. Moreover, the case mix of ART patients might change over time due to increasing ART failure and long-term ART toxicities. These changes may increase the average health-worker time required per patient because they necessitate time-consuming counseling, ART switches, and complex treatments of ART side effects [19].

In conclusion, with a slight increase in the current health work force, the South African government should be able to scale-up HIV treatment to universal access for all HIV infected people with a CD4 cell count ≤350 cells/μL. Innovative interventions will need to be developed to ensure the availability of sufficient human resources if the government decides to further relax eligibility criteria. Even though a 'treatment as prevention' strategy may reduce the required resources in the future, the upfront needs in financial and human resources are so high that a successful implementation seems unrealistic in the current situation.

3. Can HIV be eliminated through expanded access to ART?

The HIV epidemic in South Africa could be driven into an elimination phase even if treatment scale-up is continued under current treatment guidelines of only initiating ART at ≤350 cells/μL.

We show that the HIV epidemic in South Africa can be driven into an elimination phase through universal testing and immediate ART for all HIV infected individuals (chapter 3). In addition, we found that even under current treatment guidelines of ART at ≤350 cells/μL the HIV epidemic in South Africa will eventually be driven into an elimination phase around the year 2042.

Already, HIV incidence in South Africa has been declining over the past decade [20,21], as HIV prevalence remains stable while ART coverage is increasing. Therefore, elimination in South Africa is the results of the scale-up of ART in combination with the already declining incidence due to effective scale-up of condom use in the early 2000s [20,21]. Whether scaling-up treatment for patients with a CD4 cell count ≤350 cells/μL in other countries in sub-Saharan Africa will lead to elimination can only be determined by investigating these epidemics individually. In addition, the scale-up of treatment is just one of the many ways to reduce incidence, and elimination in South Africa will be achieved even faster if other prevention interventions such as condom use, male circumcision and behavior change are scaled-up alongside the scale-up of ART.

The question whether HIV can be eliminated through expanded access to ART has only been assessed by mathematical models [1,22,23], and there is currently limited empirical data available to support the claim. Recently, Tanser and colleagues were the first to show that the risk of an HIV infection in rural KwaZulu-Natal was significantly associated with the level of ART coverage [24], suggesting that ART can indeed effectively reduce transmission at the community level. However, many factors may act as a barrier for achieving elimination. In particular, the development of treatment resistance, especially when resistant strains can be transmitted, will have an impact on the elimination probabilities of HIV. It is currently unclear whether the fears of rapidly spreading drug resistance expressed at the start of the ART scale-up were justified [25]. The prevalence of drug resistance remains low in South Africa after nearly 10 years of scaling up ART [25,26]. In addition, adherence to treatment is equally high as in many high income countries [27], and survival of patients on treatment in SSA approaches general life-expectancy [28], suggesting that resistance may not become a major problem in South Africa in the near future. Another important potential barrier to achieving elimination could be the 'acute phase' of the HIV infection. The first few weeks or months of the infection - which is characterized by high viral loads and thus a high transmission potential – are hard to target with a treatment intervention and this acute phase may thus continue to drive the epidemic even under highly effective UTT interventions. However, it currently remains unclear what proportion of new infections is caused by this acute phase in SSA epidemics, with estimates ranging from only 2% to nearly 40% of all new infections [29,30]. Furthermore, both national and international migration from areas with lower treatment coverage may continue to introduce HIV into the population and thus limit complete elimination. Finally, high risk core-groups such as commercial sex workers or men who have sex with men may continue to spread HIV when the generalized epidemic is controlled through ART.

In conclusion, our results confirm previous conclusions that the HIV epidemic in South Africa can be eliminated through a strategy of universal testing and treatment at 90% coverage. Importantly, we also show that continued scale-up to universal access under current treatment guidelines of ART at CD4 cell counts of ≤350 cells/μL will have such a substantial impact on HIV incidence, that it will already drive the South African HIV epidemic into elimination around the year 2042. Empirical evidence through randomized controlled trials is needed in order to confirm the potential impact of expanded access to ART on the HIV epidemic in South Africa.

4. What is the impact of ART on the age composition of the HIV epidemic in sub-Saharan Africa?

The HIV epidemics in sub-Saharan Africa will rapidly age over the coming decades.

We show that the number of HIV-infected people aged 50 years or older in sub-Saharan Africa (SSA) will nearly triple over the coming decades, from 3.1 million in 2011 to 9.1 million in 2040. The proportion of people living with HIV being aged 50 years or older will increase from 13% in 2011 to 29% in 2040 (chapter 7). In rural South Africa, the proportion of people living with HIV

that are aged 50 years or older will increase to about 25% by 2040, compared to only 11% in 2010 (chapter 6). HIV prevalence in the population aged 50 years or older in this setting will increase for 9% in 2010 to 17% in 2040, and the total number of infected patients aged 50 years or older is expected to increase by 50%.

This ageing epidemic has important consequences for the organization of health care services and societies in general, as the disease burden in many countries, including South Africa, will go into accelerated epidemiological transition towards non-communicable diseases (NCDs). Already, NCDs are becoming more important in SSA, and the prevalence of risk factors is very high. Both diabetes and hypertension are common disorders in South Africa [31,32], and the prevalence of these conditions will only increase as diets contain high levels of salt and calories [33,34], and obesity is highly prevalent, especially among women [33,34]. In addition, both ART and HIV have been recognized as independent risk factors for many NCDs, including cardiovascular diseases, non-AIDS related malignancies, osteoporosis, liver- and kidney-failure, and neurological conditions [35-37]. Health policymakers need to anticipate the impact of the ageing HIV epidemic in their planning for the future capacity of health systems to prevent and treat diseases of old age in HIV-infected individuals.

In addition, it will become more important to focus HIV prevention interventions on the population aged over 50 years. There is currently limited knowledge on the sexual behavior of people aged 50 years and older as HIV surveillance and prevention interventions in SSA are almost exclusively targeted at the population aged 15-49 years. Although it is commonly assumed that the frequency of sexual contacts within relationships declines with age [38], there is also evidence that increased risk behavior during sex and changes in biological susceptibility may increase the risk for HIV in people aged over 50 years [39,40]. Demographic and Health Surveys show that the frequency and consistency of condom use during high risk sex decreases with age and is particularly low among older adults [40]. Also, women are more susceptible to HIV at older ages, especially after menopause, because of the thinning of the vaginal wall [39].

In conclusion, the HIV epidemics in SSA are ageing rapidly, implying important changes in the organization of health care services on the continent. Health services need to be prepared to deal with the double burden of HIV and NCDs that will become more apparent as the HIV epidemic ages. Better education and counseling on sexual behavior in older adults is needed, as well as better monitoring of HIV prevalence, incidence, and sexual activity.

8.2 Critical appraisal of STDSIM

For the studies in chapters 2, 3, 5, 6, and 7 in this thesis we used the STDSIM microsimulation model. Microsimulation models simulate the life-course of (a set of) individuals. In addition, STDSIM can also be classified as an 'agent-based' or 'individual-based model' as it simulates the actions and interactions of many individuals simultaneously. These types of models are especially useful in modeling HIV epidemics because individual level interaction and network structures can

be incorporated, allowing for an accurate representation of the underlying dynamics of the HIV epidemic [41].

One of the advantages of STDSIM over other models is the amount of detail that can be incorporated into describing the underlying processes that determine the HIV epidemic. STDSIM allows for the simultaneous modeling of several different sexually transmitted infections (STIs) next to HIV, and can simultaneously incorporate many different prevention interventions such as condom use, behavior change, male circumcision, and ART, making it the most comprehensive model of the HIV epidemic currently available [41]. However, because of the complexity and parameter density of the model, STDSIM is sometimes seen as a black box, as it can be hard to understand which underlying processes result in the observed predictions and whether these processes are correctly implemented and quantified. For example, a critical issue is the incorporation of co-factor effects of STIs on HIV transmission. It has long been recognized that STIs lead to increased inflammation in the genital track and thus enhance HIV transmission [42]. However, it is difficult to determine the exact magnitude of the co-factor effects that different STIs have on HIV transmission through primary data [43]. In STDSIM, we observe that STI co-factors are to a large extent responsible for certain predicted effects of preventive interventions. For instance, an increase in condom use in our model reduces HIV transmission not only directly, but also indirectly due to a reduced spread of STIs that act as co-factors. One of the most important STIs in this respect is chancroid. We observed that scaling-up condom use to 30% in casual and commercial sex contacts reduces chancroid prevalence to near 0% within 10 years. As chancroid is assumed to have a high co-factor effect on HIV transmission (factor=25), a decline in chancroid prevalence results in a substantial reduction in HIV incidence as well. Even though these trends for HIV and chancroid are consistent with those predicted by another model [44] (see figure 8.1), empirical evidence of the link between condom use, chancroid prevalence, and HIV incidence in South Africa is currently not available but urgently needed to be more confident about these predictions.

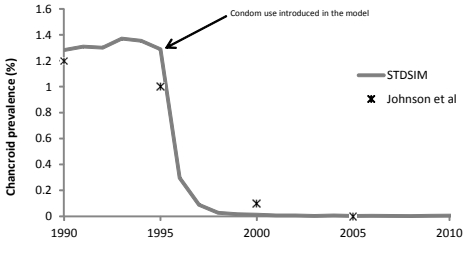

Figure 8.1. Chancroid prevalence in South Africa for the population aged 15-49 years as projected by STDSIM compared to estimates published by Johnson et al [44]. Condom use in STDSIM is scaled-up linearly from 0% pre-1995 to 30% in 2000 (STDSIM). Johnson et al incorporate condom use increases starting in 1990, but their paper contains no quantification of the assumed condom use rates in later years [44].

Another feature of STDSIM is the simulation of underlying sexual mixing patterns. In order to create a sexual network of individuals, sex- and age-specific mixing patterns need to be defined. In the model, this happens through a 'supply and demand' mechanism, in which a person selects

another individual from the opposite sex who is 'available' to start a relationship. Apart from an age-mixing matrix, mixing in STDSIM occurs at random. This simplification may be unrealistic as assortative mixing based on risk behavior, race, or educational level may also occur [45]. In addition, it is obvious that mixing is to some extent related to geographic location. Nevertheless, it seems vital to include these underlying structures in order to realistically project all processes that explain HIV epidemics and the impact of interventions. In chapter 3 we compared simpler models with STDSIM, and show that models that do not include sexual networks, STI co-factor effects, condom use, male circumcision or demographic projections tend to overestimate the impact of a universal test and treat (UTT) intervention for HIV. STDSIM predicted a cumulative number of life-years saved per ART treatment year of about 1.2 in 2050 for UTT. In contrast, a model that excludes all these structures predicted this to be about 5.6 for the same intervention, more than 4 times higher. In addition, STDSIM was better capable of replicating data on demography, sexual behavior, STI prevalence, and age-specific HIV prevalence patterns compared to the other models. Moreover, it was the only model that could capture the observed decline in HIV incidence in South Africa over the period 2002 – 2008 [20,21] .

In chapter 5, we explored the sensitivity of the predicted impact of an HIV vaccine to alternative assumptions on the underlying sexual network, background prevention interventions, and consistency of individuals in participation in health interventions. We show that, for epidemics produced by network structures that include more concurrent or serial monogamous relationships compared to the baseline, the predicted impact of the intervention changed by about 10%. In addition, assuming rapid scale-up of male circumcision and condom use alongside the vaccination campaign nearly halved the predicted impact of the vaccine. Similarly, alternative assumptions on consistency in participation changed the predicted impact by about 25%. Such individual decisions on consistency of participation do not only play a role in vaccination campaigns, but will also be important in UTT interventions, which involve annual screening of the entire adult population.

In conclusion, the complexity of the influence of the sexual network of a specific setting, the interaction between different treatment and prevention interventions that are in place, and an individual based consistency of participation in health programs merits the use of a model such as STDSIM that is capable of simulating these mechanisms. Although these complex mechanisms often rely on poor data, alternative assumptions that reflect the uncertainty in these assumptions create less variation in the predicted impact of an intervention (chapter 5) than simply ignoring the mechanisms altogether (chapter 3).

8.3. Conclusions and recommendations

Conclusions

1. Expanding treatment eligibility criteria to all HIV infected people with a CD4 cell count of ≤350 cells/μL in South Africa will result in net cost savings after just 16 years compared to continued treatment at ≤200 cells/μL.

2. Expanded access to ART may eventually eliminate the HIV epidemic in South Africa, even under treatment eligibility criteria of ART for all HIV infected people with a CD4 cell count of ≤350 cells/μL.

3. Substantial investments in human resources for health are needed if South Africa wants to offer ART to all HIV infected patients.

4. As a result of the ART scale-up in South Africa and sub-Saharan Africa, the HIV epidemics will rapidly age, implying important changes in the organization of health care services on the continent.

Recommendations

1. Countries in sub-Saharan Africa should expand treatment access to all HIV infected patients with a CD4 cell count of ≤350 cells/μL.

2. Health systems in sub-Saharan Africa should prepare for the ageing of the HIV epidemic in sub-Saharan Africa by re-organizing their health systems in order to combine treatment and care for non-communicable diseases alongside HIV.

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Summary

The aim of the research described in this thesis was to investigate the impact of antiretroviral therapy (ART) on the HIV epidemic in South Africa and other countries in sub-Saharan Africa (SSA).

Chapter 1 gives an introduction into HIV, ART, and mathematical modeling in the context of SSA. At the end of 2010, nearly 34 million people were living with an HIV infection worldwide. Although only 12% of the world's population lives in SSA, the subcontinent contains nearly 70% of all HIV-infected individuals in the world. Access to ART in SSA has been expanding rapidly over the past decades. At the end of 2010, nearly 5 million people were receiving life-saving treatment, compared to only 100,000 in 2003. South Africa is the country with the highest HIV burden worldwide, with nearly 6 million people living with the infection. In mid-2011, nearly 1.5 million people in South Africa were receiving ART, yet a further 1.5 million were estimated to be eligible but not receiving treatment.

ART reduces the viral load in an HIV-infected individual, and consequently has two important effects: 1) it slows disease progression and thus increases survival of HIV-infected individuals; and 2) it reduces the infectivity of an HIV-infected individual to his/her uninfected partner(s). Consequently, the improved access to ART over the past decade is likely to have a big impact on the HIV epidemics in SSA. In this thesis, we use the STDSIM microsimulation model and data from the Africa Centre for Health and Population Studies in KwaZulu-Natal, South Africa, to determine the impact of ART on HIV epidemic dynamics and ART treatment costs. We addressed the following research questions: 1) when should treatment with ART for HIV infected individuals be initiated in order to optimize public health benefits and resource allocation?; 2) what financial and human resources are needed for universal access to treatment under different ART treatment strategies in South Africa?; 3) can ART eliminate the HIV epidemic in South Africa?; 4) what is the impact of ART on the age composition of the HIV epidemic in sub-Saharan Africa?

Chapter 2 describes a study on the impact of the World Health Organization (WHO) ART treatment guidelines of initiating all HIV-infected people with CD4 cell counts of ≤350 cells/μL on treatment, which were released in late 2009. We used STDSIM to investigate the impact of these new guidelines on HIV epidemic dynamics and health care costs in rural KwaZulu-Natal, South Africa, and compared this to continuation of the old strategy of providing ART for all HIV-infected people with CD4 cell counts ≤200 cells/μL. We show that, during the first five years, implementing the new WHO treatment guidelines requires about 7% extra annual investments, whereas 28% more people receive treatment. There will be a more profound impact on HIV incidence when treating HIV-infected individuals at CD4 cell counts of ≤350 cells/μL, leading to relatively lower annual costs after just seven years. The resulting cumulative net costs reach a break-even point after on average 16 years of implementing the new treatment guidelines, after which net cost savings start to occur.

In chapter 3, we show that the HIV epidemic in South Africa could eventually be eliminated due to expanded access to ART. We developed 9 structurally different mathematical models of the South African HIV epidemic in a stepwise approach of increasing complexity and realism, and used these

models to confirm previous conclusions that the HIV epidemic in South Africa can be eliminated through annual screening and immediate ART for all HIV-infected individuals (Universal Test and Treat – UTT). Importantly, with the most comprehensive of the 9 models, we also show that even under treatment guidelines of ART at CD4 cell counts of ≤350 cells/μL, the HIV epidemic in South Africa could be driven into an elimination phase, be it 10 years later compared to UTT. Nevertheless, UTT is still a highly cost-effective intervention, at 170 US$ per life-year saved.

The required human resources for universal access to ART under different eligibility criteria are described in chapter 4. We performed a time-motion study, in which task-times of health care workers (HCWs) in 3 primary health care clinics in South Africa were measured. We extrapolated these task-times to provide estimates for the number of HCWs needed in South Africa as a whole for universal access to ART under different eligibility criteria. We show that, with a slight increase in the current health work force, the South African government should be able to scale-up HIV treatment to universal access for all HIV-infected people with CD4 cell counts ≤350 cells/μL. However, universal coverage for all HIV-infected people regardless of CD4 cell counts ('treatment as prevention') is likely to be extremely difficult unless substantial additional human and financial resources can be mobilized for ART delivery.

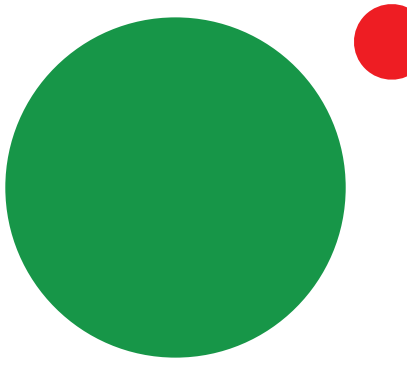
In chapter 5, we explore to potential epidemiological and public health impact of a partially effective HIV vaccine, the ALVAC/AIDSVAX vaccine. This was the only HIV vaccine ever to show a positive effect on HIV transmission in a randomized controlled trial, which took place in Thailand. The trial showed an overall incidence reduction of 31%, yet most cases were prevented in the first year since vaccination, suggesting a rapidly waning efficacy. We used STDSIM to explore the potential impact of such an imperfect vaccine in rural KwaZulu-Natal, South Africa. Our results suggest that a vaccine with limited and waning efficacy might be a cost-effective intervention in generalized HIV epidemics and can even lead to net cost savings because of prevented treatment costs in the future, provided that the immune response can be restored through revaccination and no risk-compensation takes place.

A study on how the age-composition of the HIV epidemic in rural KwaZulu-Natal will change due to ART is described in chapter 6. As ART increases survival and reduces transmission, it is likely that the rapid scale-up of the number of HIV-infected people on treatment in the area will result in a relative increase in the number of older people infected with HIV. Using STDSIM, we show that there will be divergent trends in HIV prevalence for the population aged 15-49 years and the population aged 50 years or older over the period 2010 to 2040. HIV prevalence in the population aged 15-49 years is estimated to drop from 28% in 2010 to 9% in 2040, while the prevalence in the population aged 50 years or older is projected to nearly double, form 9% in 2010 to 17% in 2040. As a result, the age distribution of HIV-infected people will change considerably. This is especially true for men, where currently less than one in 12 HIV-infected people are aged 50 years or older; in 2040, this would be one in four.

The impact of ART on the age composition of the HIV epidemics in all countries of SSA is explored in chapter 7. We quantified STDSIM to the HIV epidemics in all 43 countries of SSA, and explore the effect of continued scale-up of ART on the age composition of the HIV epidemic over the coming decades. We estimate that the total number of HIV-infected adults aged 50 years or older in SSA will nearly triple from about 3.1 million in 2011 to 9.1 million in 2040, assuming that ART scale-up continues at the current speed. In 2011, about one in seven HIV-infected people were aged 50 years or older in SSA, whereas in 2040, this ratio will be more than one in four.

Finally, chapter 8 contains the answers to the research questions, an overall discussion, and a critical appraisal of STDSIM, followed by the main conclusions and recommendations. We conclude the following: 1) expanding treatment eligibility criteria to all HIV-infected people with CD4 cell counts of ≤350 cells/μL in South Africa will result in net cost savings after just 16 years compared to continued treatment at ≤200 cells/μL; 2) Expanded access to ART may eventually eliminate the HIV epidemic in South Africa, even under treatment eligibility criteria of ART for all HIV-infected people with CD4 cell counts of ≤350 cells/μL; 3) Substantial investments in human resources for health are needed if South Africa wants to offer ART to all HIV-infected people; and 4) as a result of the ART scale-up in South Africa and sub-Saharan Africa, the HIV epidemic will rapidly age, implying important changes in the organization of health care services on the continent.

Samenvatting



Het doel van het onderzoek beschreven in dit proefschrift was om de impact van antiretrovirale therapie (ART) op de HIV-epidemie in Zuid-Afrika en andere landen in sub-Sahara Afrika (SSA) te onderzoeken.

Hoofdstuk 1 geeft een algemene inleiding in HIV, ART en het modelleren van HIV binnen de context van SSA. Eind 2010 leefden er wereldwijd ongeveer 34 miljoen mensen met HIV. Hoewel maar 12% van de wereldbevolking in SSA woont, bevat deze regio ongeveer 70% van alle HIV-geinfecteerden in de wereld. De beschikbaarheid van ART in SSA is tijdens het afgelopen decennium explosief toegenomen. Aan het einde van 2010 werden bijna 5 miljoen mensen behandeld, in tegenstelling tot slechts 100.000 in 2003. Met bijna 6 miljoen geïnfecteerde mensen is Zuid-Afrika het land met de grootste HIV-epidemie ter wereld. Medio 2011 werden bijna 1,5 miljoen mensen in Zuid-Afrika behandeld met ART, ongeveer de helft van iedereen die volgens de huidige richtlijnen in aanmerking komt voor behandeling.

ART vermindert de hoeveelheid virus in het bloed van een HIV-geïnfecteerd persoon en heeft als gevolg twee belangrijke uitwerkingen: 1) het vertraagt de progressie van de ziekte en verlaagt dus de sterfte van HIV-geïnfecteerden; 2) het vermindert de besmettelijkheid van een HIV-geïnfecteerd persoon. Daarom zal de toename van het aantal mensen op ART in SSA waarschijnlijk een grote invloed hebben op de HIV epidemieën in deze landen. Voor de onderzoeken in dit proefschrift gebruikten we het STDSIM microsimulatiemodel en gegevens van het Africa Centre for Health and Population Studies in KwaZulu-Natal, Zuid-Afrika, om de impact van ART op de HIV-epidemie en de kosten voor de gezondheidszorg te bepalen. Wij onderzochten de volgende onderzoeksvragen: 1) wanneer moet de behandeling met ART voor mensen met HIV worden gestart om een zo efficiënt mogelijke volksgezondheidswinst te realiseren?; 2) hoeveel financiële en personele middelen zijn er nodig voor universele toegang tot ART, voor verschillende behandelstrategieën in Zuid-Afrika?; 3) kan de HIV-epidemie in Zuid-Afrika worden geëlimineerd door het opschalen van toegang tot ART?; 4) wat is de invloed van ART op de leeftijdsverdeling van mensen met HIV?

Hoofdstuk 2 beschrijft een onderzoek naar de effecten van het behandelen van HIV-patiënten vanaf een CD4 niveau van 350 cellen/μL bloed of lager – zoals geadviseerd in de nieuwe behandelrichtlijnen van de Wereldgezondheidsorganisatie (WHO) – in vergelijking met het behandelen bij een CD4 niveau van 200 cellen/ μL. Met STDSIM onderzochten we de implicaties van deze nieuwe WHO-richtlijnen voor zowel de HIV-epidemie als de kosten voor de gezondheidszorg. We laten zien dat, gedurende de eerste vijf jaar, de nieuwe richtlijnen slechts 7% extra jaarlijkse kosten geven in vergelijking met het voorzetten van de oude richtlijnen, terwijl het aantal mensen onder behandeling met 28% toeneemt. Omdat het eerder behandelen van mensen met HIV een relatief grotere daling van de incidentie teweeg brengt, worden de jaarlijkse kosten van de nieuwe richtlijnen na 7 jaar relatief lager in vergelijking met de oude richtlijnen. De resulterende cumulatieve netto kosten voor het implementeren van de nieuwe behandelrichtlijnen bereiken een break-even punt na gemiddeld 16 jaar, waarna de nieuwe WHO-richtlijnen netto kostenbesparingen zullen opleveren.

In hoofdstuk 3 laten we zien dat de HIV-epidemie in Zuid-Afrika uiteindelijk zou kunnen worden geëlimineerd als het aantal mensen onder behandeling verder toeneemt. We ontwikkelden 9 structureel verschillende wiskundige modellen van de Zuid-Afrikaanse HIV-epidemie die in toenemende mate complex en waarheidsgetrouw zijn. Met deze modellen bevestigen we conclusies uit een eerder onderzoek dat de HIV-epidemie in Zuid-Afrika zou kunnen worden geëlimineerd door jaarlijkse screening en onmiddellijke behandeling van alle mensen met HIV ('Universal Test en Treat' - UTT). Echter, uit het meest realistische model van onze analyses blijkt dat zelfs onder de huidige behandelrichtlijnen (ART vanaf een CD4 niveau van 350 cellen/μL of lager) de HIV-epidemie in Zuid-Afrika zou kunnen worden geëlimineerd, zij het 10 jaar later in vergelijking met UTT. Met 170 US$ per gered levensjaar is UTT niettemin een zeer kosteneffectieve interventie.

In hoofdstuk 4 is een beschrijving gegeven van een onderzoek naar benodigd gezondheidszorgpersoneel voor algemene toegang tot ART onder verschillende behandelcriteria. Door middel van een 'time-motion onderzoek' hebben we bij gezondheidszorgpersoneel in 3 klinieken in Zuid-Afrika de duur van alle activiteiten omtrent het behandelen van mensen met HIV gemeten. Vervolgens hebben we deze geëxtrapoleerd om schattingen te maken over het totaal aan gezondheidszorgpersoneel dat nodig is om alle mensen met HIV die in aanmerking komen voor behandeling ook daadwerkelijk te behandelen. We laten zien dat, met een lichte stijging in gezondheidszorgpersoneel, de Zuid-Afrikaanse overheid in staat zou moeten zijn om iedereen met een CD4 niveau van 350 cellen/μL of lager te behandelen met ART. Echter, behandeling voor alle HIV-geïnfecteerde mensen - ongeacht het CD4 niveau - is niet mogelijk met de huidige hoeveelheid gezondheidszorg personeel in Zuid-Afrika. Om zo'n strategie te laten slagen moeten er aanzienlijk meer personele en financiële middelen voor ART behandeling worden gemobiliseerd.

In hoofdstuk 5 worden de onderzochte potentiële epidemiologische- en volksgezondheidseffecten van een HIV vaccin met een beperkte werkzaamheid - het ALVAC / AIDSVAX vaccin - beschreven. Dit is tot dusverre het enige vaccin tegen HIV dat ooit bewezen effectief is bevonden in een gerandomizeerde trial, welke plaatsvond in Thailand. Deze trial liet een algehele afname in incidentie van ongeveer 31% zien, echter de meeste gevallen werden in het eerste jaar na vaccinatie voorkomen, wat wijst op een snel afnemende werkzaamheid van het vaccin. We hebben met STDSIM de mogelijke effectiviteit van een dergelijke onvolmaakt vaccin als HIV preventie middel in een ruraal gebied van KwaZulu-Natal, Zuid-Afrika onderzocht. Onze resultaten suggereren dat een vaccin met een beperkte en afnemende werkzaamheid toch een kosteffectieve interventies is in gegeneraliseerde HIV-epidemieën en zelfs kan leiden tot netto kostenbesparingenals gevolg van voorkomen behandelkosten in de toekomst. Het is dan wel noodzakelijk dat de immuunrespons kan worden hersteld door middel van hervaccinatie, en dat er geen risicocompensatie plaatsvindt.

Een onderzoek naar de verandering van de leeftijdssamenstelling van de HIV-epidemie in ruraal KwaZulu-Natal, als gevolg van de toegenomen beschikbaarheid ART, wordt beschreven in hoofdstuk 6. Omdat ART zowel de overlevingskansen van mensen met HIV verhoogt als ook de

besmettelijkheid van deze mensen afneemt, is het waarschijnlijk dat een toename van het aantal mensen op ART zal leiden tot een relatieve toename van het aantal oudere mensen met HIV. Met behulp van STDSIM laten we zien dat de HIV prevalentie bij mensen met een leeftijd van 15 tot 49 jaar zal dalen, van ongeveer 28% in 2010 tot 9% in 2040. Echter, de prevalentie bij mensen met een leeftijd van 50 jaar of ouder zal naar verwachting bijna verdubbelen in dezelfde periode, van ongeveer 9% in 2010 tot 17% in 2040. Als gevolg van deze divergente trends zal de leeftijdssamenstelling van de HIV epidemie aanzienlijk veranderen. Dit geldt vooral voor mannen: momenteel heeft minder dan één op de 12 mannen met HIV een leeftijd van 50 jaar of ouder; in 2040 is dit meer dan één op vier.

Een onderzoek naar de effecten van ART op de leeftijdssamenstelling van de HIV epidemiën in alle landen in SSA wordt beschreven in hoofdstuk 7. We hebben STDSIM gekwantificeerd, zodat het model de HIV-epidemiën in alle 43 landen van SSA kan simuleren. Met deze kwantificaties onderzochten we de effecten van het voorzetten van de huidige opschaling van ART op de leeftijdssamenstelling van de HIV epidemieën voor de komende decennia. We schatten dat het totale aantal volwassenen van 50 jaar of ouder met HIV bijna zal verdrievoudigen over de komende jaren, van ongeveer 3,1 miljoen in 2011 naar 9,1 miljoen in 2040. In 2011 was ongeveer één op de zeven mensen met HIV in SSA 50 jaar of ouder; in 2040 zal deze verhouding ongeveer één op vier zijn.

Tenslotte staan in hoofdstuk 8 de antwoorden op de onderzoeksvragen, een algemene discussie en een kritische beschouwing van STDSIM, gevolgd door de belangrijkste conclusies en aanbevelingen van dit proefschrift. We concluderen het volgende: 1) Het eerder behandelen - dat wil zeggen bij een CD4 niveau van 350 cellen per microliter bloed - van patiënten met HIV in Zuid-Afrika levert op den duur kostenbesparingen op in vergelijking met het alleen behandelen van patiënten met een CD4 niveau van 200 cellen per microliter bloed of lager; 2) HIV in Zuid-Afrika kan worden geëlimineerd door het opschalen van het aantal mensen op antiretrovirale therapie, zelfs wanneer de huidige behandelrichtlijnen van ART bij 350 cellen per microliter bloed worden voortgezet; 3) Er zijn creatieve oplossingen nodig om voldoende gezondheidszorgpersoneel beschikbaar te hebben als Zuid-Afrika de richtlijnen voor behandeling van HIV verder gaat versoepelen en 4) Vanwege het toenemende aantal mensen met HIV dat wordt behandeld, zullen de HIV epidemiën in sub-Sahara Afrika snel vergrijzen, waadoor er aanzienlijke veranderingen in de organisatie van de regionale gezondheidszorg nodig zullen zijn.

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conversations, sharing of frustrations, etc. I hope to meet you all again at some point in time, somewhere in the world!

Joep, het proefschrift ziet er geweldig uit. Dankje! Ik ben blij dat jij mijn boekje een persoonlijk tintje hebt gegeven. Wanneer gaan we weer eens een spelletjesavond doen? David, Jan, Jeroen, Rick, dank voor alle biertjes en gezelligheid!

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About the author

Curriculum Vitae

Jan Hontelez was born on June 15th, 1985 in Wageningen. In 2003, Jan passed the exams of his secondary school in Wageningen, and started studying biomedical sciences in Nijmegen. He obtained his Bachelor of Science in biomedical sciences in 2007, and received his Master of Science in epidemiology in 2009. In addition, Jan completed the Interdisciplinary Honours Program at the Radboud University in 2009. During his studies, Jan worked for 3.5 months at the MRC laboratories in the Gambia, West Africa; 7 months at the Netherlands Institute of Public Health (RIVM); and 4.5 months at the World Health Organization in Geneva. For his work on Hepatitis B vaccinations at the RIVM, he received the "Radboud University Thesis Award" for the best graduation thesis of the academic year 2008-2009. In 2012, Jan obtained a Master of Science in Public health at the Netherlands Institute of Health Sciences (NIHES) in Rotterdam and received the "NIHES Award" for the best research paper written under guidance of a NIHES tutor in the academic year 2011-2012. Jan has worked at the Department of Public Health at the Erasmus MC, Rotterdam and the Radboud University Medical Center, Nijmegen as a PhD student since October 2009. During his PhD period, he has spent a cumulative total of 10 months at the Africa Centre for Health and Population Studies in Mtubatuba, KwaZulu-Natal, South Africa and 1 month at the Harvard School of Public Health in Boston, USA.

List of publications

This thesis

Hontelez JA, Lurie M, Bärnighausen T, Bakker R, Baltussen R, Tanser F, Hallett T, Newell ML, de Vlas SJ. Expanded access to antiretroviral therapy leads to elimination of the HIV epidemic in South Africa, even without universal test and treat. (submitted)

Hontelez JA, de Vlas SJ, Baltussen R, Newell ML, Bakker R, Tanser F, Lurie M, Barnighausen T: The impact of antiretroviral treatment on the age composition of the HIV epidemic in sub-Saharan Africa. AIDS 2012, 26 Suppl 1: S19-30

Hontelez JA, Newell ML, Bland RM, Munnelly K, Lessells RJ, Barnighausen T: Human resources needs for universal access to antiretroviral therapy in South Africa: a time and motion study. Hum Resour Health 2012, 10: 39

Hontelez JA, de Vlas SJ, Tanser F, Bakker R, Barnighausen T, Newell ML, Baltussen R, Lurie MN: The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa. PLoS One 2011, 6: e21919

Hontelez JA, Nagelkerke N, Barnighausen T, Bakker R, Tanser F, Newell ML, Lurie MN, Baltussen R, de Vlas SJ: The potential impact of RV144-like vaccines in rural South Africa: a study using the STDSIM microsimulation model. Vaccine 2011, 29: 6100-6106

Hontelez JA, Lurie MN, Newell ML, Bakker R, Tanser F, Barnighausen T, Baltussen R, de Vlas SJ: Ageing with HIV in South Africa. AIDS 2011, 25: 1665-1667

Other publications

Eaton JW, Johnson LF, Salomon JA, Barnighausen T, Bendavid E, Bershteyn A, Bloom DE, Cambiano V, Fraser C, Hontelez JA, Humair S, Klein DJ, Long EF, Phillips AN, Pretorius C, Stover J, Wenger EA, Williams BG, Hallett TB: HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLoS Med 2012, 9: e1001245.

The HIV Modeling Consortium Editorial Writing Group: HIV treatment as prevention: models, data, and questions--towards evidence-based decision-making. PLoS Med 2012, 9: e1001259

Zelle SG, Nyarko KM, Bosu WK, Aikins M, Niens LM, Lauer JA, Sepulveda CR, Hontelez JA, Baltussen R: Costs, effects and cost-effectiveness of breast cancer control in Ghana. Trop Med Int Health 2012, 17: 1031-1043

Nagelkerke NJ, Hontelez JA, de Vlas SJ: The potential impact of an HIV vaccine with limited protection on HIV incidence in Thailand: a modeling study. Vaccine 2011, 29: 6079-6085

Hontelez JA, Hahne S, Koedijk FH, de Melker HE: Effectiveness and impact of hepatitis B virus vaccination of children with at least one parent born in a hepatitis B virus endemic country: an early assessment. J Epidemiol Community Health 2010, 64: 890-894.

Hontelez JA, Hahne SJ, Oomen P, de Melker H: Parental attitude towards childhood HBV vaccination in The Netherlands. Vaccine 2010, 28: 1015-1020

Hontelez JA, Schim van der Loeff MF, Peterson I, Peterson K, Ahadzie B, Cotten M, Sarge-Njie R, Whittle H: Declining trend of serological syphilis among genitourinary medicine patients in the Gambia, West Africa. Sex Transm Dis 2009, 36: 745-749

PhD portfolio

Summary of PhD training

Name PhD Student:	Jan A.C. Hontelez
Erasmus MC department:	Public health
PhD-period:	2009 – 2012
Promotor:	Prof.dr. J.H. Richardus
Co-promotoren:	Dr. S.J. de Vlas Dr. R.M.P.M Baltussen

	Period	Workload
Master of Public Health, Netherlands Institute for Health Sciences (NIHES), Rotterdam, The Netherlands	2011 – 2012	
Erasmus Summer Program		
Principles of research in medicine	2011	20 hrs.
Clinical Decision Analyses	2012	20 hrs.
Methods of Clinical Research	2012	20 hrs.
Methods of public Health research	2011	20 hrs.
Clinical Trials	2012	20 hrs.
Health Economics	2012	20 hrs.
Cohort Studies	2012	20 hrs.
Introduction to Public Health	2011	20 hrs.
Methods of Health Services Research	2011	20 hrs.
Primary and Secondary Prevention Research	2011	20 hrs.
Social Epidemiology	2011	20 hrs.
The Practice of Epidemiological Analysis	2012	20 hrs.
Core Curriculum		
Study Design	2011	120 hrs.
Classical Methods of Data Analysis	2011	160 hrs.
Biostatistical Methods II: Popular Regression models	2011	120 hrs.
Public Health Research Methods	2011	120 hrs.
International Comparison of Health Care Systems	2011	40 hrs.
Site Visit to Municipal Health Service Rotterdam	2012	4 hrs.
Integration Module	2012	4 hrs.
Advanced Short Courses		
Advance Topics in Decision Making in Medicine	2012	40 hrs.
Mendelian Randomization	2012	40 hrs.
Planning and Evaluation of Screening	2012	40 hrs.
Presentations		
Late breaker Oral presentation 'The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa.' 18th International AIDS conference, Vienna, Austria	2010	25 hrs.
Poster presentation 'The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa.' 4th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment. Amsterdam, Netherlands	2010	10 hrs.
Poster presentation 'Future implications of the current ART roll-out in South Africa. 5th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment. Amsterdam, Netherlands	2011	10 hrs.
Poster presentation 'The potential impact of RV144-like vaccines in rural South Africa: a study using the STDSIM microsimulation model.' 5th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment. Amsterdam, Netherlands	2011	10 hrs.

	Period	Workload
Presentations		
Poster presentation 'Human resources needs for universal access to antiretroviral therapy in South Africa: a time and motion study.' 5th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment. Amsterdam, Netherlands	2011	10 hrs.
Invited speaker 'Ageing with HIV in sub-Saharan Africa' HIV and ageing in Africa: an official pre-conference of the International Conference on AIDS and STIs in Africa (ICASA). Addis Ababa, Ethiopia	2011	25 hrs.
Oral presentation 'Expanded access to antiretroviral therapy leads to elimination of the HIV epidemic in South Africa, even without universal test and treat.' 2nd International HIV Workshop on Treatment as Prevention. Vancouver, Canada	2012	25 hrs.
Invited speaker. 'Human resources needs for universal access to antiretroviral therapy in South Africa: a time and motion study'. 4th annual IAS/IAC meeting: Strengthening health systems for an AIDS free generation. Washington DC, USA	2012	25 hrs.
Oral presentation 'Expanded access to antiretroviral therapy leads to elimination of the HIV epidemic in South Africa, even without universal test and treat.' 19th International AIDS conference. Washington DC, USA	2012	25 hrs.
Oral poster presentation 'The impact of antiretroviral treatment on the age composition of the HIV epidemic in sub-Saharan Africa' 19th International AIDS conference. Washington DC, USA	2012	25 hrs.
Oral presentation 'Expanded access to antiretroviral therapy leads to elimination of the HIV epidemic in South Africa, even without universal test and treat.' 6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment. Amsterdam, Netherlands	2012	25 hrs.
Poster presentation 'The impact of antiretroviral treatment on the age composition of the HIV epidemic in sub-Saharan Africa' 6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment. Amsterdam, Netherlands	2012	10 hrs.
(Inter-)national conferences		
AIDS 2010. 18th International AIDS conference. Vienna, Austria	2010	48 hrs.
4th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment. Amsterdam, Netherlands	2010	8 hrs.
5th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment. Amsterdam, Netherlands	2011	8 hrs.
HIV and ageing in Africa: an official pre-conference of the International Conference on AIDS and STIs in Africa (ICASA). Addis Ababa, Ethiopia.	2011	16 hrs.
2nd International HIV Workshop on Treatment as Prevention. Vancouver, Canada	2012	32 hrs.
4th annual IAS/IAC meeting: Strengthening health systems for an AIDS free generation. Washington DC, USA	2012	16 hrs.
AIDS 2012. 19th International AIDS conference. Washington DC, USA	2012	48 hrs.
6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment. Amsterdam, Netherlands	2012	8 hrs.
International workshops		
Member of expert-panel for ReThinkHIV. Workshop of the Copenhagen Consensus Centre on prioritizing interventions for HIV control. Washington DC, USA	2011	32 hrs.
The Potential Impact of Expanded Access to Treatment for HIV Prevention in Sub-Saharan Africa. Stellenbosch, South Africa	2011	24 hrs.
Strengthening The Use of Mathematical Models in Community Trials. Boston, USA	2012	16 hrs.
World Health Organization antiretroviral therapy guidelines meeting. London, UK	2012	32 hrs.
Teaching activities		
Supervision of MSc student for 6 months	2011	52 hrs.
Gave a 3-day workshop on the use of STDSIM for modeling HIV and ART for PhD-students	2011	24 hrs.
One day of lectures and practical for the course 'Population Dynamics', part of the MSc curriculum 'Infection and Immunity' at the Erasmus MC, Rotterdam.	2012	16 hrs.
Involved in the design, lectures, and practical for one week of the course 'Global Health', part of the BSc curriculum for Biomedical Sciences at the Radboud University, Nijmegen	2012	32 hrs.