Modeling the impact of early HIV treatment on the HIV epidemic in South Africa

by

Bewketu Teshale Bekele

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in the Faculty of Science at Stellenbosch University

Department of Mathematical Sciences,

University of Stellenbosch,

Private Bag X1, Matieland 7602, South Africa.

Promoters:

Dr Rachid Ouifki,   Prof Wim Delva   and   Prof Farai Nyabadza

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Declaration

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07 February 2016

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Bewketu Teshale Bekele   Date

Abstract

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Bewketu Teshale Bekele

Department of Mathematical Sciences,

University of Stellenbosch,

Private Bag X1, Matieland 7602, South Africa.

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A major international randomized clinical trial from Strategic Timing of AntiRetroviral Treatment (START) has found that HIV-infected individuals have a considerably lower risk of developing AIDS if they start taking antiretroviral drugs sooner. According to the guidelines pre-released in September 2015, the World Health Organization (WHO) recommends that ART should be initiated in all adults living with HIV at any CD4 cell count. Following previous WHO recommendations, many governments have steadily changed antiretroviral therapy (ART) guidelines over the last decade. South Africa has revised ART guidelines to increase access to treatment to 500 CD4 cell counts/mm^3 or less with effect from the 1st January 2015. In ART programs, some individuals who initiate ART either fail treatment and switch regimen or dropout from ART, which might undermine the outcomes of ART programs. Thus, in the thesis, we formulated and analyzed new mathematical models that assess the impact of treatment failure and dropout on ART outcomes and associated costs. The models we considered consist of partial differential equations that are structured by time since infection and time since ART roll out. Our results confirm that early initiation of ART contributes

to a steep decline in the number of new HIV infections and HIV deaths, but also show that the benefit of ART might be limited due to the impact of dropout and treatment failure. Despite the uncertainties associated with some of the models' parameters, such as ART induced sexual behavioral change and ART access rate, with the current trend of ART access rate our simulations show that HIV elimination is not possibly achievable within a decade. To achieve HIV elimination soon, ART access rate must substantially increase, and the dropout and treatment failure rates must substantially reduce. If individuals keep dropping out of HIV treatment at current rates and they engage in risky sexual contact, HIV incidence will increase unless other intervention measures are taken. Consequently, the burden on the annual cost of providing ART will continue to increase.

Uittreksel

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Bewketu Teshale Bekele

Departement Wiskunde,

Universiteit van Stellenbosch,

Privaatsak X1, Matieland 7602, Suid Afrika.

Proefskrif: PhD Wiskunde

Februarie 2016

Die ewekansige kliniese proefneming genaamd 'Strategic Timing of AntiRetroviral Treatment (START)' het bevind dat MIV-besmette persone ´n aansienlike laer risiko vir die ontwikkeling van VIGS het indien hulle vroeg anti-retrovirale middels begin neem. Volgens die riglyne vrygestel in September 2015, beveel die Wêreld Gesondheid Organisasie (WGO) aan dat anti-retrovirale terapie (ART) beskikbaar gestel word aan alle MIV-besmette persone, ongeag hulle CD4 telling. Na aanleiding van WGO aanbevelings in die verlede, het die regerings van verskeie lande stelselmatig hul aanbevelings oor ART die afgelope dekade verander. Suid-Afrika het sy ART riglyne aangepas om sedert 1 Januarie 2015 ART beskikbaar te stel aan individue met ´n CD4 telling van 500 selle/mm^3 of laer. Sommige individue staak behandeling of hulle behandeling misluk en verander gevolglik kursus van behandeling. Dit kan die uitkomste van nasionale ART programme nadelig beinvloed. In hierdie proefskrif word nuwe wiskundige modelle geformuleer en ge-analiseer wat beoog om die impak van staking of mislukking van behandeling op ART uitkomste en verwante kostes te bepaal. Die modelle wat ons beskou bestaan uit parsiële differensiaalvergelykings wat gestruktureer word

volgens die tydverloop sedert MIV infeksie en die aanvang van die ART program. Ons resultate bevestig dat vroeë aanvang van ART bydra tot `n skerp daling in die aantal nuwe MIV-infeksies en MIV sterftes, maar wys ook dat die voordeel van ART beperk kan word deur die impak van staking of mislukking van behandeling. Daar is onsekerhede wat verband hou met `n paar parameters van die modelle, soos die verandering in seksuele gedrag veroorsaak deur ART en die beskikbaarheid van ART. Ten spyte hiervan toon ons simulasies dat, met die huidige tendens in die koers van toegang tot ART, uitskakeling van MIV nie haalbaar is binne die volgende tien jaar nie. Om MIV so gou as moontlik uit te skakel, moet beskikbaarheid van ART aansienlik toeneem en die staking van behandeling aansienlik afneem. Indien individue MIV behandeling staak teen huidige koerse en hulle meer geneig is om riskante seksuele besluite te neem, sal MIV insidensie toeneem, tensy ander voorkomende maatreëls getref word. As ´n gevolg, sal die las op die jaarlikse koste van verskaffing van ART bly toeneem.

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Dedications

to

Rahel Kiros

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Acronyms

- HIV - Human Immunodeficiency virus

- AIDS - Acquired Immunodeficiency Syndrome

- ART - Antiretroviral therapy

- HAART - Highly active antiretroviral therapy

- IeDEA - International Epidemiologic Databases to Evaluate AIDS

- ARV - Antiretroviral

- WHO - World Health Organization

- UNAIDS - the Joint United Nations Program on HIV/AIDS

- PLWHA - People Living With HIV/AIDS

- PEPFAR - President's Emergency Plan for AIDS Relief

- MSF - Médecines Sans Frontières

- PYRS - Person-years of ART

- QALY - Quality adjusted life years

- DALY - Disability adjusted life years

- LTFU - Lost to follow up

- STTR - Seek, Test, Treat and Retain

Chapter 1

Introduction

1.1   Background

Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV) [1]. HIV/AIDS is a long-duration illness with average survival of about 10 years if untreated. AIDS was first clinically observed in the United States in 1981 [2]. Since then, it has become a global health problem. Millions of individuals have died due to AIDS and millions of children have become orphaned. The two known types of HIV virus are HIV-1 and HIV-2. HIV-1, which is highly infectious, is prevalent globally. HIV-2, however, is largely confined in West Africa due to its lower virulence and low infectivity.

Since the first documented case of HIV in South Africa occurred in 1982 [3], HIV has become prevalent in South Africa. Currently it is a home for 6.8 million [6.5 million - 7.5 million] HIV positive individuals according to UNAIDS estimates of 2014. Of those, 6.5 million are adults 15 years old and above [4]. In 2012 only, an estimated 240,000 number of deaths was registered due to HIV/AIDS [5].

From the results of START (Strategic Timing for AntiRetroviral Therapy), we now have clear evidence that early treatment benefits the health of the HIV-positive people [6]. Previous researches have shown that earlier diagnosis and treatment of HIV is important to reduce HIV transmission [7, 8, 9]. Moreover, ART initiated during seroconversion (just after infection) and taken for at least 3 years could show virological control for several years even after

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treatment interruption [10]. Due to these supporting results, HIV treatment is being used for HIV prevention. Overall, the primary goals of ART use are: to improve the quality of life of the patients, reduce HIV-related morbidity and mortality, provide maximal and durable suppression of viral load, and restore and preserve immune function [11].

Following results from different trials, governments and organizations have been changing HIV treatment guidelines. In September 2015 (the published guidelines to come in 2016), the World Health Organization (WHO) recommends ART initiation to everyone at any CD4 level. Successful global implementation of updated guidelines could greatly increased the reduction of new HIV infections and deaths.

There are efforts being made to change behavior, to use treatment to save lives and most recently, treatment guidelines are being changed to increase the ART provision thresholds. These could help us use 'treatment as prevention', which the world is moving towards. The current efforts seem not to be sufficient and hence HIV/AIDS might still continue to be a health challenge to South Africa. Unless commitments to increase HIV funding continue, we may not achieve elimination of HIV within short a period of time, where reaching HIV incidence of 1 per 1000 susceptible individuals is used as a threshold for HIV elimination by some studies [12, 13, 14].

1.2 The biology and immunology of HIV

At the time of HIV infection, the level of HIV RNA (HIV genetic material) copies becomes high (several million virus per milliliter of blood). This usually continues for a short period of time accompanied by a short-flu like illness. The diagnosis of the infection at this stage is often missed. This stage is characterized by a decline in the number of HIV RNA copies, and the number of HIV RNA copies remain at a lower level for about 8 to 10 years. The infected person stays asymptomatic but remains infectious. Finally, as HIV progressively destroys the body's immune system, it leads to AIDS. At this stage, the person starts showing symptoms of the disease and other opportunistic diseases may occur. The stages of HIV infection can generally be broken down into three distinct stages: primary infection (known as acute infection), clinical latency and AIDS stage. The stages of the disease (HIV time course) description

are given in Figure 1.1.
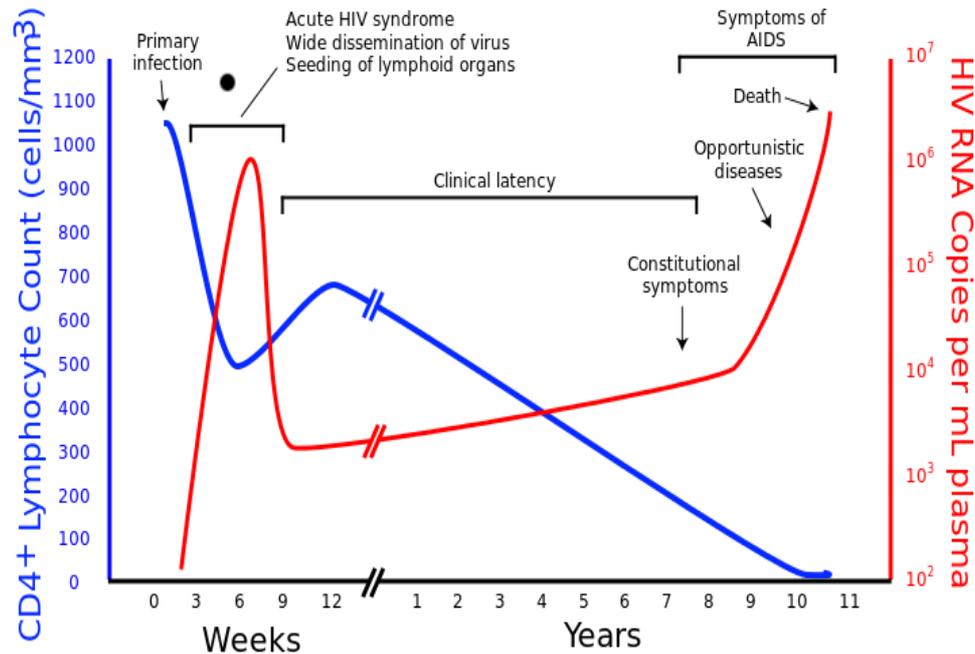
Figure 1.1: HIV-time course: HIV copies (viral load) and CD4 cell counts over the average course of untreated HIV infection [15]

1.3 Epidemiology of HIV

HIV is transmitted through fluids of the body: blood, semen, vaginal fluid and breast milk. The modes of transmission mainly include sex, needle sharing (during injected drug use) and mother to child transmission through the birthing process. In sub-Saharan Africa heterosexual contacts are believed to be the main mode of transmission [16]. However, a different result was published in 2003 [17], which stated that only 25-29% and 30-35% of HIV incidence in African women and men, respectively, were attributable to sexual transmission. On the other hand, in countries such as the United States, a significant proportion of new HIV cases are caused by homosexual contacts [18]. In 2010, the majority of new HIV infections in the United States were attributed to male-to-male sexual contacts (63% overall and 78% among males), while in women the largest percentage of new HIV infections come from heterosexual contacts (84%).

According to estimates by UNAIDS, 36.7 million adults and children were living with HIV in 2014 globally [19]. In the same year approximately 2 million new infections occurred and an estimate of 1.2 million individuals died due to HIV/AIDS. The number of new infections in 2014 are, however, less than the estimates of 2013 and 2012 where 2.1 million and 2.3 million new infections occurred in the respective years [20, 21]. Figure 1.2 shows that the number of new HIV infections and AIDS-related deaths were declining globally. A summarization of the reduction of new HIV infections averted and HIV deaths is presented in Table 1.1. These figures are encouraging to ART programs which invest a lot to fight against HIV. This could be because of the increase in the number of individuals receiving HIV treatment (see Figure 1.3). Additional contributing factors for the reduction might be natural epidemic dynamics of the disease and change of behavior by the people in general. However, we do not see a declining trend for both the prevalence and the number of individuals living with HIV. Because ART prolongs patients' life and hence the prevalence might stay at a similar level even though there is a declining trend of the number of new HIV infections. But as the efforts to put many individuals on ART continue for a longer period, it might be inevitable to see significant decline of HIV prevalence.

By region, sub-Saharan Africa remains the most heavily affected by HIV/AIDS. The region has accounted for 66% of the global total new HIV infections [19]. In 2014, an estimated 25.8 million [24.0 million - 28.7 million] were living in the region as compared to the previous estimates: 24.7 million and 23.5 million in 2013 and 2011, respectively [5, 20]. According to the estimates of 2014 of UNAIDS, 1.4 million [1.2 million - 1.5 million] new infections and 790,000 [670,000-990,000] deaths occurred. These figures showed a decrease from 2013 estimates, where an estimated 1.5 million [1.3 million - 1.6 million] new HIV infections and 1.1 million [1.0 million - 1.3 million] deaths occurred [20].

1.4   HIV/AIDS in South Africa

South Africa is the single country in the world most affected by the HIV epidemic. According to estimates by UNAIDS, 6.8 million [6.5 million - 7.5 million] South Africans were living with HIV/AIDS in 2014 [4], which showed an increase from 6.3 million and 6.1 million estimates

Table 1.1: The massive scale up of ART is saving more lives and averting new infections. All data are according to UNAIDS estimates of 2015 [19].

	Indicators	percentage changes
Globally	- New HIV infections	35% decrease since 2000
	- AIDS-related deaths	42% decrease since 2004
	- New infections in children	58% decrease since 2000
	- Access to ART	41% of adults as of March 2015
sub-Saharan Africa	- New HIV infections	41% decrease since 2000
	- AIDS-related deaths	48% decrease since 2004
	- Access to ART	41% of all PLWHIV

in 2013 and 2012 [5, 24]. This is approximately 12% of its population. But the prevalence in the adult population (15 years and above) is much higher: 18.9% [17.9% - 19.9%] [4]. From the total of 6.8 million individuals infected with HIV, 340,000 [310,000 - 370,000] are children below 15 years old. This showed a decline from 2012 estimates (410,000) [5]. Moreover, an estimated 140,000 [100,000 -190,000] deaths due to AIDS occurred in the same year, 2014, compared to 200,000 deaths which occurred in 2013 [24] and 240,000 deaths which occurred in 2012 [5].

According to the human science research council (HSRC), the estimates of HIV prevalence show that 15.6% 16.2% 16.9% and 18.8% of adults (15-49) were living with HIV in 2002, 2005, 2008 and 2012, respectively. The trend of HIV prevalence in adults in South Africa is shown in Figure 1.4 as taken from [25]. The prevalence of HIV in South Africa varies significantly across its provinces, KwaZulu-Natal being the most severely affected with an HIV prevalence of 25.8% and Western Cape province being the least affected (5.3%). The HIV prevalence among antenatal women is also one of the highest in the region. In 2011, in South Africa, 29.5%[28.7-30.2%] of pregnant women were living with HIV [26]. KwaZulu-Natal still has the highest disease prevalence in pregnant women: 37.4%. HIV incidence rates are also estimated to be 2.2% (0.9%-4.0%) from 2002 to 2005, 1.9% (0.8% -3.3%) from 2005 to 2008 and 1.9% (0.8%-3.1%) from 2008 to 2012 [27]. The annual HIV incidence in 2012 alone is estimated as 1.72% (1.38% - 2.06%). Moreover, South Africa ranks first in HIV incidence in the world with an estimated 396,000 (318,000-474,000) new HIV infections occurred in only 2012 [27]. Western Cape and KwaZulu-Natal provinces have the lowest and the highest incidence, 0.5% and 2.3% respectively [28].
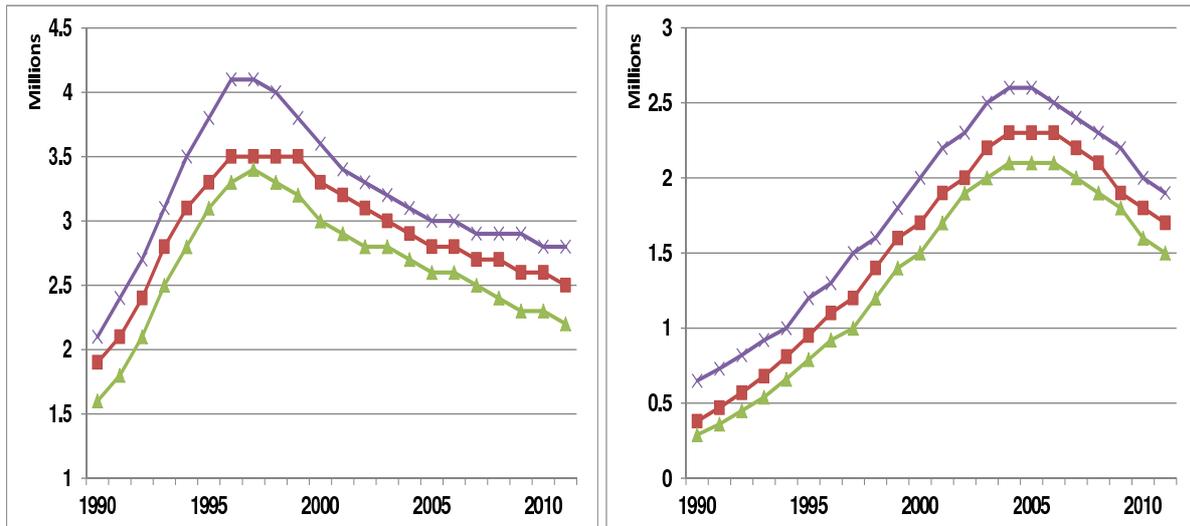
(a) New HIV infection, adults and children

(b) AIDS related deaths, adults and children
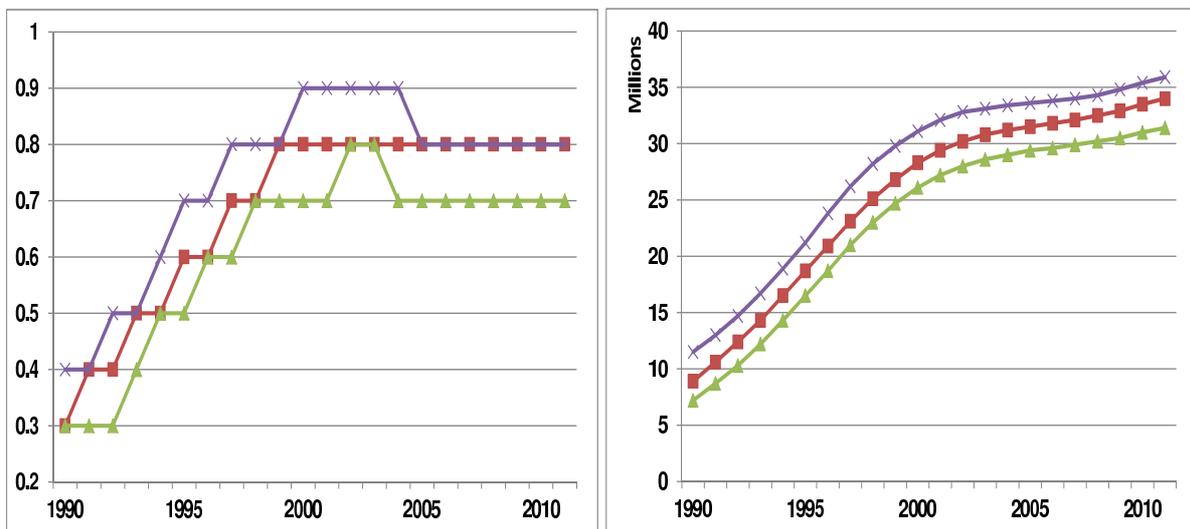
(c) Adult HIV prevalence (15-49)

(d) Number of people living with HIV, adults and children

Figure 1.2: UNAIDS 2012 estimates and surrounding plausibility bounds (the upper and lower lines in each figure) of HIV prevalence, numbers of people living with HIV, new HIV infections, and AIDS deaths, 1990-2011 [22]. HIV prevalence is the proportion of individuals who are infected with HIV from the total population. All numbers are in millions.

1.5   Antiretroviral therapy

Efforts to find an HIV vaccine and a drug which cures the disease are increasing. The only drugs currently available to treat HIV are antiretroviral (ARV) drugs, which do not cure the infection but maintain a low viral load (VL) and prolongs the life expectancy of HIV infected
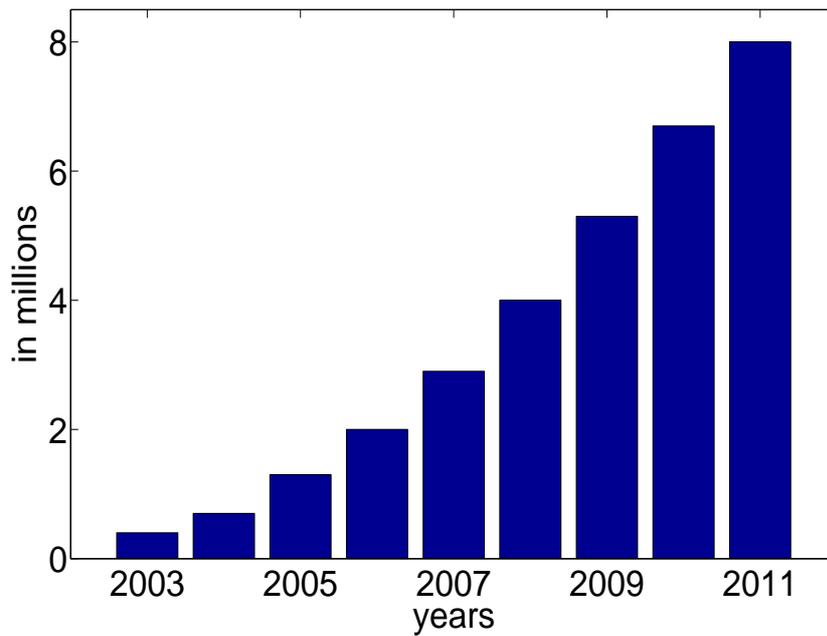
Figure 1.3: Estimates of HIV positive individuals receiving HIV treatment in low- and middle-income countries [5, 23].
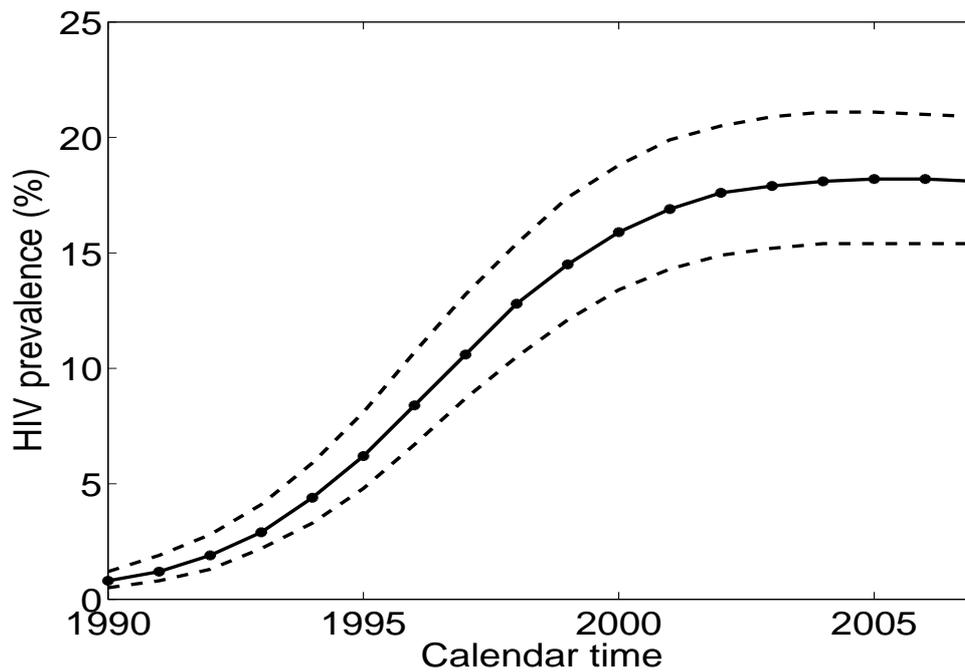
Figure 1.4: South African HIV prevalence (adults) estimate and its surrounding plausible bounds[25]. The lower and upper curves are low and high estimates, respectively.

patients. In general, ARV drugs are the tools we have to reduce the risk of infecting others in addition to preserving the health of people living with HIV.

1.5.1 Antiretroviral, globally

Due to the encouraging results from different studies of the impact of ART, the early initiation of antiretroviral therapy (ART) has progressively increased in the last decade. WHO has been revising HIV treatment guidelines. The 2013 guidelines recommend a raise in CD4 cell count threshold to 500 cells/mm^3 (from a threshold of 350 cells/mm^3) for general adult population and recommend that HIV positive people in certain groups should access treatment regardless of CD4 cell count: children younger than five years, pregnant women, people co-infected with TB or hepatitis B and people in serodiscordant relationships [29]. The guidelines are to change in 2016, according to the early-released treatment guidelines by WHO which suggests ART initiation to individuals at any CD4 cell count [30].

An estimated 15 million people are on ART in 2014, globally [31]. Additionally, as a result of revised guidelines and huge investment, the number of individuals receiving antiretroviral therapy in low- and middle-income countries has increased significantly over the last decade from 400,000 in 2003 to 8 million by the end of 2011. Moreover, the number in 2011 shows a 21% increase (1.4 million) in only one year as compared to the previous year [5, 23]. The rate of scale up of ART provision has increased exponentially recently. At the end of 2012, 9.7 million people (an increase from 8 million in 2011) in low- and middle-income countries had access to antiretroviral therapy [32]. This increased further and an estimated 11.7 million people had access to ART in 2013 [33].

Despite the new treatment guidelines, most countries were behind schedule. It is estimated that 90% of all countries were using the 2010 WHO guidelines in 2013, which is a threshold of 350 cells/mm^3 for the general population as opposed to the 2013 WHO guidelines. Only few had high ART coverage at the time. Countries such as Algeria, Argentina and Brazil were already offering antiretroviral therapy at 500 cells/mm^3 [34]. But these countries have low HIV prevalence compared to South Africa with a threshold of 350 cells/mm^3 [35], which was the threshold implemented until 2014. South Africa has recently revised the threshold to 500 CD4 cell count, starting from January 2015 [36]. A review article of ART guidelines of 70 countries was published in [37], which showed the commitment of the government towards ART programs. 42 countries out of 70 countries, which were represented

in the review article follow 2010 WHO's ART guidelines for asymptomatic people and recommend ART initiation at CD4 cell count ≤ 350 cells/mm^3. Only nineteen countries are recommending and considering an earlier ART initiation above CD4 cell count ≥ 350 cells/mm^3 for asymptomatic people, pregnant women and/or serodiscordant couples.

The success of ART scale up programs (treatment as prevention) entirely depends on seeking out those people possibly HIV infected, testing, treating and retaining to care. This is commonly referred to as Seek, Test, Treat and Retain (STTR), and it is vital to design programs which stress these four objectives. ART scale up must include both the short-term stresses of initiating individuals on treatment and the long-term problems of managing a life-long chronic disease. In health care, prevention often provides good value for money. For example, little is spent per quality adjusted life years (QALY) averted. However, a low cost per QALY averted does not usually indicate a net saving program over a certain period. Because net savings represent the reduction in total costs due to added costs of expanded ART and averted costs from different health outcomes such as averted infections and QALY [38].

Figure 1.5 presents the ART coverage of selected southern African countries based on WHO 2010 guidelines. In all the countries listed, the ART coverage have shown an increment over years. South Africa, Swaziland and Botswana have reached nearly or above 80% in 2012. But Lesotho's ART coverage in 2012 was below 55%.

1.5.2   ART and other interventions in South Africa

In South Africa, antiretroviral therapy is a major intervention mechanism to fight against HIV. An estimated 2.6 million were receiving ART in 2014 [40] which is approximately 38% of the total number of individuals infected with HIV. While ART programs in South Africa started early in 2001 in some sectors, the largest public sector program started in 2004 [41, 42, 43, 44, 45]. Since its adoption, many lives have been saved and the ART coverage has significantly increased. In South Africa, following the launch of a major campaign of HIV testing, the number of people receiving treatment reached 2.15 million in 2012. According to 2010 WHO antiretroviral guidelines, this can be translated as 85% coverage which is a
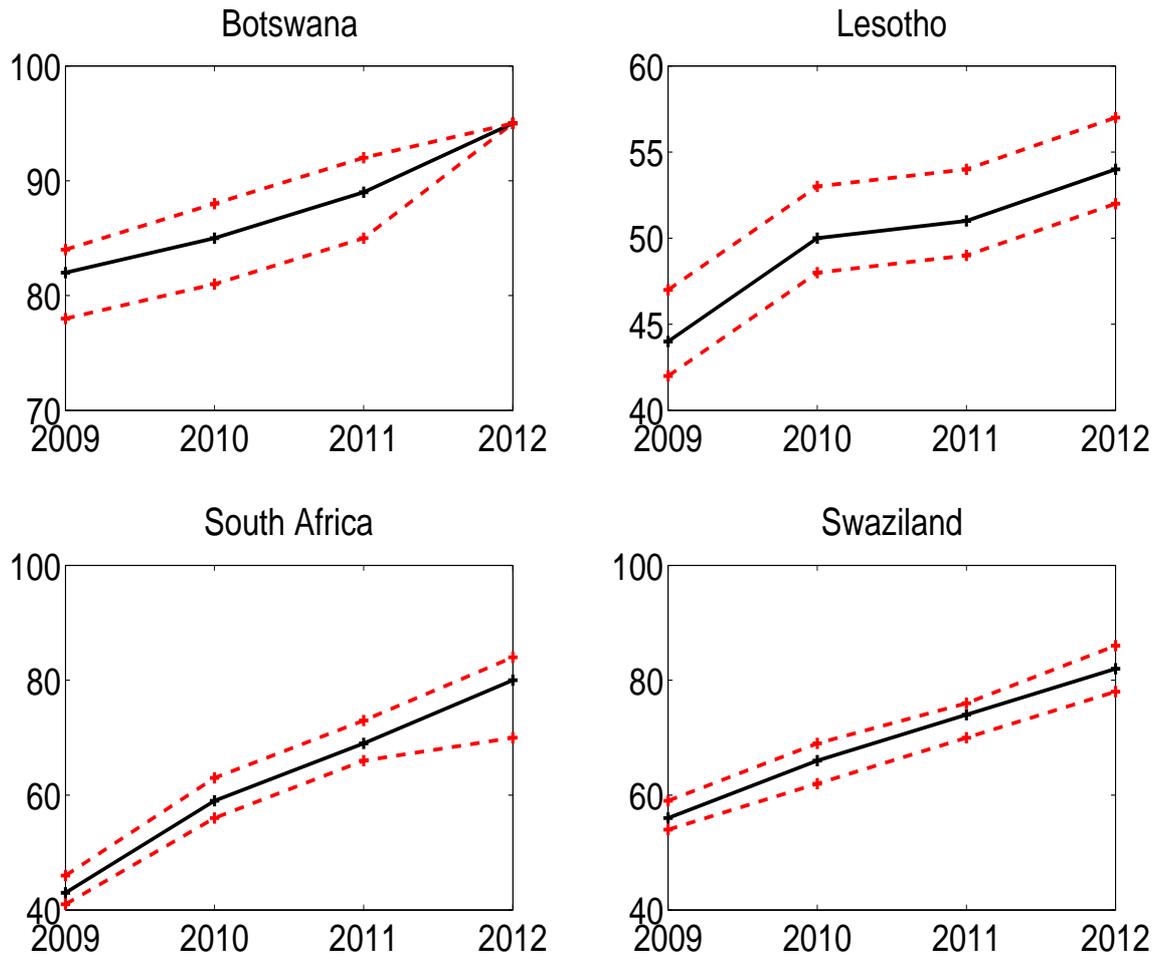
Figure 1.5: Estimated ART Coverage based on WHO 2010 ART guidelines for selected Southern African countries (all numbers given in percentages) [39].

27% increase from the previous year [21]. In past 10 years, South Africa's ART guidelines have changed significantly, see Table 1.2. Currently, South Africa's HIV treatment program is considered as one of the largest in the world [46, 47].

Other than antiretrovirals, condom use is also one of the encouraged interventions in the fight against HIV. Condom usage in both genders in South Africa has increased over years, from 57% in 2002 to 87% in 2008 among young males and from 46% to 73% among females [48]. It also varies significantly with marital status. In a South African survey, 69% and 52.4% of single respondents used a condom during their last sexual encounter from the age group 15-24 and 25-49, respectively [49]. Individuals who had three or more partners were more likely to use a condom: 81.1% and 60% among 15-24 and 25-49 age groups, respectively.

Table 1.2: Time line and changes of ART guidelines in South Africa.

Years/guidelines	eligibility
2001-2003	only to beneficiaries of medical schemes and individuals receiving treatment through workplace treatment program
2004-2010	CD4 count ≤ 200 cells/mm^3, or an AIDS-defining illness
2010 guidelines	includes access to HIV-TB and pregnant mothers
2013 guidelines	- CD4 count ≤ 350 cells/mm^3 irrespective of WHO clinical stage - irrespective of CD4 count (HIV-TB patients, pregnant and breast feeding) - WHO stage 3 or 4 irrespective of CD4 count
2015 guidelines	- CD4 count ≤ 500 cells/mm^3 irrespective of WHO clinical stage - irrespective of CD4 count (HIV-TB patients, pregnant and breast feeding) - WHO stage 3 or 4 irrespective of CD4 count

Despite these encouraging statistics, condom usage data has always been difficult to validate as self reporting is the only method used during collection of the data.

1.6   Motivation

We know that ART has health impacts, primarily by saving lives and averting new infections [50]. Evidence of population impact, cost and cost-effectiveness (CE) is available from modeling studies, but evidence is fragmented over many different studies: tuberculosis by [51]; HIV incidence, prevalence by [52]; HIV incidence, prevalence, person years of ART (PYRS of ART) cost and CE by [12]; PYRS of ART by [53]. This thesis presents an internally consistent body of evidence on all of the above, generated from the same model under the same set of parameter assumptions. To achieve this, we have developed and applied an epidemiological model of HIV transmission, ART expansion criteria in hyper endemic settings like South Africa.

Now we know that TasP works, the question is how do we expand it? What does the ART scale up scenario in South Africa mean with respect to cost and cost-effectiveness and the overall effectiveness of the program at the population level? If individuals become eligible for treatment at any CD4 count, by how much does the number of individuals who need HIV treatment increase? With even ART access rates unchanged, more individuals will be on ART with higher ART provision scenario, leading to an increase of annual spending. If

the annual spendings and efficiency of logistical management do not increase and become more effective, the treatment access rate becomes small. ART initiation threshold changes (treatment guidelines) mean nothing unless more people are put on ART.

Despite the introduction of ARVs and their current usage as a prevention mechanism to fight the HIV/AIDS epidemic, the disease still claims the lives of many people in the world, especially in sub-Saharan Africa. Only 41% of adults are on ART globally. The efforts may not yet be sufficient to curb the disease [19]. A number of challenges may face the current treatment scenarios, including whether to initiate ART at a threshold of 350 or 500 CD4 cell count, as well as loss to follow up, and switching drug regimen as a result of treatment failure. Loss to follow up refers to HIV patients who at one point were receiving ART, but have become lost from treatment programs. Transport and waiting time, religious beliefs in some settings and stigma might be few of the reasons as to why individuals become lost from programs. We also do not really know how individuals behave sexually and how disease progressions happen after stopping treatment. Thus, it might be of great importance to analyze the impact of loss to follow up and of treatment failure in the overall fight against the HIV epidemic.

There is a general move, among governmental and non-governmental bodies, towards the use of HIV treatment as prevention. The phrase 'HIV treatment as prevention' refers to HIV prevention methods that use antiretroviral treatment to decrease the risk of HIV transmission. However, as ART scale up develops, loss to follow up and drug resistance become growing challenges. Drug resistance generally refers to the reduction of the effectiveness of a drug. Thus, the impact of early HIV treatment might be limited due the growing challenge of drug resistance. Due to the occurrence of drug resistance, infections may be harder to control and hence manufacturing of advanced drugs is vital which usually increases program costs. In this thesis, we also look at the scale of the problem in a hypothetical case and study the increased cost as a result of switching to second-line treatment.

1.7   Objectives of the study

The aim of this research is to assess the impact of ART scale up in South Africa taking into consideration ART access rate, treatment dropout and treatment failure.

The specific objectives of the study are:

- To evaluate the impact of early HIV treatment for different ART initiation scenarios.

- To do a cost-effectiveness analysis of different ART initiation scenarios.

- To analyze level of loss to follow up and its impact in treatment programs.

- To analyze program cost of ART as a result of switching drug regimen.

1.8 Structure of the thesis

In chapter 2 we give a review of the literature of mathematical models of early HIV treatment. A review of the trend of the cost of ARV is also presented. In chapter 3 we define the necessary mathematical concepts and provide an algorithm for calculating the distribution of CD4 cell count by time since infection that has previously been derived by [54]. In chapter 4 we give a model for the dynamics of HIV transmission structured by time since infection. Numerical analysis of the model for different thresholds of ART initiation is also given. In chapter 5, we present the cost-effectiveness analysis of the first HIV model, presented in chapter 4. In chapter 6 we present another model for the transmission of HIV dynamics which is structured by time since infection, and time since the start of HIV treatment, which incorporates treatment failure and dropout. Simulations of key epidemic out puts will be discussed. In chapter 7, numerical analysis of the model is given for different scenarios of cost ratios between the second-line regimen and first-line regimen. Additionally, cost-effectiveness analysis will be discussed. Finally, in chapter 8 we give conclusions of the main findings. In this chapter we discuss the differences in the model structure between chapters 4 and 6 and present the new insights.

Chapter 2

Literature review

Following research advances on antiretroviral drugs for HIV/AIDS, a number of researchers have developed and analyzed mathematical models to study the impact of HIV treatment, cost and cost-effectiveness of various HIV intervention scenarios. In this chapter we review some of the studies which looked at the impact of early ART. We also review studies done to measure retention, loss to follow up as well as the trend of cost of ARV drugs.

2.1   Review of models and impact of ART

In May 2015, results from START showed that ART has important benefits for people with high CD4 cell count. The study is considered to be as one of the most important HIV studies and major international randomized trial which included 4685 HIV positive individuals from 36 countries. The main results include: risk of serious illness is halved, ART is safe and effective if administered early, and most importantly about 98% of people who started treatment had an undetectable viral load at the end of their first year of treatment, according to START [6]. The HIV Prevention Trails Network (HPTN) 052 showed a 96% (95% confidence interval, 73%-99%)reduction of HIV transmission in serodiscordant couples if treatment is administered early [9]. In another study [8], ART use by HIV-1 infected participants was associated with a 92% reduction in risk of transmission. ART reduces mortality and morbidity in individuals infected with HIV [55, 56, 57, 58, 59]. Significant decline of adult mortality due to ART roll-out in rural KwaZulu-Natal was reported in [59]. Survival due to ART can be as-

sociated with the starting CD4 cell count. Individuals with higher CD4 cell count thresholds (500 cells/mm^3 and above) have better survival [58]. Moreover, ART reduces the hazard of HIV acquisition in HIV negative adults.

There has been a trend towards increasing ART coverage since the start of public ART roll out in 2004 [60]. In a study in a rural South African population, a 1.7% decline in incidence was observed for every 1% ART scale up [61], providing further evidence for the reduction of the hazard of HIV acquisition in HIV negative adults when on ART. Increased ART coverage was also associated with reduced HIV incidence in another study, [62]. HIV incidence decreased by 21%, 38% and 37% for the proportion of all HIV-infected people receiving ART are 20-30%, 30-40% and above 40%, respectively.

More supporting results of benefits of ART have been published recently. Results from a seven year Temprano study also showed that starting ART at a CD4 cell count less than 800 reduced risk of serious illness including tuberculosis, and health by 44% [63]. This study was conducted in Ivory Coast, aiming to test the safety and efficacy of early ART. Early ART initiation (CD4 ≥ 500) has been shown to have a better chance of viral suppression at 9 months. It also helps to be adherent at least 95% overtime. Most importantly, patients will have less probability of developing any resistance [64].

Following evidence of substantial reduction of HIV transmission after treatment [7, 8, 9], studies have focused on understanding the potential prevention benefits of HIV treatment. The increasing interest of understanding the projected impact of early HIV treatment has been discussed in [12, 13, 14, 52, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74]. A pioneering mathematical model for universal test and treat was published in the Lancet in 2009 [13]. The study presents a strategy for elimination of HIV transmission (elimination being defined as less than 0.1% HIV incidence, i.e. one new HIV infection per thousand susceptible individuals). HIV elimination could be possible within less than a decade for 99% HIV transmission reduction assumption due to ART and with annual HIV testing with immediate ART initiation if tested positive [13]. Since then a lot of mathematical and statistical models have been formulated, the impact of early HIV treatment has been evaluated and predictions have been made for certain time horizon in the future. In [52], twelve independent mathematical models which evaluated ART intervention scenarios in South Africa were reviewed. Most models

consistently suggested that ART provided at a high level of access and high adherence leads to significant reduction of new HIV infection. In a PLoS Medicine collection, researchers have discussed the impact of ART, challenges during implementation and suggestions to optimize programs [75]. In [68], a study reviewed different ways in which access to HIV treatment could be optimized to achieve the most benefit. It could mean prioritizing particular groups based on clinical and behavioral factors. Modeling the cost of antiretroviral treatment is discussed in [76]. Others have looked at different aspects such as cost-effectiveness analysis of pre-exposure prophylaxis (PrEP) which was studied in [77, 78]. Research in [79] used a mathematical model to analyze impact of condom usage and antiretroviral coverage in the South Africa HIV epidemic.

ART scale up reduced the number of AIDS-related deaths significantly. A study examined database of UNAIDS from 1990-2013 to examine AIDS deaths, HIV incidence and prevalence, ART coverage and other key epidemic outputs [80]. Projection for South Africa and including Nigeria were done for four different scenarios: 1) No ART, 2) maintaining current ART coverage, 3) 90% ART coverage based on 2013 WHO guideline and 4) UN 90-90-90, target by 2020. The results show that between 1990 and 2013, ART has averted approximately one million deaths in South Africa. Moreover the recent declines are huge as South Africa has experienced a 52% decline in AIDS-related deaths. According to the estimates from [80], 42%(40%-44%) of the people living with HIV were on ART as compared to 13% in 2010.

Condom usage has an impact on the reduction of the HIV transmission in South Africa. In a modeling work in [79], the impact of increased condom usage was discussed. The results of the model suggest that HIV incidence in South Africa has declined significantly since the year 2000. The major decline is attributed from the increase in condom usage, change of behavior or any other intervention mechanism. Willingness of individuals for HIV testing and starting treatment might be one of the limitations which hinder the success of ART scale up programs. Individuals refuse treatment despite the fact that their CD4 cell count is less than a threshold (CD4=200) [81, 82]. 'Feeling healthy' is one of the reasons given for refusal. Another hindrance to success, especially in developing countries, is resource limitation.

2.2 Linkage to care, retention, loss to follow up

Among 185 individuals who initiated ART in South Africa between March 2010 and August 2012, 22 were transferred out. Of the remaining 163, 81.0% (95%CI: 74.4-86.5%) were retained in care through two years on treatment [83]. In South Africa, the mortality rate after ART initiation has decreased from 9% to 6% over 5 years from 2002/03 to 2007. However, loss to follow up (LTFU) has increased every year from 1% (2002/03) to 13% (2006) [84]. Of 13,227 patients initiated ART between April 2004 and March 2010 in Lethu Clinic, Johannesburg, South Africa, below 11% died at all calendar years, while we see an increase in the proportion of those who are lost from the program from 8.5% in 2004 to 12.1% in 2009 (RR: 1.42; 95%CI: 1.18-1.71) [85]. The LTFU likely reflects the cumulative burden of increasing patient numbers as the program matures [84, 86]. Of those individuals who initiated ART in 2007, nearly a third have already been lost from the program. In the first year of ART initiation, patients with low baseline CD4 cell count (50-199) were less likely to be lost compared with those with higher CD4 cell count (> 200). Similar results which show the challenges of ART expansion were presented in a recently published article of a multi-cohort analysis of 8 African and Asian HIV treatment programs [87]. Larger program size was associated with increased early LTFU (adjusted hazard ratio=1.77[1.04-3.04] for program size $\geq 20,000$ versus < 500 patients). Rate of program expansion was also strongly associated with increased LTFU. Adjusted hazard ratios of 2.31[1.78-3.01] and 2.29[1.76-2.99] for early and late LTFU, respectively, was observed for enrollment programs greater than 125 versus less than 25 patients per month [87]. Similarly in Malawi, an 8% treatment dropout rate was seen immediately or soon after starting ART [88]. But in the long term, it has declined and some models assumed annual dropout rate of 1.5% for model projections [13]. Study by [89] presented that retention time on ART was exponentially distributed with a mean of 10 years, giving a dropout probability of 9.5% in the first year. In the same study, 50% of individuals who dropout from treatment may re-initiate ART by means of new voluntary test. Sometimes treatment outcomes vary with age group. A study [90] presents treatment outcomes of adolescents (9-19 years) as compared with those of young adults (20-28 years), from a prospective cohort be-

tween September 2002 and June 2009 from a community-based antiretroviral therapy clinic in South Africa. Overall mortality rates in adolescents and young adults were 1.2 (0.3-4.8) and 3.1 (2.4-3.9) deaths per 100 person-years, respectively. Whereas, treatment failure rates were 8.2 (4.6-14.4) and 5.0 (4.1-6.1) per 100 person-years in the two groups.

In South Africa, only 38% males and 27% females from the total HIV-infected male and female population, respectively, were on ART in 2012. Moreover, only 28% males and 19% females are virally suppressed, respectively. The overall percentage of HIV positive individuals with viral suppression among the total HIV infected individuals was 25%. This means, the rest 75% of HIV infecteds are potentially infectious (translated to approximately 4.5 million according to 2012 estimates) [91]. This is far from the UN-90-90-90 target which targets 73% viral suppression from the total HIV infected individuals [92]. This is a target of achieving ART coverage for HIV-positive persons under which 90% are tested, 90% of those are on ART and 90% of those on ART achieve viral suppression.

Linkage to care is a critical aspect of an HIV treatment program. According to WHO, only 39% of HIV positive individuals residing in the sub-Saharan Africa were aware of their HIV status [93]. Among those who knew their status, only 57% checked for ART eligibility. The exit continues at each stage, and approximately two-thirds of those eligible to start ART (see schematic demonstration in Figure 2.1). A different way of visualizing this is through HIV/AIDS treatment cascade, a process which arranges treatment steps such as testing, eligibility and ART initiation in a series or sequence of diminishing proportions. It is a way to show the number of people living with HIV/AIDS (PLWHA) who are currently receiving the intended benefits of the medical care and treatment [94]. Even in highly developed countries like the United States, a significant number of PLWHA fall off from the stages of the cascade. Hence a minority of patients receive treatment care. According to CDC in the USA, in 2009 approximately 55% of adults aged 18-64 did not receive a single HIV test [94]. In another study in USA [95], only 75% of those in need of ART were currently on ART in the cascade. Moreover, only less than a quarter of the total number of HIV infected individuals were accessing treatment.

As in other parts of the world, linkage to care and retention are also problems in the South African treatment programs. The proportion of individuals retained in ART ranges from
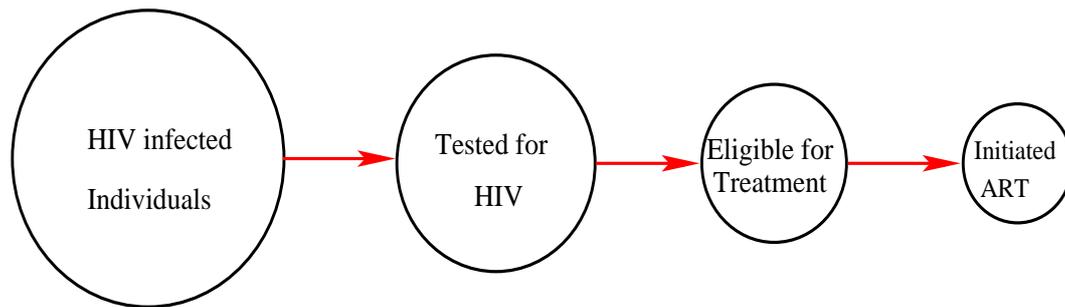
Figure 2.1: An illustration for HIV treatment pathway: the size of the circles indicate the relative number of individuals in each class. In this context, eligible for treatment refers to individuals who fulfill the current ART recruitment criteria.

67.2% to 90.3% for a follow up period of 19.5 months and 12.3 months, respectively [96]. In an observational cohort study conducted at a primary clinic in Johannesburg, South Africa, 73.5% (69.0% to 77.6%) of eligible patients were retained during pre-ART stage 3, but only 38.8% were able to start ART [97]. This figure was relatively low compared to some programs from the developed world. Similarly in an outpatient clinic in Durban, South Africa, only 39% of eligible individuals started ART (based on CD4 cell count less than 200 eligibility criteria) [98]. Retention might vary with CD4 category. In a study in a rural setting in KwaZulu-Natal [99], retention by initial CD4 cell count 201-350, 351-500, and > 500 cells/mm^3 was 51.6%, 43.2% and 34.9%, respectively.

Once individuals are lost to follow up, it is difficult to study the disease progression. However there are some studies that looked at this with supervised treatment interruptions. In this procedure, patients are supervised to stop treatment when the viral load becomes less than 400 copies of HIV-1 RNA per ml (i.e. reaching undetectable level) and re-initiate treatment when 5000 copies per ml (the thresholds may vary depending on the study). Successful treatment of HIV infection usually leads to viral suppression. After interruption 5 out 8 patients remained off therapy (< 500 RNA copies per ml plasma) after a median 6.5 months [100]. In some cases significant viral replication might be observed in a one-week time period since treatment interruption [101]. Viral load rebound in a series of separate treatment interruptions significantly increases risk of getting opportunistic disease or death [102]. In this study for instance, opportunistic disease or death from any cause occurred in 3.3 per 100 person years.

Table 2.1 presents a summary of the total retention of ART programs as indicated by few

Table 2.1: Summary of a few South African studies between 2004 and 2007 which show loss to follow up and total retention. All the figures are given in percentages except the follow up which is given in months.

Study site	Follow up months	Died	Stopped ARVs	LTFU	attrition	retention	References
Gugulethu	12.3	6.8	-	2.9	9.7	90.3	[96, 44]
Multiple places	18.7	5.0	-	25.1	30.1	69.9	[96, 103]
Khayelitsha	13.9	13.2	3.0	0.3	16.5	83.5	[96, 43]
Multiple places	19.5	5.4	-	25.4	30.8	69.2	[96, 104]
Lusikiski (hospital)	12.0	13.5	-	19.3	32.8	67.2	[96, 105]
Lusikiski (clinics)	12.0	16.8	-	2.2	19.0	81.0	[96, 105]

South African studies. The follow up months range from 12.0 to 19.5 months. The percentages of individuals who are still retained at the end of the program gives the retention rate. The percentages of LTFU indicate the percentage of individuals who are neither dead nor still on ART program, except for the Khayelitsha site as 3% from this site have stopped ARV. Though it is difficult to be certain about which program has high retention with each study having different duration of study, Gugulethu site has a retention of 90.3% (for a study follow up period of 12.3 months) as compared to a 67.2% retention level at Lusikiski hospital (for a 12.0 month follow up period). On contrary, Lusikiski hospital has high LTFU as compared to Gugulethu site. Usually it is assumed that programs with high retention are effective. Note that Lusikiski has two data sets; one for the twelve clinics and the other for the town hospital. In all health centers of Lusikiski, individuals were followed for a similar duration of 12 months.

2.3   Switching to second-line

In a South African public ART program (2000-2008), treatment failure rate was 4.5 per 100 PYRS (equivalent to 9.9% failure over median follow up of 16 months (IQR: 12-23)). Overall, within 5 years on ART, 10.1% have switched to second-line therapy [106]. When first generation drugs fail to suppress the viral load, patients will switch to second generation drugs, commonly referred to as second-line treatment. In another study [107], 14% of the patients had failed virologically by the end of five years and 12.2% had switched to second-line therapy with an average delay of about 5.3 median months (IQR: 2.2-11.2) in the first-line. These

show that a substantial number of patients may need second-line treatment as the program matures. The backlog of those not able to switch treatment regimen may arise from program management problems as well as from extended duration of programs. As a result many patients might stay on first-line regimen for longer periods without switching [41]. In this study, it was shown that 3.7% and 17.9% of adults were on second-line at two and four years on ART, respectively.

WHO recommends switching therapy when viral load is persistently above 5000 cells/mm^3 [108]. In some cases, patients may continue first-line treatment even after failure, which might be due to resource limitation. The median time for switching to second-line after failure was 4.6 months (IQR: 2.1-8.7) from International Epidemiological Databases to Evaluate AIDS (IeDEA) data in South Africa [106]. By the end of 2010, rates of switching to second-line were very low, only 3% of patients in resource-limited settings (excluding the Americas) [109]. In [110], the rate of switching was shown to be different for different drug types, though not significantly different. The rate of switching was 2.8%(2.1-3.7), 2.4%(2.1-2.7) and 2.9%(2.0-3.9) for Zidovudine, Stavudine and Tenofovir, respectively.

Table 2.2: Summary of characteristics of ART programs in South Africa included in the IeDEA analysis [111].

Study site	Start of program	switching (%)	rate of switching (per 100 PYRS)	Routine viral load testing	Patients with viral load test (%)
Gugulethu, Cape Town	2002	23	1.8	Yes	89
Khayelitsha, Cape Town	2001	45	2.4	Yes	95
Themba Letu, Johannesburg	1999	97	6.5	Yes	60
PHRU, Soweto	2004	2	0.8	Yes	88

A study conducted in KwaZulu Natal, South Africa shows that 80% of patients with failure of a first-line treatment had ARV drug resistance [112]. Viral load and treatment failure thresholds vary. In [113], HIV positive individuals' viral load is considered to be high when greater than 1000 copies/ml. And treatment failure, which usually needs a change of the drug regimen, is defined as two consecutive high viral loads. At the end of 2011, 6296 patients from Ubuntu clinic in Khayelitsha, South Africa, were receiving ART of which 7.4% (463) were on second-line ART. In South Africa an estimated 14% of patients experienced

laboratory virological failure and 12% were switched from first-line to second-line treatment after 5 years on ART [113].

The benefits and effectiveness of ART could be limited with HIV-1 transmitted drug resistance (TDR). The Africa Centre which hosts a large demographic and health surveillance in KwaZulu Natal, South Africa, showed that TDR rate in 2002 was 6.67%(3.09% - 13.79%) where the levels returned to less than 5% after 2002. It did not show statistically significant increase between 2002 and 2010 [114]. Second-line treatment failure is also becoming a challenge. Treatment failure was shown to be 12% in first-line [115], where second-line treatment failure is shown to be as high as 33% [115] and 40% in South Africa [116].

In Gabon, the overall rate of virological failure was 41.3% (36.4%-46.4%) where a total of 375 patients were enrolled between March 2010 and 2011[117]. The median time on ART was 33.6 months (range, 12-107). We also see high first-line treatment stop in developed nations. A study which describes the rates and predictors of discontinuing first-line ART was done in British Columbia between 1992-2010 [118]. The study shows that discontinuation rates of first-line ART have decreased over time. However, the rates were still high with recent era (2006-2010), where discontinuing at 12, 24, and 36 months was 36%, 47% and 53%, respectively. The main predictors were younger women on PI regimen, and those not achieving optimal adherence.

2.4   Trends of the cost of ARVs

With programs growing, per patient costs usually drop rapidly [119], mainly because patients share similar facilities, such as building and nurse staff. It could also be due to reduction of the cost of the drug itself [120]. In Botswana, Ethiopia, Nigeria, Uganda, and Vietnam, nearly two-thirds of ART cost is spent on ARV drugs. The rest is spent on personnel, management, building costs and other costs. However, data from Clinton Health Access Initiative (CHAI) suggests that ARVs could cost nearly 50% of the entire cost [121]. The mean cost of HIV treatment per patient per year for programs in Malawi, Ethiopia, Rwanda, Zambia and South Africa are $136, $186, $232, $278 and $682, respectively. The median per-patient costs in successive 6 months is presented in Figure 2.2. The figure shows that per-patient cost

declines in successive periods.
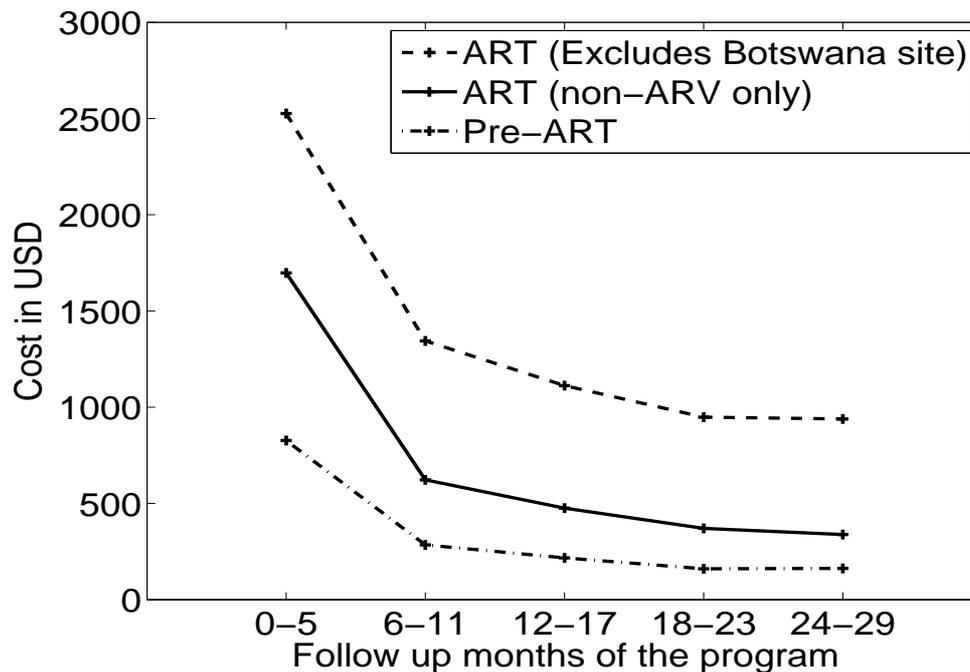
Figure 2.2: Change in median per-patient financial costs in successive 6 month periods, from start of HIV treatment scale up in each site through 2006-2007 (2009 US$) [119]. The median was calculated for Botswana, Ethiopia, Nigeria, Uganda and Vietnam.

Médecines Sans Frontières (MSF), which is an international, independent, and medical humanitarian organization, provides medical assistance to people affected by different epidemics. For example, in South Africa, it has been assisting in response to HIV and TB epidemics since 2000. This pioneering organization put the first patient on ARV treatment in May 2001 in Khayelitsha, South Africa [120]. According to records of MSF [120], prices of HIV drugs has dropped by more than 99% over the last decade. Prices of first-line TDF/FTC/EFV (1 pill once a day) dropped from $487 (June 2007) to $158 (June 2013) per patient per year (see, Figure 2.3). Similar reduction in the first-line drugs were observed for TDF/3TC/EFV (1 pill once a day) and AZT/3TC + EFV (1 pill twice a day + 1 pill once a day) over the last seven years from $426 to $139 and $410 to $158, respectively. However, in some cases patients need the latest drugs, which are usually expensive [122]. In South Africa, with the old treatment guidelines (before the WHO 2010 guidelines), individuals were given d4T as first-line regimen and it costs 3520 South African rands(430 USD, July 2012 exchange rate, for the first six months of ART) and 5151 rands (629 USD, July 2012 exchange rate) for the rest of the drug

regimen. With similar guidelines, either TDF or AZT regimen could be much more expensive (see the summary in Table 2.3). This makes it difficult to estimate the overall increase or decrease of HIV drug cost. As in the first-line, prices of the second-line have also declined dramatically, $1,198 (2006) to $303 (2013) per patient per year [120].
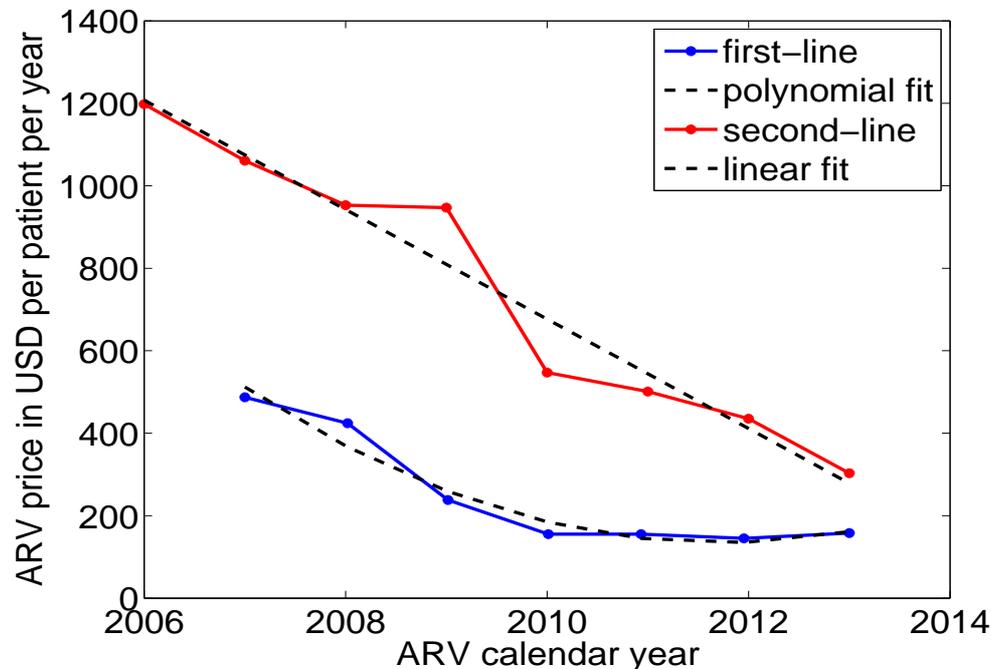
Figure 2.3: Data showing the price decrease for the first and second-line regimens as per WHO recommendations [120]. However, their data show different kind of first-line regimen, here we only show TDF/FTC/EFV (1 pill once a day) regimen.

Table 2.3: Cost of providing ART per patients per year [122]. Cost of ARV drug, staff, VCT and pre-ART care for eligible patients are included in the cost calculation except inpatient cost. All costs are in South African rand (2009).

Cost per patient per year	Old guidelines - d4T	2010 WHO guidelines - TDF	2010 WHO guidelines - AZT
First-line, first 6 months	3,520	4,320	3,302
First-line, after 6 months	5,151	6,126	5,393
First-line, failure	5,281	6,149	5,423
Second-line	11,747	8,740	9,471

2.5   Cost-effectiveness analysis studies

Averting new HIV infections is the main motivation for starting treatment early (possibly at higher CD4 cell count) in a treatment as prevention program [38]. The benefits are large, approximately seven DALYs per one HIV infection averted. Different studies [66, 123, 124, 125, 126] have considered different cost-effectiveness ratios. Highly active antiretroviral therapy (HAART) was cost-saving for patients with AIDS in South Africa due to saving in hospitalization and other health expenditure. The incremental cost per life years gained ranges from $675 to $1,622 for two HAART prices [123]. HAART could cost $1631 per QALY gained for all HIV patients [124]. These incremental ratios could vary by region and country. In a study which covered many developing countries, incremental cost-effectiveness ratios (ICER) were found to vary from $547 to $5175 per DALY [66]. ICER calculates the increase in the cost needed for a new intervention per the change of outcome intended. Moreover, cost-effectiveness ratios could vary depending on the full package, on whether routine viral load or CD4 cell counts were measured or not. In a study in Cote d'Ivoire, cheaper ART therapy (without CD4 testing) costs $620 per life year gained [125]. However, it could cost nearly twice as much ($ 1180 per life year gained) if ART initiation decision incorporated CD4 test results. The same difference in the cost-effectiveness ratio is observed in other resource-poor settings based on the full package of ART and the kind of drug regimen used [126, 127]. ART with only first-line ARV regimen would cost $628 per QALY, while $238 additional cost might be needed for an ART program with CD4 monitoring. And a huge further additional of $16,139 could be needed for viral load monitoring [126]. Recent modeling study examined expanding ART initiation to CD4 cell count < 350 cell count for South Africa [127]. Stavudine one regimen could cost $610 per year of life saved (YLS), whereas $1,140 and $2,370 is the cost of Tenofovir one regimen and Tenofovir two regimen, respectively. Another study which looked at effectiveness and ICER ratios presented the lost opportunity of immediate ART [128]. They compared immediate versus CD4-based, where the thresholds are quite different from those used by many as some are able to initiate ART even above the threshold stated making more realistic. In the immediate scenario, 15.1% of males and 22% females initiate ART immedi-

ately after tested HIV positive extrapolated from 2004 to 2014 and after 2014 37.8% males and 55% initiated ART. In the CD4-based at 2008 the majority initiate when CD4 < 200 (few still with CD4 >200) and changed to a threshold to 60% of those with CD4 < 200, 40% of those with CD4 between 200 and 350 and 10% of those with CD4 > 350. It was shown that immediate treatment could have saved 500,000 deaths and averted 401,000 from 2004 to 2014. Compared with no AR, the ICER ratios for the same period was estimated to be $3,712, $3,553 and $835 per HIV infections averted, HIV deaths averted and QALYs gained, respectively.

Cost-effectiveness varies greatly between interventions. Male circumcision is a procedure which has lifelong protective benefit. As a result it has a smaller cost-effectiveness ratio (CER) and hence regarded as highly cost-effective. A study estimated a CER of $181 for providing male circumcision service per HIV infection averted [129], because the cost of providing one male circumcision (including every cost) was estimated to be $55 [129, 130]. Mass media campaign could also be regarded as highly cost-effective intervention. ICER value of $58 per HIV infection averted or $3 per DALY [66] was estimated when mass media is considered as intervention mechanism, whereas, ART programs are costly even if the drug cost has shown a gradual decline in recent years [131, 132]. This is because ART is a life-long intervention strategy whereby individuals have to be on treatment for the rest of their life. In [67], the ICER value through the use of ART and no ART was $1,102 from a cohort followed for a maximum of four years on ART. Similarly, in another study, ICER values of $4937 and $3057 per QALY gained were presented in [133] for late (CD4 less than 200) and early (CD4 200-350), respectively, as compared to no preventive therapy. The reference scenarios were, however, different for these studies. The weighting for the quality of life assumed in their study was 1, 0.7, 0.85, and 0.8 for the following disease status: no sickness early (CD4 200-350), TB or opportunistic disease, no sickness late (CD4 less than 200), and no sickness on ART, respectively. A study examined whether if early ART is cost-effective in a generalized epidemic like South Africa, changing threshold of CD4 < 350 to CD4 < 500, changed the ICER from $273 to $1691 per DALY averted over 20 years [134]. Whereas all versus CD4 < 350, the ICER ranged from $438 to $3790 (from all the seven South African models discussed). These show that early ART is cost-effective as the ICER per DALY is less than South Africa's GDP per capita ($8040).

WHO has developed a metric to help decision makers. If ICER for DALY is less than GDP per capita, the intervention is considered to be very cost-effective. If less than three times GDP it is cost-effective, otherwise it is considered as not cost-effective [135]. This metric is widely used in health economics.

In this chapter we have reviewed a few studies in the area of our interest. In the following chapter we will be defining some terminologies which will be used frequently. Additionally, we will show the algorithm to calculate the distribution of CD4 cell count as derived by [54].

Chapter 3

Mathematical concepts and definitions

In the previous two chapters we have discussed the background of the study and reviewed some studies. Here we present different mathematical concepts and definitions. We will use them frequently in the next few chapters. The algorithm for calculating the distribution of CD4 cell count which will be presented here will be used for the simulation part using matlab programing language.

3.1   Terminologies

- ART coverage is the ratio between the number of individuals receiving treatment at a point in time and the number of individuals who are eligible to receive treatment at the same point in time (it includes those who are currently on treatment).

- Adherence is defined as the act or condition of sticking to a drug regimen.

- Retention in care is defined as the fraction of patients who remain alive and in HIV care.

- Treatment failure: a broad term that describes failure of anti-HIV treatment to adequately control HIV infection. It can be virologic, immunologic or clinical failure. Poor adherence, drug-resistance and drug toxicity might be contributing factors for treatment failure.

- The incidence rate is the number of new cases per population at risk in a given time period.

- Prevalence is the proportion of a population found to have a condition (typically a disease). Here we refer to point prevalence, the number of persons with disease in a time interval (example, one year) divided by the number of persons in the population.

- CD4 cells or T-cells are a type of white blood cells that play a major role in protecting the body from infection. They send signals to activate the body's immune response when they detect "intruders", like viruses or bacteria.

- The HIV/AIDS treatment cascade is a way to show, in visual form, the numbers of individuals living with HIV/AIDS who are actually receiving the full benefits of the medical care and treatment they need. This model was first described by Dr. Edward Gardner and colleagues [136].
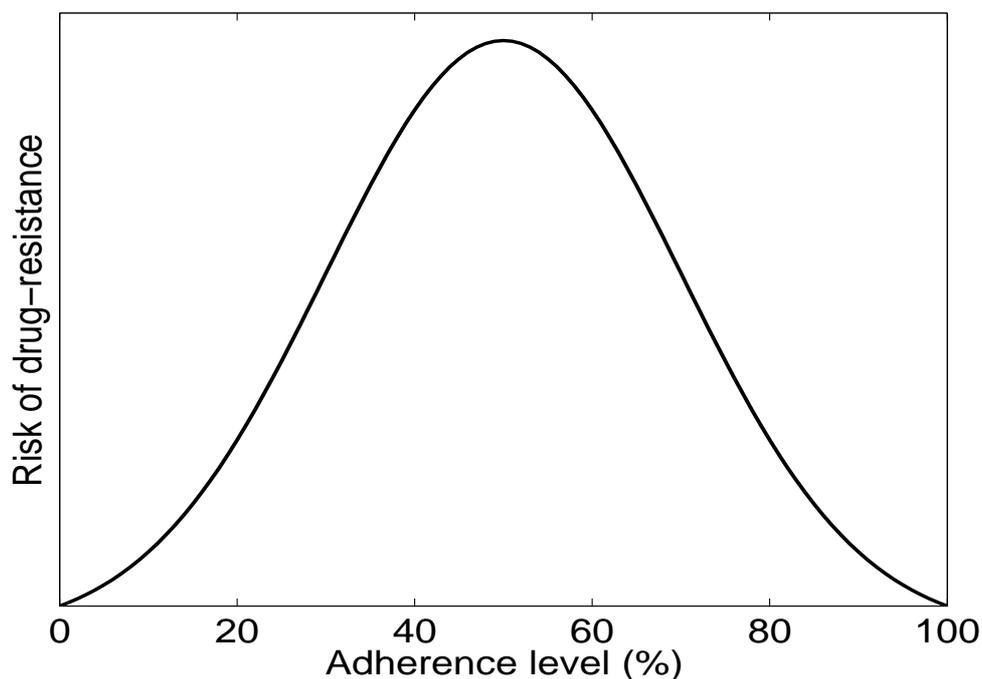
Figure 3.1: The risk of drug-resistance as a function of adherence level. 0 and 100% level of adherence shows no drug-resistance. This is mainly meant for illustration purpose, as we can not talk about drug resistance when individuals do not take any drug at all. Drug resistance increases with adherence level and then later declines. Here it is not entirely clear at what level of poor adherence highest risk achieved, and hence this is only for illustration purpose.

Figure 3.1 illustrates the relationship between adherence level and the risk of drug resistance. But it is not always the case to see lower risk of drug resistance with moderately higher adherence. It may depend on the kind of the drug regimen. Non-nucleoside reverse transcriptase inhibitor treated individuals rarely develop resistance at higher level of adherence due to virological effectiveness of these regimens. In contrary, single protease inhibitor treated individuals may develop resistance at high level of adherence [137]. In another study, virologic failure was shown to be related to the duration of viral suppression. Among individuals with moderate levels of adherence (80%-95%), the probability of virologic failure was 0.85 and 0.08 after being suppressed for 12 months and 72 months, respectively [138].

3.2   Health economic concepts

There are different methods for economic evaluation. Cost-effectiveness analysis (CEA), Cost-utility analysis (CUA) and Cost-benefit analysis, to mention a few. CEA compares two or more health interventions. The outcomes measured could be the number of lives saved, deaths averted, new infections prevented, or others.

Incremental cost-effectiveness ratio (ICER) is an important economic metric which encapsulates how much will need to be spent to buy additional health outcome relative to the competing alternative. If we have two intervention scenarios, intervention 1 and intervention 2, with corresponding outcomes, outcome 1 and outcome 2, then the incremental cost-effectiveness ratio, [139] takes the form:

$$\text{ICER} = \frac{\text{Cost of intervention 2} - \text{Cost of intervention 1}}{\text{Outcome of intervention 2} - \text{Outcome of intervention 1}} \tag{3.2.1}$$

The health outcomes may include: the number of HIV infections averted, the number of HIV deaths averted, disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs) gained.

The Commission on Macroeconomics and Health defined interventions [135] defined three broad categories of cost-effectiveness. Cost less than gross domestic product per capita are defined as *very cost-effective*; those averting each DALY at a cost between one and three times gross domestic product per capita are *cost-effective*; and the remainder are *not cost-*

effective. Therefore the ICER value for DALYs is used as a metric to decide whether an intervention is cost-effective or not.

3.3   Estimation of the proportion of individuals who become eligible for treatment

CD4+ Lymphocytes (CD4) are widely used to determine eligibility for initiating ART. They also help to monitor the response to therapy in HIV-positive patients.

CD4 cell count in HIV-negative individuals vary widely within and between populations [54]. This is influenced by many factors such as genetic, immunological, physiological and behavioral factors [54]. Due to these, countries' median CD4 for HIV-negative population varies a lot. Median CD4 cell count of 890/mm^3 (95%CI: 359-1954) and 725/mm^3 (95%CI: 114-1074) were observed in two sites of Malawi, Karonga (rural) and Blantye (urban) respectively [140]. CD4 cell count distribution might also vary by gender. In Central African Republic, a survey of a sample of healthy adult population showed a median CD4 cell count of 851 for males and 912 for females [141].

CD4 distribution of treatment eligible individuals in South Africa has substantially changed from 2000-2008 [142]. The study presented percentages of HIV +ve adults in different stages by year. The different stages include individuals who are: receiving ART, untreated AIDS, pre-AIDS - CD4 < 200, pre-AIDS - CD4 between 200 and 350, pre-AIDS - CD4 between 350 and 500 and pre-AIDS -CD4 > 500. The proportion of individuals at different stages such as untreated AIDS, pre-AIDS (for example CD4 < 200) have reduced. However, the proportion of individuals who are receiving treatment increases with the calendar time. This might be due to the fact that ART scale up has increased in recent years.

For the calculation of the distribution of CD4 cell counts, we implement the algorithm presented in [54]. The following are the model inputs:

- CD4 cell counts of HIV-negative individuals

- the decrease in CD4 cell count immediately after infection

Table 3.1: CD4 cell count distributions among HIV-negative and positive adults in Africa. The table is adopted from ([54], Table 1).

Group, location	Time	HIV prevalence	Median CD4 cell count		CD4 cell count (%)			
			observed	fitted	0-200	200-350	350-500	≥ 500
HIV-negative								
Addis Ababa, Ethiopia	1997-98	12	758	756 ± 49	0	1	11	88
Bandim, Guinea Bissau	1990-92	0.5	1000	1050 ± 134	0	1	4	95
Jos, Nigeria	2001-02	5		856 ± 78	0	0	1	99
Orange Farm, South Africa	2002	22	1116	1115 ± 27	0	0	1	99
Dar es Salaam, Tanzania	1988-97	14	797	796 ± 31	0	1	4	95
Kampala, Uganda	1991-92	28		1160 ± 116	0	0	1	99
Lusaka, Zambia	1999	35	780	792 ± 50	0	1	8	91
HIV-positive								
Addis Ababa, Ethiopia	1997-98	12	299	296 ± 42	26	34	19	20
Orange Farm, South Africa	2002	22	475	443 ± 41	18	26	19	37
Shirati, Tanzania	1993	13	657	598 ± 132	1	12	22	65
Dar es Salaam, Tanzania	1988-97	14	410	399 ± 25	2	33	40	25
Lusaka, Zambia	1999	35	330	327 ± 58	34	28	16	23
Harare, Zimbabwe	1993-97	20	345	341 ± 23	19	32	22	27

- the survival distribution after infection with HIV, assuming only that survival is independent of the pre-infection CD4+ cell count

- time trend of HIV prevalence

To make the reading easier for the readers, we present the whole algorithm of calculating the proportion of eligible individuals for treatment as it is presented in [54].

Estimating incidence from prevalence

Time trends in the prevalence of HIV infection, $P^*(t)$, were obtained by fitting logistic curves to data about the prevalence of HIV among women attending antenatal clinics. If no one died of AIDS, $I_0(t)$, the incidence of HIV at calendar time t would be equal to the time derivative of the prevalence, $P^*(t)$, so that

$$I_0(t) = \frac{dP^*(t)}{dt}. \tag{3.3.1}$$

To correct for AIDS-related mortality, we needed the survival distribution, $W(t)$, which we took to be a Weibull distribution function with median of 9.0 years and a shape parameter of 2.25 [143]. Then, $D(t)$, the probability (per unit of time) that people die t years after initial

infection, was

$$D(t) = -\frac{dW(t)}{dt}. \tag{3.3.2}$$

Because deaths reduce prevalence, we added deaths from previous incident infections to our initial estimate of incidence, so that

$$I(t) = I_0(t) + \int_0^\infty I(t - \tilde{t})D(\tilde{t})d\tilde{t} \tag{3.3.3}$$

(in equation (3.3.3) and below, t indicates calendar time, $\hat{t}$ and $\tilde{t}$ indicates time since seroconversion). $\hat{t}$ refers and takes any value of time after seroconversion till death. Whereas, $\tilde{t}$ is the time after seroconversion when death occurs. We solved equation (3.3.3) iteratively, because the integrand depended only on the incidence at times preceding time t. Mortality followed directly from incidence and survival.

Distribution of time since infection as a function of time

The number of people infected at time $\hat{t}$ before time t and surviving to time t was

$$N(\hat{t}|t) = I(t - \hat{t})W(\hat{t}), \tag{3.3.4}$$

so that the probability density function (PDF) of time since infection, $\hat{t}$, at time t was

$$P(\hat{t}|t) = N(\hat{t}|t) / \int_0^\infty N(\hat{t}|t)d\hat{t}. \tag{3.3.5}$$

CD4$^+$ cell count distribution as a function of time

We assumed that CD4$^+$ cell count decreases to a value C_i immediately after seroconversion and then decreases linearly with time [143] to a value of C_f when the person dies. We assumed initially that survival was independent of the pre-infection CD4$^+$ cell count [144, 145, 146]. To simplify the analysis, we scaled the CD4$^+$ cell count, C, to get a new variable ,c, where

$$c = \frac{C - C_f}{C_i - C_f} \tag{3.3.6}$$

so that, as C decreases from C_i to C_f , the scaled variable c decreases from 1 to 0. (We introduced c purely as a mathematical device to simplify the analysis; precisely the same final

result could be obtained without introducing this new variable.) Then, if a person dies at time $\tilde{t}$ after seroconversion, the scaled $CD4^+$ cell count c at time $\hat{t}$ after seroconversion is

$$c = 1 - \frac{\hat{t}}{\tilde{t}}. \tag{3.3.7}$$

Note that, $\hat{t}$ is always less than or equal to $\tilde{t}$, following the definitions provided above.

The probability density function of t could thus be given by $D(t)$, as defined in equation (3.3.2), so that the probability density of c, at time $\hat{t}$ could be given by $P(c|\hat{t})dc = D(\tilde{t})d\tilde{t}$. From equation (3.3.6), we then obtained

$$P(c|\hat{t}) = D(\tilde{t})\frac{d\tilde{t}}{dc} = D\left(\frac{\hat{t}}{1-c}\right)\frac{\tilde{t}^2}{\hat{t}}. \tag{3.3.8}$$

We also needed to allow for the distribution of the initial CD4$^+$ cell counts. Let the PDF of the CD4$^+$ cell count in HIV-negative people be $P(C_i)$. Then the PDF of the CD4$^+$ cell count among those people who seroconverted at time $\hat{t}$ before the present time could be given as

$$P(C|\hat{t}) = \int_0^\infty P(c|\hat{t})P(C_i)dC_i. \tag{3.3.9}$$

Finally, from equation (3.3.5), the PDF of the CD4$^+$ cell count in all HIV-seropositive people at time t was

$$P(C|t) = \int_0^\infty P(C|\hat{t})P(\hat{t}|t)d\hat{t}. \tag{3.3.10}$$

Distribution of survival at a given CD4$^+$ cell count

Consider an HIV-infected person whose initial scaled CD4$^+$ cell count is a, who seroconverted at time $\hat{t}$ before the present, and who dies at time $\tilde{t}$ after seroconversion. If their present scaled CD4$^+$ cell count is c, their present life expectancy (from the onset of infection) is $\tau = \tilde{t} - \hat{t}$,

where

$$\tau = \frac{c\tilde{t}}{a}. \tag{3.3.11}$$

The key result which we are interested in is the expression in equation 3.3.9. It will be frequently used in the expression which defines the rate at which individuals start HIV treatment as a function of time since infection. To achieve this, the incidence, calculated from the

derivative of the prevalence and the death rate (per unit time), calculated from the derivative of the survival function are used in the algorithm. In the expressions we attempted to show CD4 cell count distributions as a function of calendar time and time since infection.

Similar to the assumption in the formulation of the algorithm above, in this study we also assume that after HIV infection, the individual's CD4 cell count decreases immediately to a certain CD4 cell count, which we refer as initial CD4 cell count at HIV seroconversion. We consider a 25% immediate decline in CD4 cell count after infection. After seroconversion, we assume that CD4 cell count declines linearly. There are some studies which support both assumptions. CD4 cell count decreases significantly immediately after infection [147, 148]. For instance in the United States, men's CD4 cell counts decreased by 24% of the pre-infection level [147], and by 22% according study by [148]. Moreover, studies have shown that survival of patients is independent of CD4 cell count before seroconversion. And the rate of the decrease of CD4 cell count after seroconversion is linear [143, 149, 150].
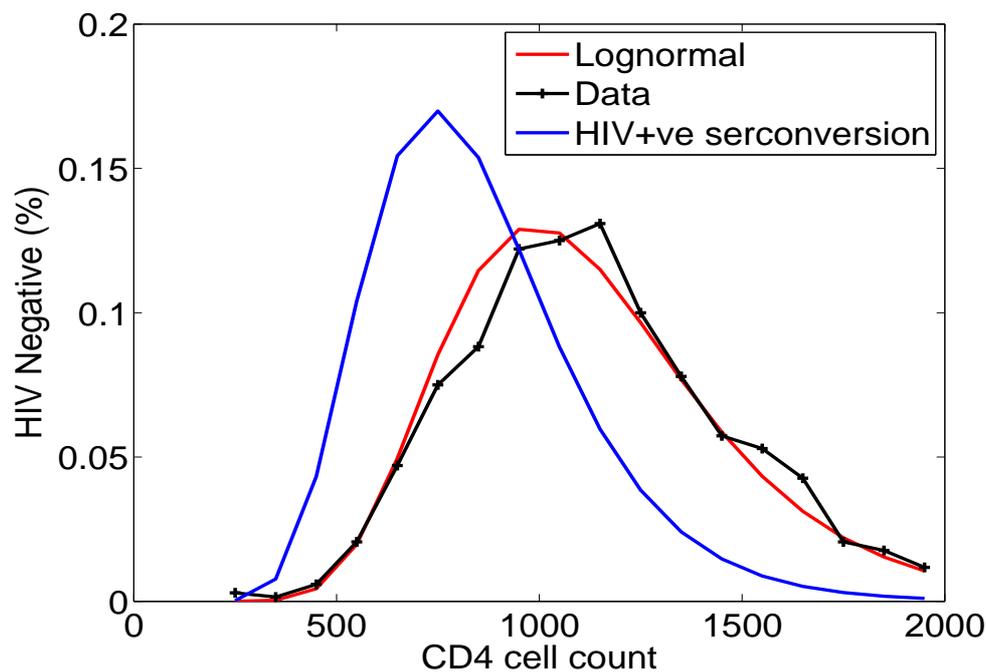
Figure 3.2: CD4 cell count distribution of South African population. It shows the distribution of HIV-negative population fitted (log normal) to a data from [54]. and the distribution of HIV-positive individuals who just got infected. Here we assume that CD4 cell count declines by 25% from HIV infection up to seroconversion.

Figure 3.3(a) shows distribution of individuals with different time since infection as a function of CD4 cell counts. The distribution for time since infection equal to one year is

(a) The area under the curve gives the proportion of individuals who survived up to the corresponding τ.

(b) CD4 distribution of HIV-positive individuals, normalized to the number of HIV patients having the corresponding τ. The area under each curve is equal to 1.
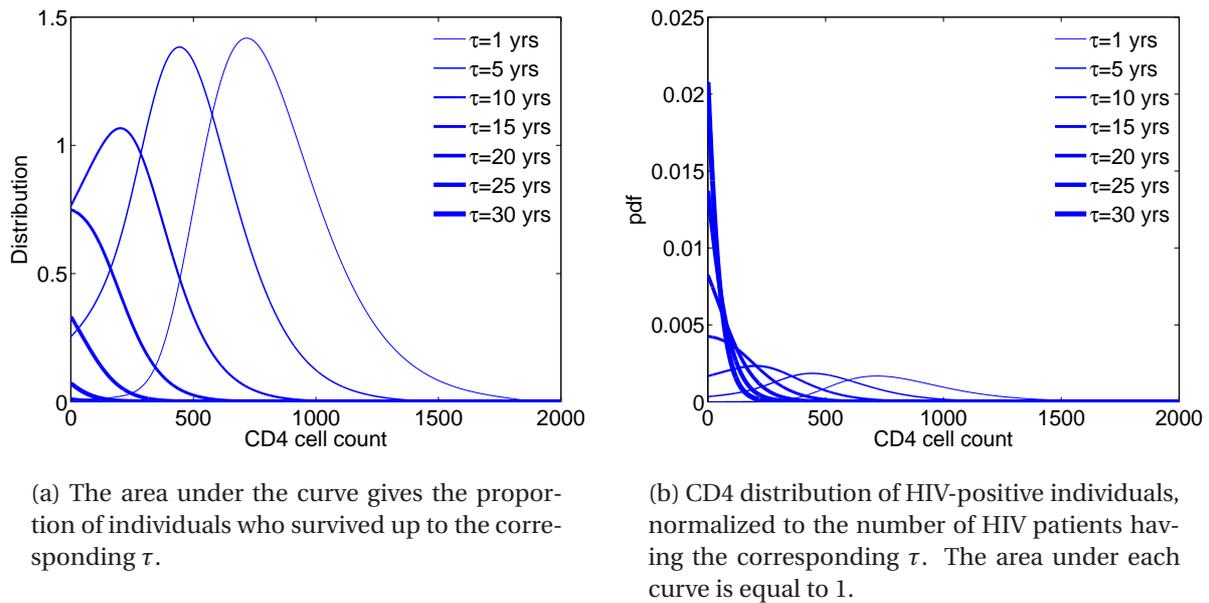
Figure 3.3: CD4 distribution of HIV-positive individuals. These are calculated using the expression (3.3.8).

similar to that of the distribution at seroconversion (Figure 3.2). However, for larger time since infection, the distributions become positively skewed (the peak shifts to the left). This shows that for longer time since infection, τ, the majority of individuals who survived will have fewer CD4 cell counts. Figure 3.3(b) is the same as that of (a) except that here we plotted the pdf. It is easier to see the proportion of individuals with certain CD4 cell count ranges.

Figure 3.4 is a different way to look at distributions. Here the distribution of the number of individuals for certain CD4 threshold is a function of time since infection. Evidently, the distributions become positively skewed as the threshold for ART provision increases. This agrees with our intuition. For higher ART initiation threshold the majority of individuals waiting for treatment will have smaller time since infection value. That is, the majority of those waiting for treatment could have been recently infected (having approximately 2 to 7 years of time since infection). One can also look at the τ value which gives the peak pdf value.

We consider four CD4 cell count scenarios for ART initiation: 200 cell count/mm^3, 350 cell count/mm^3, 500 cell count/mm^3 and ART initiation regardless of CD4 cell count. The distributions in Figure 3.4 shift to the left for higher CD4 cell count. This shows that more and more individuals could access ART at the early stage of the disease if the threshold for
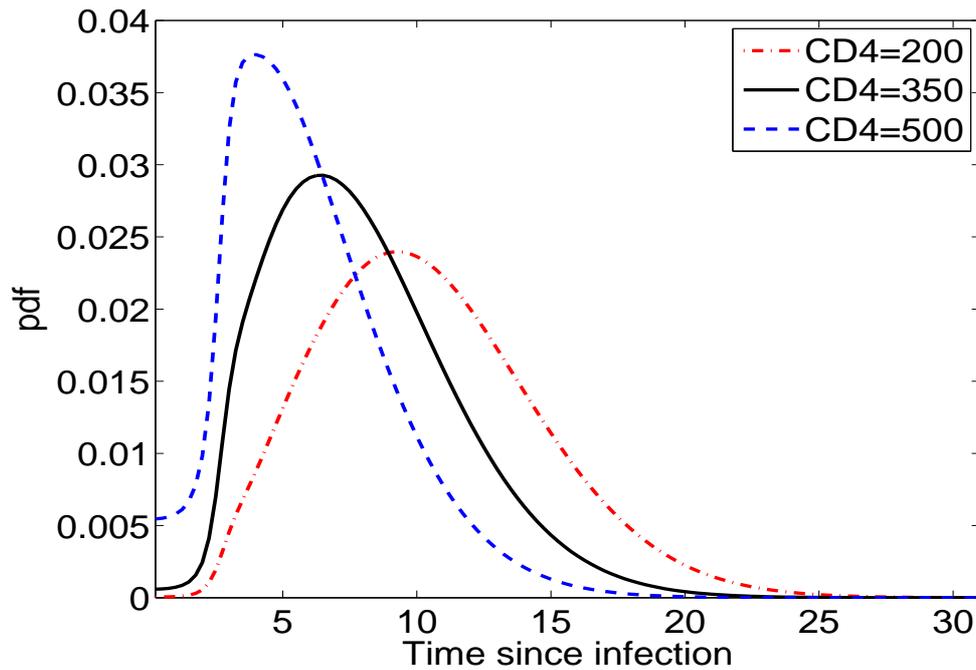
Figure 3.4: Probability density function of time since infection for different CD4 values by time since infection.

ART is higher CD4 cell count. This could also be displayed in another way as shown in Figure 3.5; the higher the CD4 cell count threshold, the more likely the patients will be eligible for treatment at an early stage (smaller τ) after HIV infection. For the last scenario, the proportion of individuals eligible for treatment is equal to 1 for each τ. It means individuals are automatically eligible, irrespective of their CD4 cell count. Therefore, we only show the other three scenarios. We will use the result displayed in Figure 3.5 more frequently in the expression for the force of HIV infection in the following chapters. It shows that the likelihood of accessing treatment for those individuals who were recently infected increases as the ART provision threshold is increased.
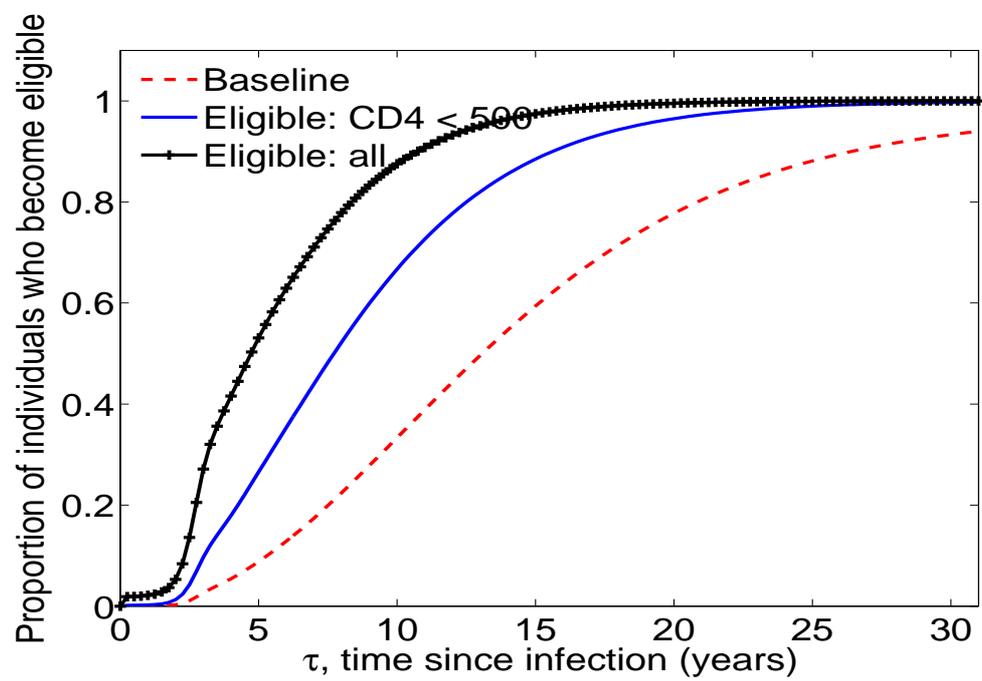
Figure 3.5: Cumulative fractions of individuals who are eligible for HIV treatment. This is calculated using the expression in (3.3.9).

Chapter 4

Modeling the impact of early HIV treatment

4.1   Introduction

In this chapter, we develop a basic mathematical model of HIV to study the impact of ART on HIV in South Africa. For this, we develop a basic mathematical model with ART that is structured by time since infection. We consider three different thresholds of ART initiation provision: baseline scenario, scenario '500' and scenario 'all'. In the baseline scenario individuals initiate ART at a CD4 cell count threshold of 200 cells/mm^3 before 2013, and from 2013 individuals initiate at a threshold of 350 cells/mm^3. In scenario '500' and scenario 'all', individuals initiate ART at 500 cells/mm^3 CD4 cell count threshold and irrespective of CD4 cell count, respectively. Scenario '500' and 'all' are ART scale up scenarios which we implement starting from 2016. Even if South Africa has changed the threshold of ART initiation from 350 to 500 CD4 count starting from January 2015 [36], because many challenges face the country with regard to drug delivery system and sufficient stock of ARVs, thresholds might not immediately implemented [151, 152]. Thus, we consider a threshold of 350 as a baseline.

To explore how ART provision threshold impacts the HIV epidemic in South Africa, we linked time since infection and CD4 cell count, due to the fact that CD4 cell count is usually used as a metric/threshold for eligibility of ART initiation. In chapter 3, we were able to use the mathematical expressions and algorithms from [54], which is a novel approach, to find

the distribution of individuals by time since infection. This helps to estimate the proportion of individuals who become eligible to treatment as a function of time since infection based on certain ART initiation thresholds. Other studies mainly worked with either CD4 cell count categories [128, 153] or HIV/AIDS stages as in [13]. The linkage of the algorithm by [54] with the time since infection structured model will also help us estimate the proportion of individuals below a certain time since infection or CD4 cell count using probability distribution function. Moreover, we can clearly see the distribution of time since infection of ART naive individuals, treatment eligible individuals and those who newly initiate ART evolving with calendar time.

4.2   Model formulation

We consider a scenario in which a population is sub-divided into three different disease states: susceptible, infected and treated. For this thesis we only consider the sexually active population (15-49) of South Africa as this age group is highly affected, and contribution for new HIV infections is significant. New sexually active individuals enter the susceptible class at a recruitment rate which we refer to as an adult recruitment rate (B). Susceptible individuals become HIV infected at a rate commonly known as the force of HIV infection (ϕ). Individuals who are already infected start treatment following an eligibility criteria based on a CD4 cell count threshold for ART initiation and HIV treatment access rate. That is individuals start HIV treatment at a rate $e(t, \tau)\pi(t)$, where $e(t, \tau)$ is the proportion of individuals who become eligible to receive ART under certain ART initiation criteria and $\pi(t)$ is the rate at which individuals access treatment among those who are eligible for treatment. $e(t, \tau)$ depends on calendar time (as eligibility threshold has changed over time) and with time since infection, because not everyone is eligible for a certain CD4 cell count threshold. Even though the world is moving towards eligibility for ART regardless of CD4 count, resource limitation, willingness of individuals and other factors may lead us to prioritize certain groups of individuals. Individuals who have been infected for a longer time are likely to seek treatment compared to those who have become infected recently.

To allow for a change of behavior or other external interventions, we let the HIV trans-

mission decrease with HIV/AIDS mortality rate and prevalence. The external interventions could include increased condom use, delayed age of sexual debut and fewer sexual partners. Whatever the reason for the decline of HIV incidence and gradual decrease of prevalence at later stage, we can add an external 'control' which lets the force of HIV infection decline over time. A similar approach is used by [154] to account for external intervention. Thus we have considered an exponential function, $e^{-(\alpha_1 M(t)+\alpha_2 P(t))}$, with α_1 and α_2 as scale parameters, and $M(t)$ and $P(t)$ are HIV mortality rate and HIV prevalence at a calendar time t, respectively. Similar approach for estimating the expression for the infection rate is also considered in [13, 154, 155].
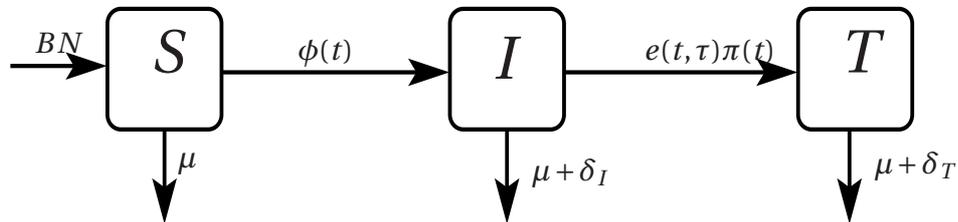
Figure 4.1: Model without treatment failure and dropout: flow diagram of a model for HIV dynamics. S, I, and T refer to the susceptible, infected and treatment class. The definitions of the parameters are given in Table 4.1.

System of equations:

$$\frac{d}{dt}S(t) = BN(t) - \left(\phi(t) + \mu\right)S(t),$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right)I(t,\tau) = -\left(e(t,\tau)\pi(t) + \mu + \delta_I(\tau)\right)I(t,\tau), \tag{4.2.1}$$

$$\frac{d}{dt}T(t) = \int_0^\infty e(t,\tau)\pi(t)I(t,\tau)d\tau - (\mu + \delta_T)T(t),$$

with boundary conditions,

$$I(t,0) = \phi(t)S(t).$$

Here $I(t,\tau) = 0$ whenever $\tau > t$. τ is time since HIV infection. The force of HIV infection is given as:

$$\phi(t) = e^{-(\alpha_1 M(t)+\alpha_2 P(t))}\left(\frac{\int_0^\infty \beta_I(\tau)I(t,\tau)d\tau + \beta_T T(t)}{N(t)}\right). \tag{4.2.2}$$

where $\beta_T = (1 - \eta)\beta$. β is average HIV transmission probability if individuals are not on HIV treatment, whereas η refers to the reduction in HIV infectivity as a result of HIV treatment.

$\int_0^\infty \beta_I(\tau)I(t,\tau)d\tau$ gives the contribution for new HIV infections of the infected class (I), which is the average infection rate by the infected individuals who are not on ART, $\beta_T T(t)$ represents the contribution from the treatment class (T).

Table 4.1: Definitions of parameters of the model described in Figure 4.1.

Symbols	Definitions of the parameters
B	per capita adult recruitment rate to the sexual active population
$\beta_I(\tau)$	HIV transmission probability of individuals in the infected class
β_T	HIV transmission probability of individuals in the treatment class
η	the reduction in infectivity as a result of HIV treatment
μ	natural exit rate from the age group 15-49 (either through non AIDS-related death or ageing)
$\delta_I(\tau)$	disease induced death rate of infected individuals
δ_T	disease induced death rate for individuals in the treatment class
N	the number of the total population, $N = S + I + T$

4.2.1   Model assumptions

To assess the impact of willingness of individuals to start treatment, we have assumed that seeking treatment is dependent on the person's health status (which can be linked with time since HIV infection). Thus, in this study it is modeled using the proportion of individuals who become eligible as a function of calendar time and time since infection. The rate at which individuals start ART among eligible people is a function of calendar time which determines ART access rate.

Studies have documented cost-effectiveness analysis of HIV/AIDS interventions in South Africa [12, 66, 67]. Some compared the incremental cost of HIV treatment by different CD4 cell count scenarios (CD4 <200, <350, <500, all CD4). Some looked at compartmental models, where individuals are grouped under certain CD4 category (50-100, 101-200, 201-350, 350 and above) [128, 153]. But in our study, we consider continuous distribution of CD4 cell count. This way the analysis will help us link time since seroconversion with CD4 cell count distribution; hence, distribution of individuals eligible for treatment will be estimated. Unlike many models [12, 14], in the model assumption for scenario 'all' (treatment scenario

irrespective to CD4 cell count) is a less intensive ART scale up scenario. For instance, a universal test and treat scenario was scaled linearly from 2012 reaching 90% coverage in 2019 [14]. Since not every individual can access HIV treatment due to resource limitation and the huge demand for ARVs and management, we assumed realistic and low ART access rate. We considered an ART access rate which increases logistically from zero value in 2001 to 0.52 per year around 2013 and stabilizes afterwards (see Figure 4.2). We will refer to as the 'current' access rate. We believe that these two components, eligibility criteria and ART access rate, will make the modeling more realistic due to resource limitation for ART programs and differences of willingness of individuals to start treatment immediately after diagnosis with HIV infection.

4.3 Model parameters

4.3.1 Eligibility criteria

We used an algorithm detailed in chapter 3 as formulated by [54] to estimate the distribution of the CD4 cell count of individuals by time since infection. The result was used to estimate the proportion of individuals who become eligible as a function of time since infection under a specific threshold of CD4 scenario, as in Figure 3.5 of chapter 3.

4.3.2 Adult access to ART

ART access rate over years has changed mainly because of two reasons. Firstly, this is due to the changes of treatment guidelines, and governments and donors commitments to meet the demand for ARVs. Secondly, it is due to an increased effort in the treatment cascade which helps to examine continuum of care and service delivery. Cascade helps identify the gaps between care and retention. The values of the ART access rate takes the shape of a generalized logistic function with constants described below (see Figure 4.2). The function we used is calendar year dependent smooth curve which stabilizes at 0.52/yr.

$$\text{ART access rate}(t) = \frac{K}{(1 + Qe^{-R(t - t_m)})^{1/v}}$$

where the constants attain the following values:

$K = 0.52$, $R = 0.61$, $V = 0.27$, $Q = 0.04$, and $t_m = 7.0$.
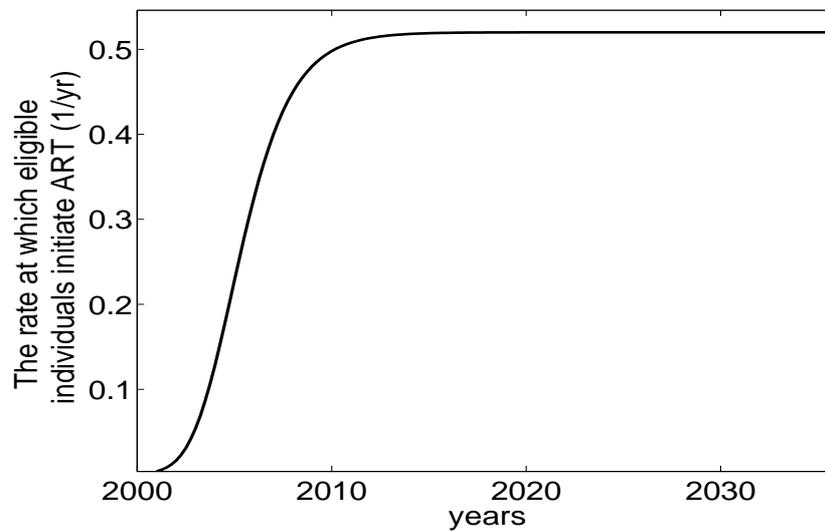
Figure 4.2: Rate at which individuals initiate treatment among those who are eligible.

4.3.3   Survival rate without HIV treatment

Survival times of HIV patients who are not on treatment vary by study site. In a study of South African miners, median survival was 11.6 years, whereas in an east African cohort it was 11.1 years; in Haiti 8.3 years and in Thailand 7.5 years [156]. In another study survival for those who are not on ART is assumed to follow a Weibull distribution with a median survival time of 10.2 ± 0.5 years and shape parameter of 2.28 ± 0.12 [143]. For this study we considered a Weibull distribution with median survival of 10 years and shape parameter of 2.2 (see Figure 4.3(b)).

No evidence of increased risk of HIV death was noted in individuals on ART who have undetectable viral load or whose CD4 cell count is above 500 cells/mm^3 compared to that of the general population [157]. However, here we consider mortality rate due to HIV for individuals in treatment. This is because we did not capture the effect of modest dropout cases or interrupted interventions which usually increase complications with the patients' health. Hence people may still die from the disease while they are on treatment. In [12] ART

dropout rate was the only mechanism used to account for the increase in mortality due to earlier ART initiation, to which we also applied the same approach.

4.3.4 HIV transmission probability

Different studies have published different values for relative reduction of infectiousness for individuals on ART. In [9], a 96% (95% confidence interval, 73%-99%) reduction in infectiousness was presented, while in [8], the relative reduction is 80%-92%. Different models used different values for the input value of reduction of HIV transmission due to ART [13, 52, 79], values from as low as 78% to 99%. For this study, we assumed that individuals in the treatment class are 90% less infectious compared to individuals who are not on ART and presented few selected key epidemic outputs for higher HIV transmission reduction (96%) for comparison purposes. Hence $\eta = 0.9$ was considered for the simulation results. We have used the expression below to smoothen the function of the variability of infectiousness of HIV positive individuals by time since infection comparing with the viral load curve for HIV by time since infection. The plot is given in Figure 4.3 (a). The following expression is used to estimate HIV transmission probability of individuals in the infected class:

$$
\beta_I = d_1 + (\beta^* - d_1)\frac{e^{k_1(\tau-t_1)}}{e^{k_1(\tau-t_1)} + e^{-k_1(\tau-t_1)}} + (d_3 - \beta^*)\frac{e^{k_2(\tau-t_2)}}{e^{k_2(\tau-t_2)} + e^{-k_2(\tau-t_2)}}
$$

where, $k_1 = 1, k_2 = 1, d_1 = 3.8\beta^*, d_3 = 2\beta^*, t_1 = 0.5, t_2 = 9$. k_1, k_2 and k_3 are shape parameters which determines the increase or decrease of infections of individuals with time since infection. β^* is the HIV transmission probability for individuals during chronic stage (see Figure 4.3 (a)). d_1 and d_3 refer to the relative infectiousness of individuals during acute and AIDS stage, respectively, with respect to chronic stage. t_1 is the time since infection at which chronic stage begins and t_2 is the time at which AIDS stage starts.

4.3.5 Adult recruitment rate

The population we considered is the adult population of South Africa from age 15 to 49. We used the following procedure to estimate the number of 14-year-old individuals who become 15-year-old (or join the sexual active population) per 1000 adult population (15-49).
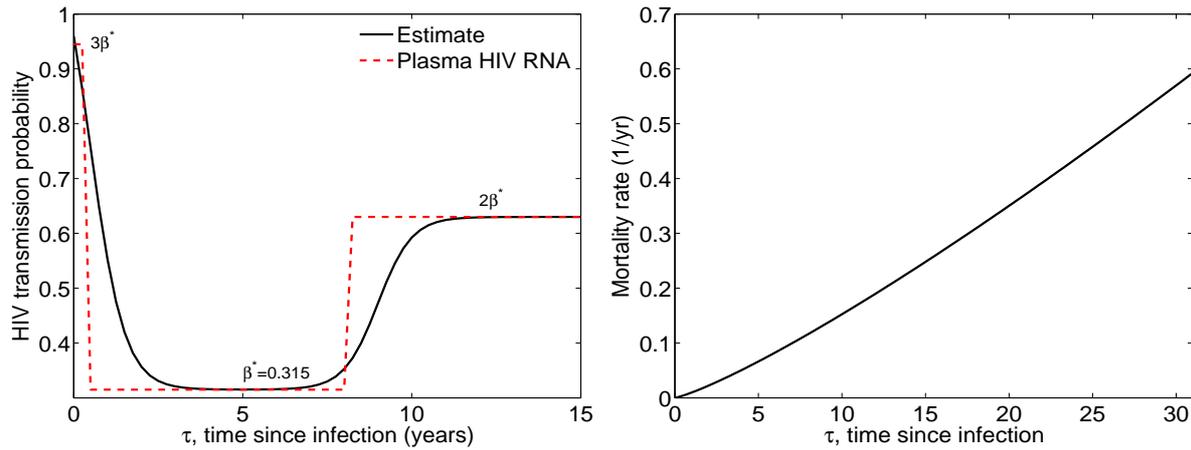
(a) HIV transmission probability as a function of time since infection.

(b) HIV mortality rate, using hazard of Weibull function [143] (also discussed in detail in section 4.3.3).

Figure 4.3: Parameter values used in the simulation. Estimates are for those who are not on HIV treatment.

The crude birth rate (CBR) of South Africa varies with calendar time (see Table 4.2). Additionally, due to variation of the data source, CBR values may even vary for the same year. Thus, we present values we obtain from different references. Table 4.2 shows the crude birth rate of South Africa from 2002 to 2014 according to estimates by statistics South Africa [158].

Table 4.2: The crude birth rate of South Africa from 2002 to 2014, all given per 1000 population.

Years	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
CBR	24.4	24.2	24.0	23.8	23.6	23.4	23.2	23.1	23.0	22.8	22.7	22.6	22.4

We need to select certain value for the crude birth rate and then calculate the adult recruitment rate using that value.

$$
\begin{aligned}
\text{CBR} &= \frac{\text{No. of births}}{\text{Total population}} = \frac{\text{No. of births}}{\text{population of the age 15-49}} \times \frac{\text{population of the age 15-49}}{\text{Total population}} \\
\text{CBR} &= \text{CBR}_{\text{Age15-49}} \times \frac{\text{population of the age 15-49}}{\text{Total population}},
\end{aligned}
$$

$$
\text{where, } \text{CBR}_{\text{Age15-49}} = \frac{\text{No. of births}}{\text{population of the age 15-49}} \tag{4.3.1}
$$

Thus, we have the following:

$$\text{CBR}_{\text{Age15-49}} = \frac{\text{CBR}}{\dfrac{\text{population of the age 15-49}}{\text{Total population}}} \tag{4.3.2}$$

Table 4.3: South African population by age group for 2003 [159].

Age groups	Population by age group	% from the total population	Cumulative percentage
0–4	4,436,683	0.096	0.096
5–9	4,898,700	0.106	0.201
10–14	5,190,005	0.112	0.313
15–19	5,263,274	0.113	0.426
20–24	4,392,357	0.095	0.521
25–29	4,100,416	0.088	0.609
30–34	3,422,110	0.074	0.683
35–39	3,216,513	0.069	0.752
40–44	2,794,291	0.060	0.812
45–49	2,241,976	0.048	0.861
50–54	1,779,225	0.038	0.899
55–59	1,249,427	0.027	0.926
60–64	1,127,147	0.024	0.950
65–69	795,652	0.017	0.967
70–74	691,433	0.015	0.982
75+	830,614	0.018	1.000
Total population	46,429,823		
% of 15-49	0.5477		

From Table 4.3 approximately 55% of the South African total population are adults between 15 and 49-year-old. From the data above (Table 4.2) the CBR can take any value between 22.4 and 24.4 per 1000 population. Using the formula mentioned in (4.3.2), we can find the following range for CBR$_{\text{Age15-49}}$.

$$\text{CBR}_{\text{Age15-49}} \quad \in \quad \left[\frac{22.4}{0.55}, \frac{24.4}{0.55}\right].$$

$$\text{CBR}_{\text{Age15-49}} \quad \in \quad [40.73, 44.36]. \tag{4.3.3}$$

We can estimate the mortality rate of the age group 0-14 (μ_{0-14}) using the data from Table 4.4.

Table 4.4: Estimation of mortality rates by age groups for South African population in 2001[160].

Age group	0-1	1-4	5-9	10-14	15–19	20–24	25–29	30–34	35–39	40–44	45–49
Population size	908,406	3,541,409	4,853,555	5,061,917	4,981,721	4,294,523	3,934,939	3,340,901	3,071,770	2,619,465	2,087,380
Mortality rate per 1000	45.93	6.68	1.40	0.97	2.23	5.88	9.84	11.74	11.69	11.37	12.53

$$\mu_{0-14} = \frac{\sum_1^n \mu_i P_i}{\sum_1^n P_i}, \tag{4.3.4}$$

where μ_i is the mortality of the sub-age group i in the 0 to 14 age group and P_i is the respective population size for the sub-age group i),

$$\mu_{0-14} = \frac{45.93 \times 908406 + 6.68 \times 3541409 + 1.40 \times 4853555 + 0.97 \times 5061917}{908406 + 3541409 + 4853555 + 5061917}$$

$$= 5.36 \text{ per 1000 population.}$$

For a value of CBR in the range (4.3.3), the corresponding adult recruitment rate is given by:

$$B = e^{-\mu_{0-14}*15} \times \text{CBR}_{\text{Age15-49}}$$

The expression $e^{-\mu_{0-14}*15}$ gives the proportion of individuals who survived up to the age of sexual debut (15-year-old).

$$B = e^{-0.00536*15} \times 40.73 = 37.58, \text{ for } 40.73$$

and

$$B = e^{-0.00536*15} \times 44.36 = 40.93, \text{ for } 44.36$$

Therefore the adult recruitment rate could lie in the range $[37.58, 40.93]$ per 1000 adults (15-49).

When we use a different source we find different values for the CBR. From [161], according to the demographics of South Africa, CBR could be as low as 20.5 per 1000 population in 2013. But we see higher values for years before 2000. For example, from 1995 to 2000 the average CBR was assumed to be 25.1 per 1000 population. Therefore, using a similar procedure as above the adult recruitment rate could lie in a range $[34.39, 42.11]$ per 1000 adults (15-49).

Using the data from Table 4.4, the average mortality of individuals in the age group 15-49 can be calculated using the formula (4.3.4).

$$\mu_{15-49} = \frac{2.23 \times 4981721 + 5.88 \times 4294523 + 9.84 \times 3934939 + 11.74 \times 3340901 + 11.69 \times 3071770 + 11.37 \times 2619465 + 12.53 \times 2087380}{4981721 + 4294523 + 3934939 + 3340901 + 3071770 + 2619465 + 2087380}$$

$$\mu_{15-49} = 8.469 \text{ per 1000 population.} \qquad (4.3.5)$$

Table 4.5: Total number of deaths (all causes), and numbers and percentages of AIDS related deaths for the period 2002-2014 [162].

Year	Total number of deaths (all causes)	Total number AIDS related deaths	% of AIDS related deaths
2002	631,383	275,444	43.6
2003	667,902	313,477	46.9
2004	697,473	344,141	49.3
2005	716,083	363,910	50.8
2006	694,227	343,194	49.4
2007	647,827	297,659	45.9
2008	617,202	257,504	41.7
2009	590,322	228,051	38.6
2010	578,953	213,864	36.9
2011	580,460	211,839	36.5
2012	575,546	203,293	35.3
2013	565,310	189,376	33.5
2014	551,389	171,733	31.1

We know that this mortality rate is over estimated as it does not consider the excess mortality due to HIV/AIDS. We followed some steps to estimate the excess mortality due to HIV by the group. From Table 4.5, we see the proportion of deaths attributed to HIV/AIDS by calendar year. Age specific HIV deaths are usually high for the adult age group. Let us assume that 40% of deaths are due to HIV/AIDS. Thus, the natural mortality rate for the group becomes $0.6 \times 0.008469 = 0.0051$. Now we are left with estimating the rate at which 49-year-old individuals exit the age group 15-49.

The proportion that exit the age group 15-49 due to ageing we refer to as μ_a, calculated using:

$$\mu_a = \frac{N_{49}}{N_{15-49}}, \qquad (4.3.6)$$

where N_{49} refers to the population of individuals who are 49-year-old and N_{15-49} refers to the total population in the age group from 15-49 in the same year. From Table 4.4, the population size in the age group 45-49 is 2,087,380. Assume that the number of individuals who are 49-year-old is one-fifth of the population in the age group 45-49 (for easy calculation and estimation). Then, the number of individual who are 49-year-old (N_{49}) is 417,476. In addition, the total number of individuals in the group can be found by adding the populations in the respective age groups.

$$
\begin{aligned}
N_{15-49} &= 4,981,721 + 4,294,523 + 3,934,939 + 3,340,901 \\
&+ 3,071,770 + 2,619,465 + 2,087,380 = 24,330,699
\end{aligned}
$$

Therefore, the proportion that exit the age group 15-49 will be:

$$
\mu_a = \frac{417,476}{24,330,699} = 0.0171.
$$

Finally, the total exit rate without including HIV/AIDS attributed deaths from the age group 15-49 is the sum of exit due to the ageing rate and natural death rate. i.e. $0.0171 + 0.0051 = 0.0222$. Please note that the adult recruitment rate we considered is constant independent of calendar year.

Table 4.6: Summary of parameter values used in the simulation.

Parameter	Value	Remark
B	0.036/yr (0.034-0.042)	explained in the parameter discussion section
μ	0.022/yr	explained in the parameter discussion section
η	0.1	using results from [8, 9]
δ_T	0.02/yr	assumed
β	0.267/yr	estimated using per sexual contact transmission probability

4.4 Simulation Results

In this section, we present simulation results of the time since infection structured mathematical model. For the simulations we took the sexually active population of South Africa.

We have the following initial conditions and main inputs for the model simulation. We numerically solved our system of differential equations in the form finite difference scheme solved by Euler's method. We have used smaller step size, $dt = 0.25$ years, to decrease the Euler error. Matlab 2010 version is used for simulating all the results. The following are the initial values, initial time for the simulation and events with ART scale up scenario.

t0=1950: the starting year for the simulation

tf=2036: the final year for the simulation

tHIV=1982: the year when HIV is introduced to the population

N0=13,350,000: initial adult population of South Africa (in 1950)

tART=2001: the year when ART roll out started

tART350=2013: is when the 2013 ART guidelines started implementation

tARTScale=2016: year when ART scale up scenarios start

4.4.1   Clinical and epidemiological outcomes

The model is fitted with data from HSRC [27], which estimated adult(15-49) HIV prevalence of 15.6% (13.9%-17.6%) 16.2%(14.9%-17.7%) 16.9%(15.5%-18.4%) and 18.8%(17.5%-20.3%) in 2002, 2005, 2008 and 2012, respectively (as it is shown in Figure 4.4). Our model projection shows that HIV prevalence might reduce to 10% in 2036 if treatment is provided early irrespective of individuals' CD4 cell counts. But we see a gradual decline of HIV prevalence with the baseline scenario. This gradual decline of HIV prevalence is due to the fact that millions of individuals are receiving ART which prolongs their survival and new infections which occur with less inclusive CD4 cell count criteria (i.e. the baseline scenario) are higher than the new infections which occur with scenario 'all'. Thus, the HIV prevalence stays at a fairly high level.

The curve for the incidence rate reaches its peak in 2000, before the peak of that of the HIV death rate (see Figure 4.5). The incidence rate could go down to approximately 0.3% in 2026 (ten years through the time horizon), if individuals access treatment irrespective
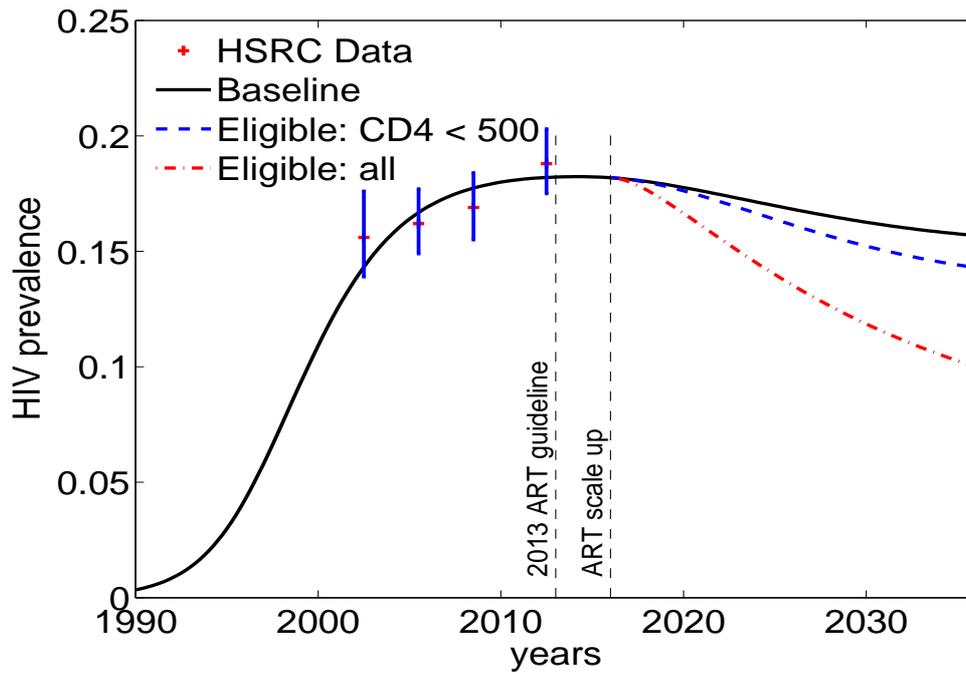
Figure 4.4: HIV prevalence graphs: The figure presents the prevalence of HIV for three ART initiation scenarios. All the graphs of the model projections show a similar trend of decline but more gradual decline of HIV prevalence for baseline and scenario '500' as compared to scenario 'all'. The confidence intervals are from HSRC data [27].

(a) HIV incidence rate   (b) HIV death rate
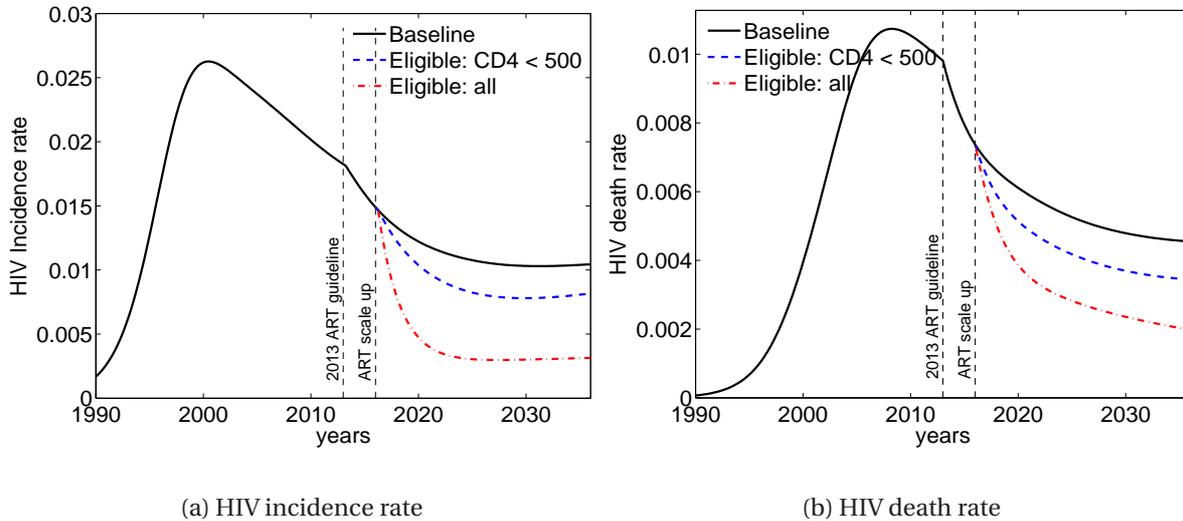
Figure 4.5: HIV incidence and death rates for different ART scale up scenarios. The incidence rate graph for the baseline scenario declines starting from 2000. Further decline is seen in 2013, with implementation of 2013 ART guideline. Moreover, HIV infection drops most sharply with higher ART use due to more inclusive CD4 cell count criteria. The graphs of HIV death rate show the impact of expanded ART.

of their CD4 cell count as compared to a 1.1% and 0.8% incidence level if ART initiation

continues with the baseline scenario and to scenario '500', respectively (see Figure 4.5(a)).

Similarly, in 10 years the HIV death rate could be reduced to 0.28% (which showed a slight increase in 2026 and stabilized later) and 0.4% for scenario 'all' and scenario '500', respectively as compared to a higher HIV death rate of 0.5% if we keep the baseline scenario (see Figure 4.5(b)). The confidence intervals for HIV incidence estimates by HSRC [27] are wide making it difficult to include them as it easily distorts the scale of the graph. Additionally, the estimates are for periods, not for a specific year. Therefore, unlike HIV prevalence estimates, we decided not show the confidence interval on the graphs but only discussed it in a text. HIV incidence in the 15-49 age group is estimated to be 2.2% (0.9%-4.0%), 1.9% (0.8% -3.3%) and 1.9% (0.8%-3.1%) for the periods 2002-2005, 2005-2008 and 2008-2012, respectively [27]. However, from a similar survey by HSRC, we have HIV incidence estimate of 1.72%(1.38%-2.06%) in 2012. Our estimate is in line with these estimates, even though we have a point estimate and other estimates are estimates for periods of years.

(a) new HIV infections

(b) HIV related deaths
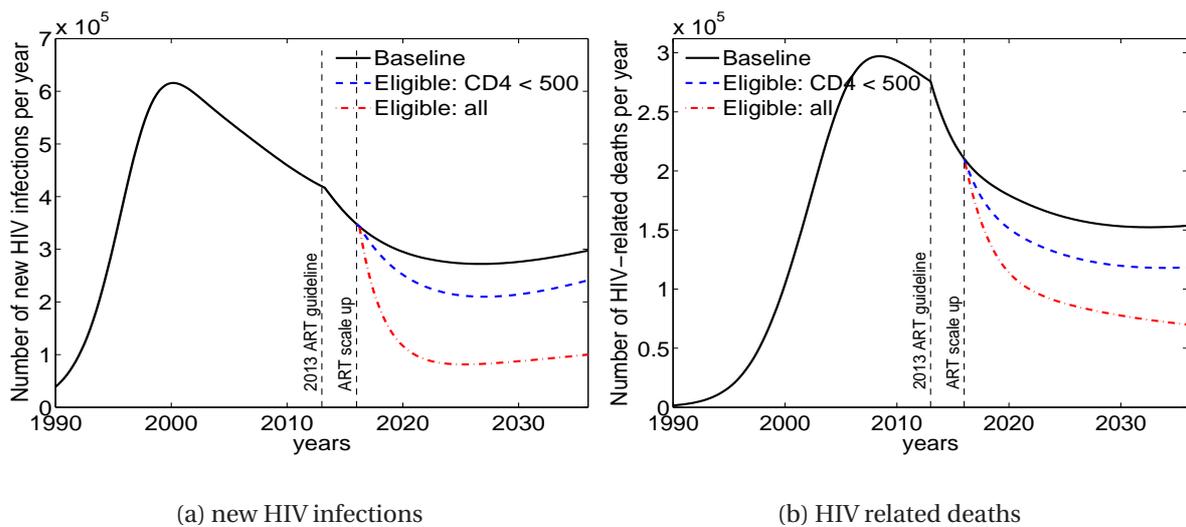
Figure 4.6: Key epidemic indicators by ART scenarios over time, for enhanced prevention scenarios from 2016-2036. a) shows the number of new HIV infections and b) the number of HIV-related deaths.

The plots in Figure 4.6 show the number of new HIV infections and HIV-related deaths per year for three different ART initiation threshold scenarios. The number of new HIV infections started declining in 2000, while the decline of the number of HIV related deaths has a delay of about eight years. The reason for this delay has been widely discussed in different publications. HIV is a slow dynamics disease where individuals stay 'healthy' (not showing symptoms of sickness) for an average of ten years and hence a long survival period. The de-

cline in the number of new infections became significant as the ART provision threshold is increased. But still we do not have complete elimination of HIV infection, even for scenario 'all'. The model results show that approximately 100,300 new HIV infections might still occur in 2021 if individuals initiate ART irrespective of their CD4 cell count and ART access rate becomes 0.52 per year from 2013 onwards. Similarly, approximately 105,300 HIV-related deaths might still occur in 2021. However, the benefit of ART in reducing new HIV infections and deaths could increase if ART access rate is increased. We have presented results for higher access rate in section 4.4.4 which, of course, needs more annual spending and other logistics. However, it is difficult to properly estimate this parameter value.

HSRC estimates show that approximately 396,000(318,000-474,000) new HIV infections occurred in 2012 only [27], then whereas our simulation results show that approximately 432,000 new infections occurred in 2012. The estimate is in line with HSRC estimate. Moreover, the results show that approximately 288,000 HIV-attributed deaths were registered in 2011, which is in line with the prediction of 270,000 HIV-related deaths recorded in 2011 presented at [163].

With scenario '500' as the ART provision scenario, the number of new HIV infections over a five years period might decline from 348,000 in 2016 to 238,600 in 2021 as compared to a decline to 288,000 new HIV infections if we continue with the baseline ART provision scenario. Similarly, the number of HIV deaths in 2021 might decline to 144,900 within five years of the ART provision scenario shift to scenario '500' as compared to a reduction to 174,800 HIV deaths if we continue with the baseline ART provision scenario. Here we see declines in both numbers of new HIV infections and HIV deaths. We can also look at the number of new HIV infections and HIV deaths which could be averted over the five years of period when we shift ART initiation threshold from baseline to scenario '500'. 147,200 new HIV infections might be averted if we change the ART initiation threshold, which is a 9.0% decline (see Figure 4.7 and Table 4.7). Additionally, 105,800 (10.6% reduction) HIV deaths might be averted over the next five years of period due to the shift of the ART provision scenario. We see a greater number of new HIV infections being averted by approximately 654,000 (39.9%) and 242,800 HIV deaths averted (24.4%) for scenario 'all'. If we consider a longer time horizon, we see a more significant decline in the number of new HIV infections
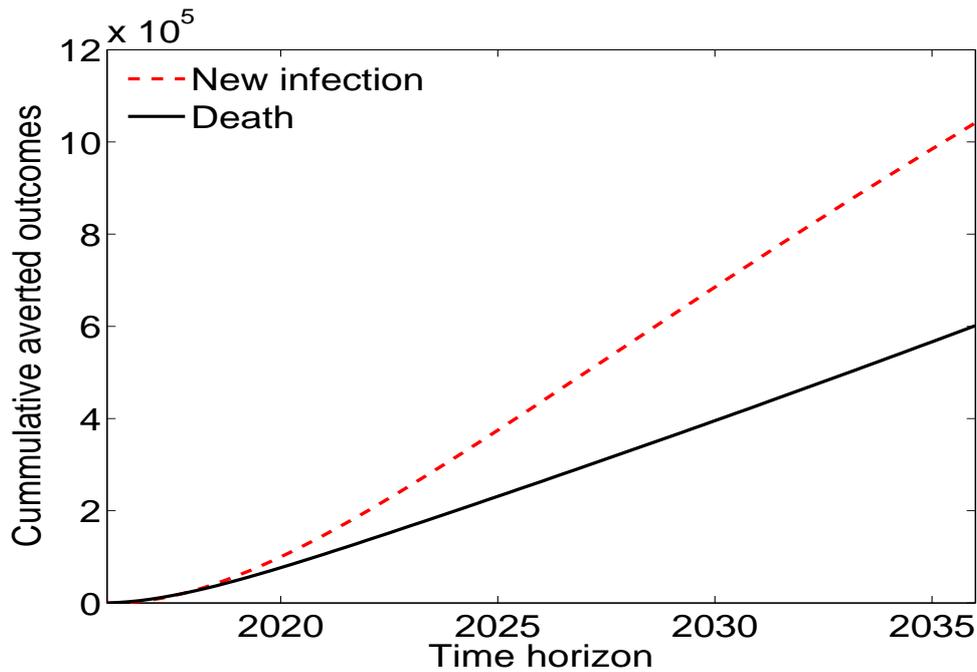
Figure 4.7: Cumulative number of averted cases of new HIV infections and HIV deaths for scenario '500'.

and HIV deaths averted (see Table 4.7).

With higher ART provision scenario, it is clear that the number of people on ART grows significantly every year. Table 4.7 shows the percentage increase with the change of the ART initiation scenarios. For instance, the cumulative number of person years of ART might increase by 11.2% and 40.1% over the five years of the time horizon for scenarios '500' and 'all', respectively. It means we might encounter a 1.675 million and 5.972 million person years of ART due to the shift from baseline to scenarios '500' and 'all', respectively. With calendar time the cumulative person years of ART decline more significantly for scenario 'all'. This is because new infections reduced significantly and hence a smaller number of individuals on ART in long term.

Table 4.7: This table presents the percentage change of the cumulative numbers of different variables of the new strategy as compared with the baseline scenario. Negative values indicate a reduction or decline of the indicator.

Time horizon	Scenario '500'			Scenario 'all'		
	5yrs	10yrs	20yrs	5yrs	10yrs	20yrs
New HIV infection	-9.0	-14.4	-17.5	-39.9	-53.3	-59.2
HIV deaths	-10.6	-14.5	-17.1	-24.4	-33.2	-39.1
PYRS of ART	11.2	12.8	11.7	40.1	35.0	23.7

The need for huge immediate investment cost of ART comes from the increase in the number of person years of ART (PYRS) (in all ART scale up scenarios, see Table 4.7) and also illustrated from the plots for the number of individuals receiving HIV treatment (see Figure 4.8). Compared with the baseline scenario, the number of people starting ART and the number of those who are already receiving treatment are initially much higher for scenario '500' and 'all'. Moreover, these numbers keep increasing throughout the time horizon in all the scenarios except for the scenario 'all' which starts declining in 2020. The simulation results presented here estimate that approximately 958,300 and 1,146,000 individuals were already on treatment in 2010 and 2011, respectively. Additionally, future predictions estimate an increased need of ART to approximately 2.43 million and 3.41 million individuals by 2016 and 2026 respectively, for the baseline scenario. A South African study also estimated that in 2010 and 2011, approximately 1,173,000 and 1,641,000 adults (15+) were on treatment, respectively [164]. The data presented adults (15+), whereas we consider 15-49-year-olds. The prevalence in the above 50-year-old age group might be small. In addition, because we do not have confidence intervals it is difficult to arrive at a conclusion of whether it is an overestimate or not. If individuals are eligible for treatment irrespective of their CD4 cell count, the number of individuals who will be on ART increases drastically for a few years needing high 'front loaded' investment and starts to decline later. The number of individuals receiving ART with scenario 'all' break even with that of scenario '500' before 2029 and breakevens that of the baseline scenario in 2033.

4.4.2   ART coverage

The plots of ART coverage are shown in Figure 4.9. Since the baseline scenario has two thresholds for ART initiation, less than 200 CD4 cell count (before 2013) and less than 350 CD4 cell count afterwards, we see a sharp decrease of the ART coverage at 2013. Moreover, we see a sharp drop of ART coverage at 2016 for the remaining scenarios. These sharp drops are due to the fact that when ART provision scenario become more inclusive, the denominator in the formula of ART coverage (the number of individuals already on ART in addition to those who are eligible but yet not on ART, which is defined in chapter 3) grows and hence
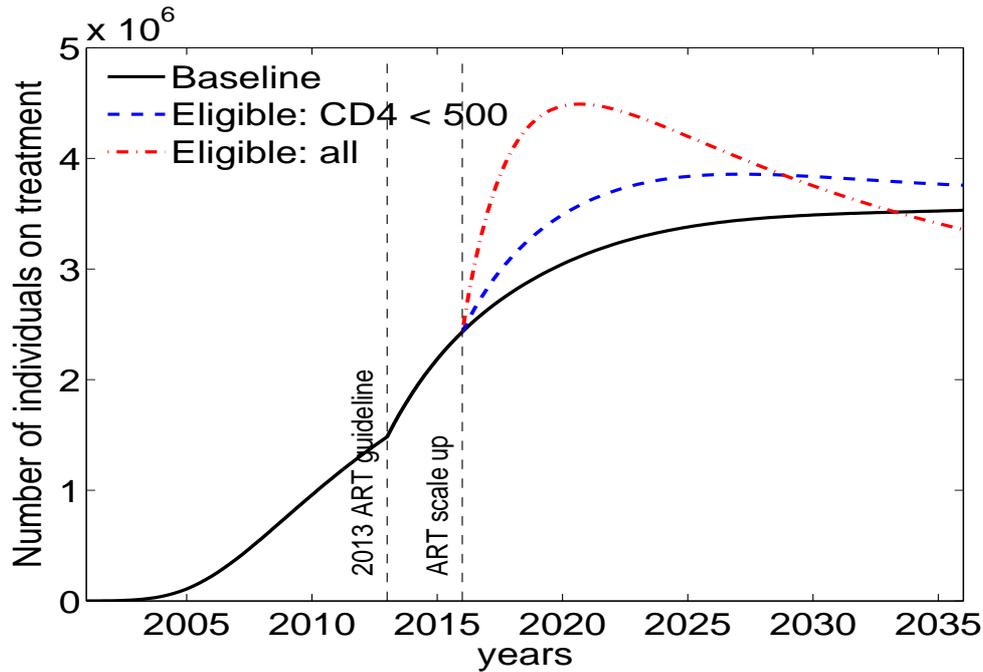
Figure 4.8: Total number of HIV positive individuals receiving HIV treatment. With expanded ART, the number of individuals on ART increases most sharply with more ART use. The drastic increase for scenario 'all' starts to decline within five years and breakevens the graphs of scenario '500' and baseline scenario in 2029 and 2033, respectively.

the ratio becomes small. The simulation results show that ART coverage increases in all the scenarios and becomes asymptotic to 92%, 93% and 96% coverage after around 2030. Adult treatment coverage by mid 2011, close to 80% was presented in a South African study [164] as compared to our estimate of a 72% ART coverage in the same year. But in [12], 67% of estimated need (still < 200 was the eligibility criteria) as of mid 2010, which is in line with our estimate 69.8% at the mid of 2010 (see Figure 4.9). It is usually difficult to conclusively conclude about the program's achievement by only looking at the ART coverage as ART coverage gives the proportion of individual to those in need of treatment. It can give an insight into the overall progress of ART programs. An ART coverage of 80% indicates that 80% of individuals who are eligible for treatment are currently receiving treatment and hence protected from having disease progression and fewer health complications, if they are successfully treated.

4.4.3   Plots of distributions of time since infection

The model structure and the linkage between time since infection and CD4 cell count help us to clearly visualize how the distribution of ART naive individuals, eligible individuals and
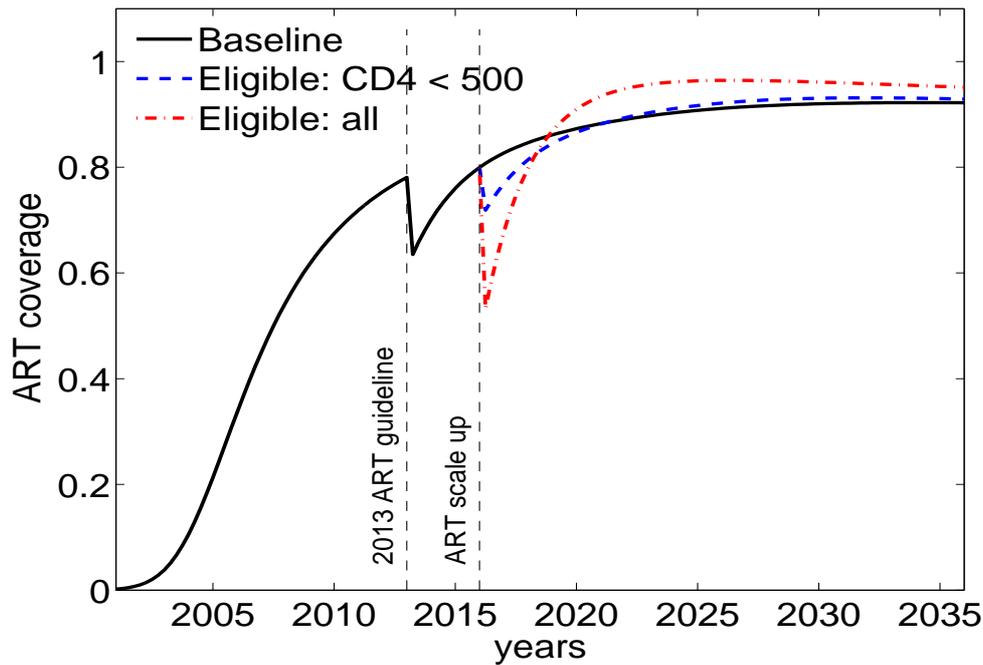
Figure 4.9: Estimation of ART coverage: ART coverage in 2013 is due to the implementation of 2013 ART guideline. Similarly we have a sharp drop in 2016 because of ART scale up scenarios due to more inclusive CD4 criteria. All the graphs seem to stabilize above 90% before 2036.

individuals who newly initiate ART with time since infection evolve.

Figure 4.10 illustrates the distribution of ART naive individuals for particular years: 2016, 2021 and 2036. In ten years from now we might still have a significant proportion of patients who have been infected for a longer period waiting for treatment (may be even more than five years after being eligible). Hence it is important for governments to increase threshold for ART provision to a more inclusive CD4 cell count criteria. When we see the distribution of ART naive individuals in 2036 for scenario 'all', the individuals who are not on ART are those who are recently infected (have smaller time since infection).

The graphs can also give us the proportion of ART individuals with $\tau <$ specific τ^* of interest by calculating the area of region under the curve to the left τ^* (or under the curve to the right of τ^* for the proportion of those with $\tau >$ specific τ^*). The projections show that, in 2036, approximately 25.6%, 16.2% and 3.1% might still be waiting for ART who have been infected for more than five years for baseline scenario, scenario '500' and scenario 'all', respectively. All graphs show that with more inclusive CD4 criteria, individuals wait less time before they were put on treatment. Whereas, if we continue with baseline scenario for ART initiation, treatment might not still be accessible for many individuals (with longer time since infec-

(a) Baseline Scenario

(b) Scenario '500'
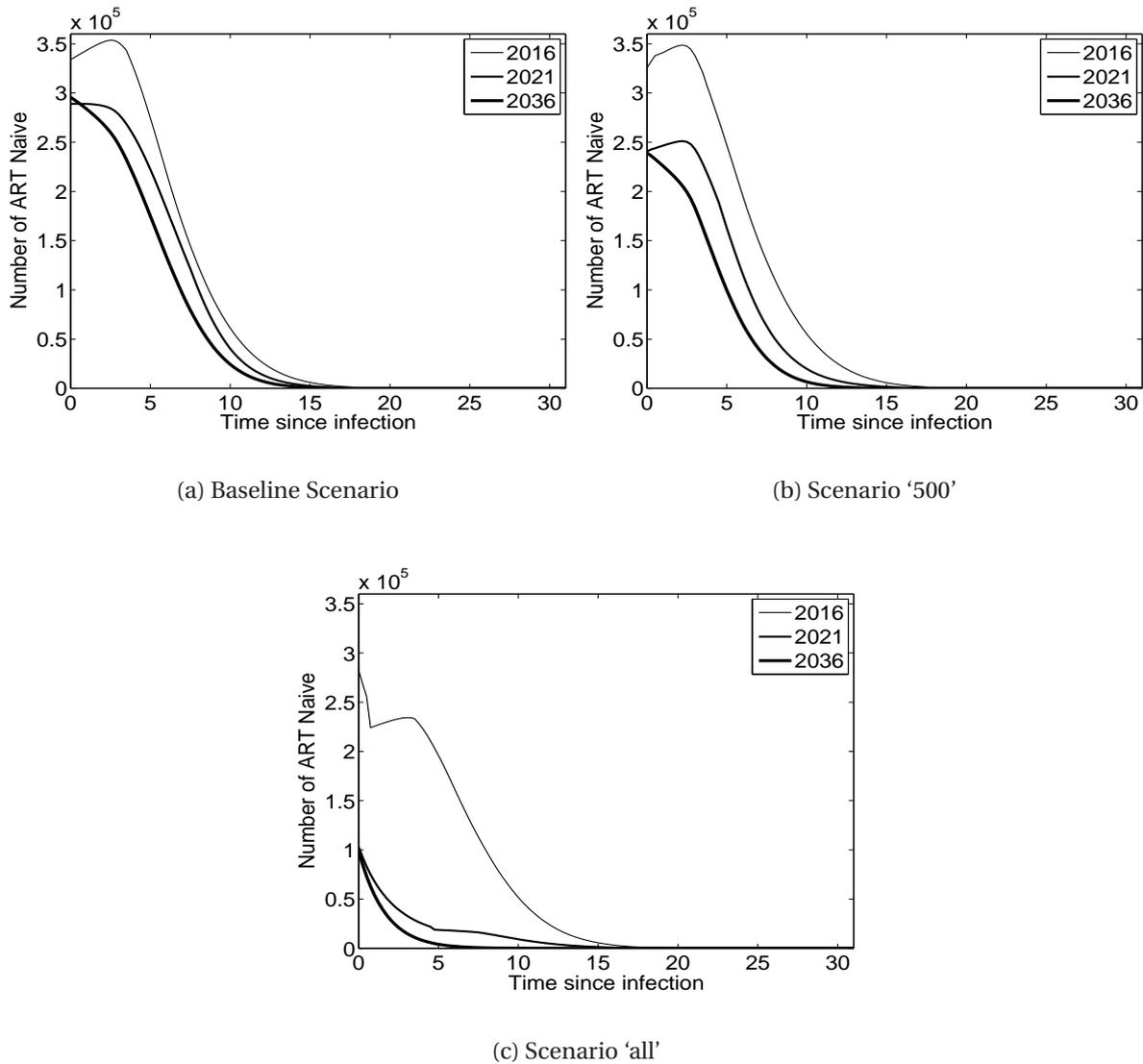
(c) Scenario 'all'

Figure 4.10: Number of ART naive individuals by different ART initiation scenarios: the baseline scenario, scenario '500' and scenario 'all'. The areas under each curve give the total number of HIV positive individuals who are not on treatment. To make the comparison easier we have put similar limits for the y-axes.

tion) even after two decades. These are somewhat intuitive results, but here we tried to give a clearer picture of the trends and the actual number of individuals by time since infection.

Results in Figure 4.11 show the distribution of the number of treatment eligible individuals for the three ART initiation scenarios as a function of time since infection for particular years: 2016, 2021 and 2036. The area under each curve gives the total number of individuals eligible for treatment. In all the scenarios, the absolute number of individuals eligible for treatment decreases with calendar time (2016, 2021, and 2036). This is mainly for two reasons. Firstly, the number of new HIV infections is declining with calendar time because

(a) Baseline Scenario

(b) Scenario '500'
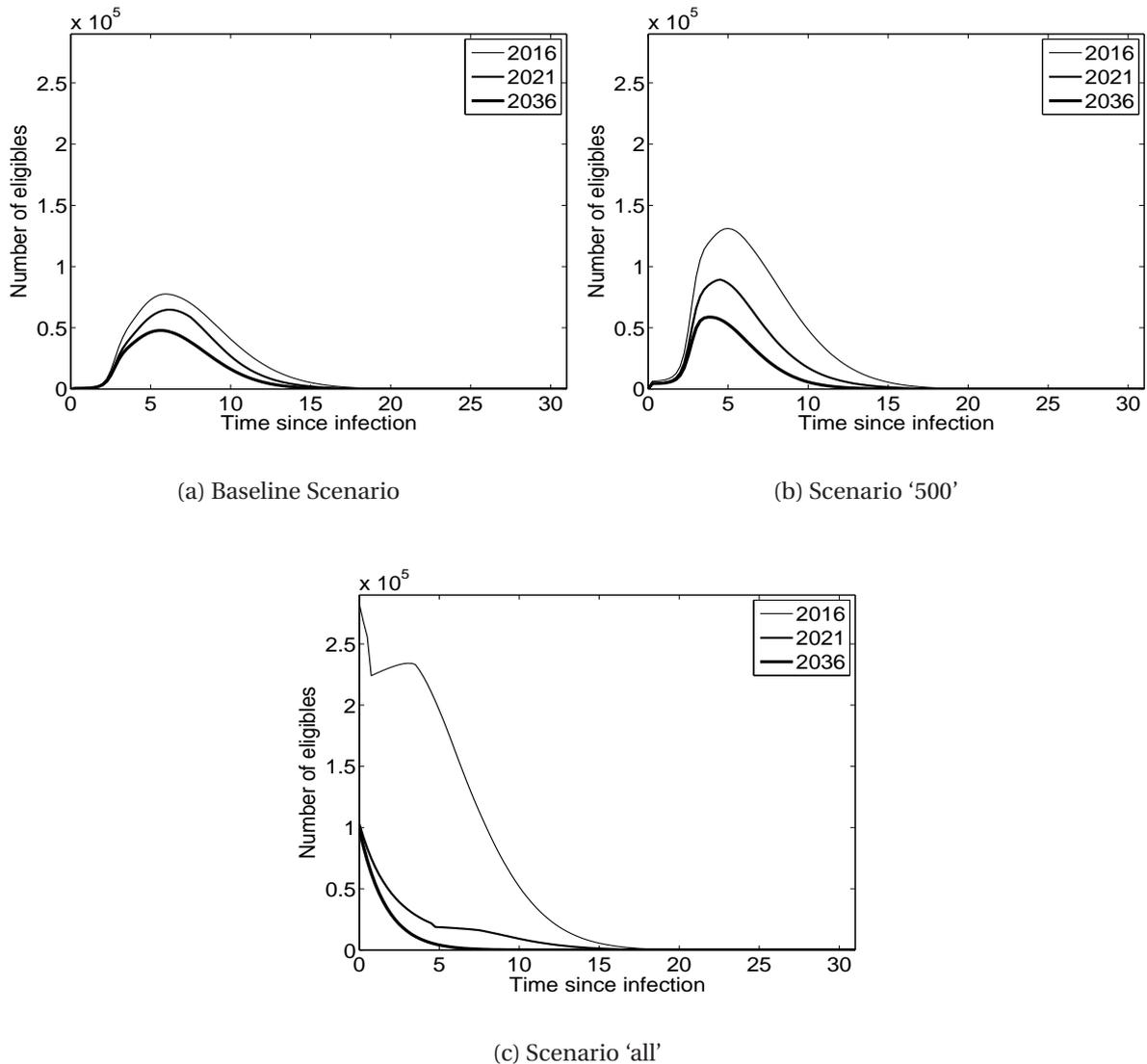
(c) Scenario 'all'

Figure 4.11: Number of individuals eligible for treatment by different ART initiation scenarios: the baseline scenario, scenario '500' and scenario 'all'. The areas under each curve give the total number of HIV positive individuals who are eligible with respect to the ART initiation threshold. To make the comparison easier we have put similar limits for the y-axes.

of reduction of HIV transmission as a result of HIV treatment. Secondly, a certain proportion of individuals start treatment immediately which reduces the number of ART eligible individuals who are still waiting for treatment. More and more individuals initiate treatment with time. Another intuitive result is that the peak of the distribution shifts to the left with calendar time. For instance, the peaks of the graphs of the number of individuals eligible for treatment for scenario '500' are around five years. Whereas for the baseline scenario, it is around seven years. In two decades' time (in 2036) the distribution will shift to the left, and as a result only a few individuals who have been infected for longer will still be waiting for

treatment. For scenario 'all', the proportion of individuals waiting for treatment after being eligible with large τ (time since infection) is high in 2016. Whereas, in 2036 the majority of eligible individuals waiting for treatment are those who are recently infected (mostly with time since infection being less than five years).

The simulation results estimate that 62.7%, 82.8% and 99.3% of HIV individuals eligible for treatment will have time since infection value of seven years for the baseline scenario, and scenarios '500' and 'all'. This shows that with higher ART use due to more inclusive CD4 cell count criteria, the majority of individuals who are eligible for treatment are those who have smaller τ infected increases. We clearly see the impact of the different ART provision scenarios on the distribution of the number of individuals eligible for treatment.

The graphs of the distribution of the number of individuals who newly initiated treatment for particular years: 2016, 2021 and 2036 (Figure 4.12) have similar trends as graphs of those eligible for treatment. However, the absolute numbers, which can be calculated by calculating the areas under the curves, are different. These are individuals who newly initiate ART and they are fewer, as a proportion of individuals initiate treatment every year. Plots in Figure 4.12(b) and 4.12(c) show that more individuals can be recruited to the ART program earlier for more inclusive CD4 criteria. More specifically, Figure 4.12(c), we observe that even with a 0.52 per year ART access rate, most individuals can initiate ART before 5 years of time since infection. The projections show that in 2036 approximately 62.7%, 82.8% and 99.4% of individuals who just initiated have time since infection value less than seven years for the baseline scenario, scenario '500' and scenario 'all', respectively.

Figure 4.13 shows: (a) bar plots of the number of individuals who have never been on treatment, (b) the number of individuals who are eligible for treatment and (b) the number of individuals who newly initiated ART for specific years: 2016, 2021 and 2036. These bar plots are plotted using the results of the distribution of time since infection graphs from Figures 4.10 - 4.12. In all the three subplots of Figure 4.13, the respective numbers decline with calendar time for all the scenarios. This is because the number of new HIV infections decline with calendar time and those individuals who need treatment are already on treatment. The

(a) Baseline Scenario

(b) Scenario '500'
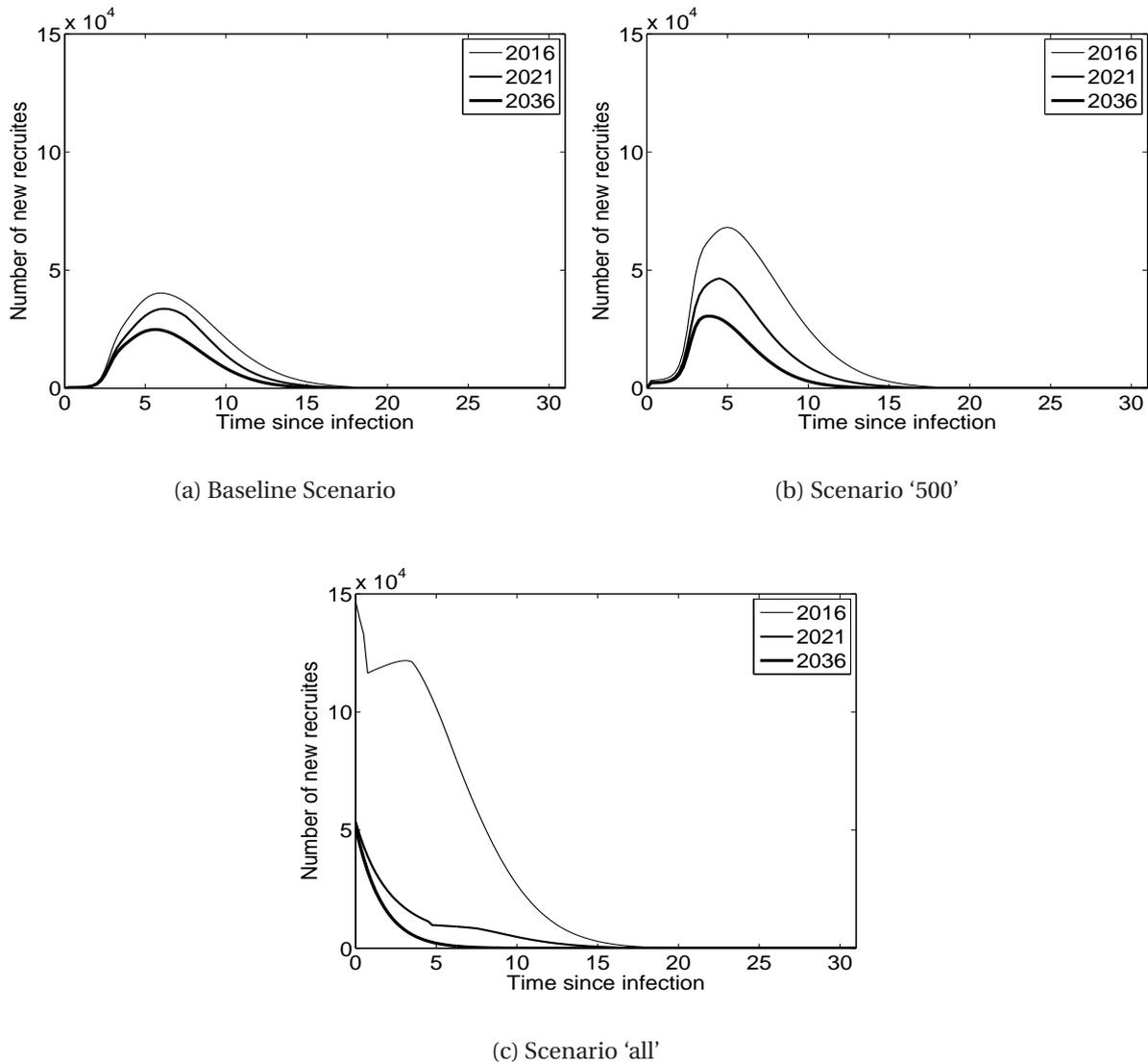
(c) Scenario 'all'

**Figure 4.12:** Number of individuals who newly initiated treatment by different ART initiation scenarios: the baseline scenario, scenario '500' and scenario 'all'. The areas under each curve give the total number of HIV positive individuals who newly initiated ART. To make the comparison easier we have put similar limits for the y-axes.

only difference is that by how much does the respective numbers decline? For instance, for the scenario '500' the number of ART naive individuals decrease from 2,466,000 (in 2016) to 1,590,000 and 1,162,000 in 2021 and 2036, respectively. Similarly, the number of eligible individuals for treatment decrease from 895,000 (in 2016) to 498,000 and 287,000 in 2021 and 2036, respectively. With higher ART provision scenario, the decline of the number of eligible individuals for treatment over calendar time is more significant compared to the baseline scenario. It is because more individuals initiate ART every year for higher ART provision with fewer new infections occurring every year.

(a) Number of ART naive individuals

(b) Number of eligible individuals for treatment

(c) Number of individuals who newly initiated ART
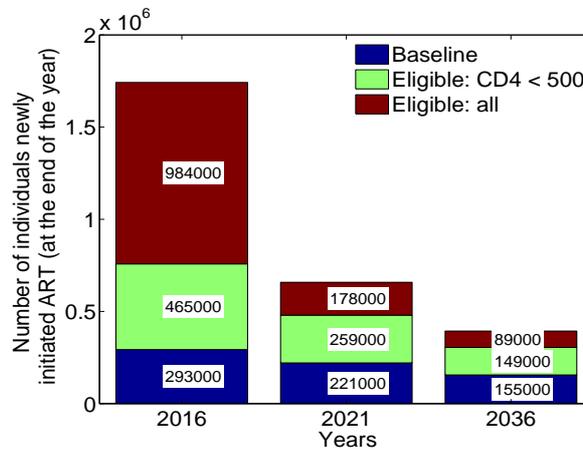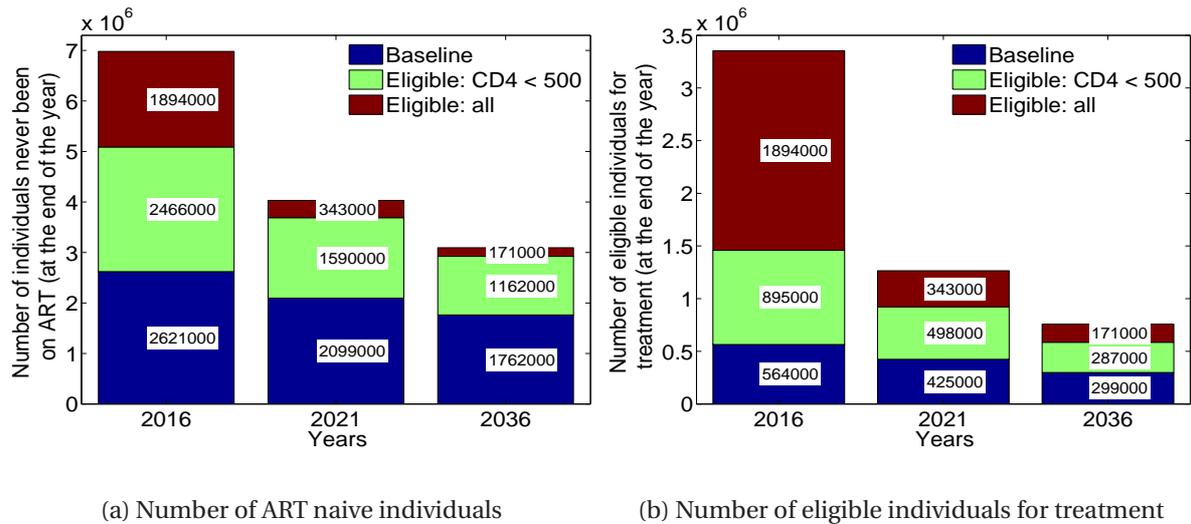
Figure 4.13: Number of individuals who are eligible, ART naive and who newly initiated ART. All the numbers are estimates at the end of the year. Note that the scale for the y-axis are different. Always the number of individuals who newly initiated ART is less than the number of treatment eligible individuals which is less than the number of ART naive individuals in a particular year.

The bar plots in Figure 4.13 (b) are scaled values of the respective bar plots in Figure 4.13(a), i.e. the number of ART naive individuals multiplied by the proportion of individuals eligible for treatment. Of course the numbers of ART naive individuals and eligible individuals for treatment for scenario 'all' are the same as everyone who is eligible for scenario 'all'. Similarly, Figure 4.13 (c) is obtained by multiplying the bar plots in Figure 4.13 (b) with the ART access rate. Increasing the ART access rate means increasing the number of individuals who newly initiate. Even if the number of those who newly initiate ART decreases with time, for the first few years higher ART provision scenario means more new individuals initiating

ART. As a result, the total number of individuals receiving ART for scenario 'all' is significantly higher than the projections for the baseline scenario and scenario '500'. The number of individuals on ART for scenario 'all' breakevens with that of the baseline scenario and scenario '500' before 2030, at different times, depending on ART access rate and the HIV transmission reduction assumption (see Figures 4.8, 4.14 (d) and 4.15 (d)). The important question to ask is: does South Africa have the resources to increase both ART access rate and ART provision scenario (i.e. initiating ART to everyone)? This is debatable and it is difficult to predict the future, but the past trends were not promising as many challenges face the current ART programs in different regions of the country [152]. In the next section, we thus explore ambitious scenario of high ART access rate and high viral suppression leading to high reduction of HIV transmission by those who are on ART.

4.4.4   Projections for higher ART access rate and reduction of HIV transmission

According to UNAIDS, the global target of ART is to achieve ART coverage for HIV-positive persons under which 90% are tested, 90% of whom are on ART and 90% of whom on ART achieve viral suppression (commonly referred as UN 90-90-90 strategy by 2020) [92]. If these targets are met, then approximately 73% of all HIV infected individuals will be virally suppressed. Even if we do not have recent figures for South Africa, the 2012 estimates show that South Africa is really behind the UN 90-90-90 target. According to results at a recent CROI (Conference on Retroviruses and Opportunistic Infections) meeting in 2015 [91], only 25% of the total HIV positive individuals were virally suppressed in 2012 in South Africa. These figures might not increased over the past three years. However, we need to have recent estimates (figures) with regard to the viral suppression to understand the progress South Africa is making. Otherwise the benefit of ART will be limited because of low ART coverage and as a result, low percentage of viral suppression in the population.

In addition to the above challenges in South Africa, there is a lot of uncertainty on the values used for the parameter of reduction of HIV transmission and ART access rate to use as input for model projections. In a model comparison study [52], model projections of HIV

prevalence and incidence were presented for different assumptions. The parameter value for the reduction of HIV transmission was taken as 90%(78% - 98%) [79], and 99% [13]. Model structures and assumptions are the major reasons for differences in model projections. For comparison purposes we have presented projected results with higher reduction of HIV transmission and higher ART access rate. Firstly, we only consider high reduction of HIV transmission and then increase the ART access rate at the same time.

Figure 4.14 (a) shows that HIV prevalence can reduce significantly for higher reduction of HIV transmission assumption. For a 96% reduction assumption, HIV prevalence reduces to 14.7%, 12.9% and 8.2% in 2036 for baseline scenario, scenario '500' and scenario 'all', respectively as compared to 15.7%, 14.3% and 10% for the respective ART scenarios in 2036 for a 90% HIV transmission reduction assumption (see Figure 4.4). This is, of course, an intuitive result as the risk of infecting others reduce with higher assumption for the reduction of HIV transmission. If viral suppression is to be achieved effectively and as a result risk of infecting others is reduced, we will almost have achieved the goal of HIV elimination within less than a decade as HIV incidence rate reduced to 0.14% before 2026. For a 96% reduction of HIV transmission assumption, HIV incidence rate is 0.93%, 0.65% and 0.14% in 2036 for baseline scenario, scenario '500' and scenario 'all', respectively, which showed a reduction from 1.04%, 0.82% and 0.31% for the respective ART scenarios, with 90% reduction of HIV transmission assumption. We see a similar trend of reduction for HIV-related deaths, where higher reduction of HIV transmission means higher reduction of HIV-death rates. The number of individuals on ART for scenario 'all' breakevens the number of individuals on ART for scenario '500' and the baseline scenario at 2027 and 2030, respectively. This shows that for higher reduction of HIV transmission assumption, the reduction of new HIV infections becomes significant and hence the number of individuals on ART for scenario 'all' decreases significantly after a sharp increase up to 2020.

Reduction of the risk of infecting others while on ART, depends entirely on the effectiveness of the drug and individuals' adherence. Now let us assume that the government is committed to increase the annual spending to make ARVs more available and patient management is high. Then we see the model projections for higher access rate and higher HIV transmission reduction.

(a) HIV prevalence

(b) HIV Incidence

(c) HIV death rate

(d) Number of individuals on ART
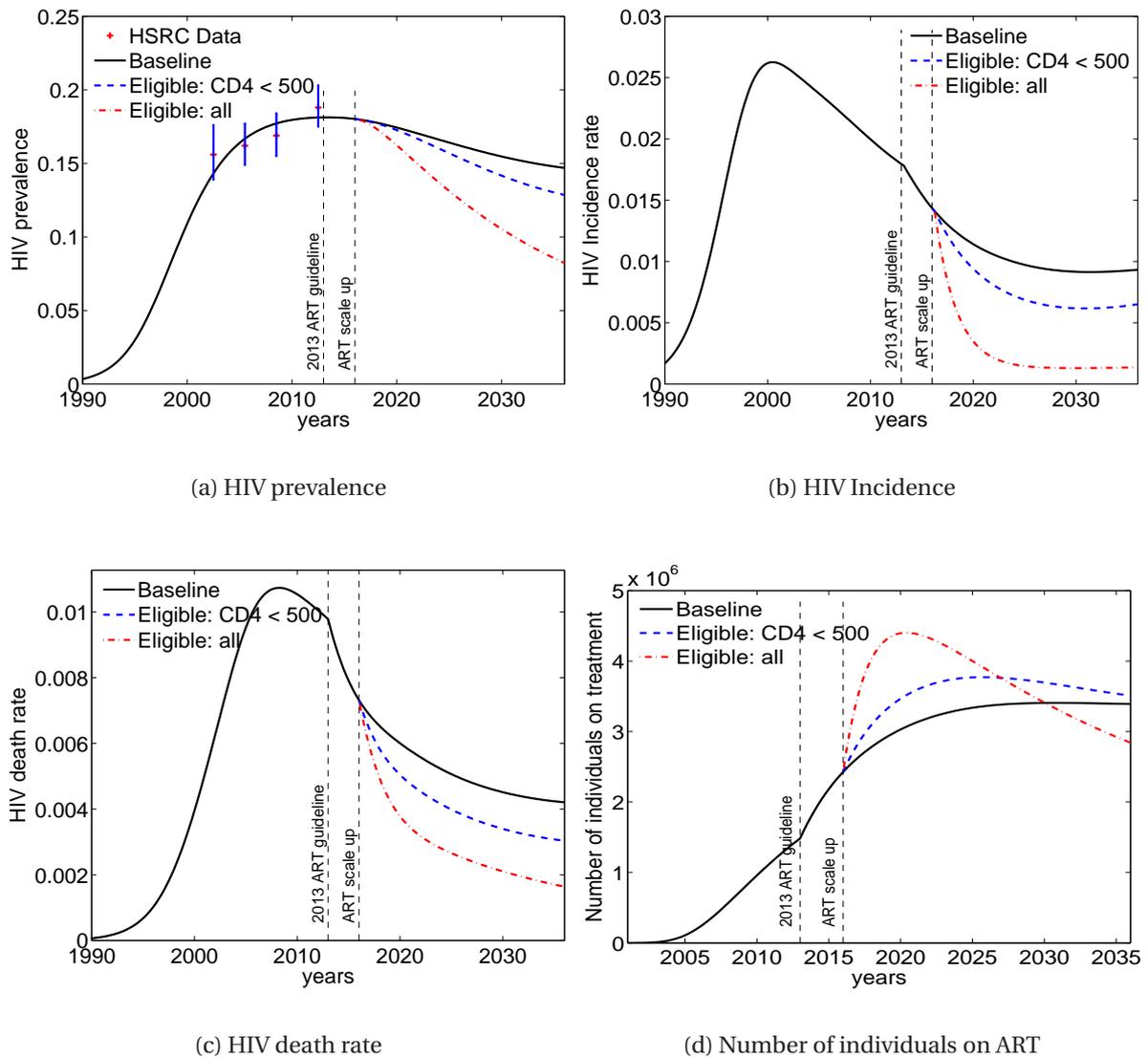
Figure 4.14: Key epidemic results for higher reduction of HIV transmission due to ART. Here we considered a 96% reduction of HIV transmission due to ART with the current ART access rate.

HIV prevalence in 2036 with 90% ART access rate and 96% HIV transmission reduction assumptions are 13.38%, 11.3% and 7.6% for the baseline scenario, scenario '500' and scenario 'all' respectively (see Figure 4.15(a)), which significantly decline from 15.7%, 14.3% and 10% for current access rate and 90% HIV transmission reduction (see Figure 4.4). Similarly, HIV incidence rate declines to 0.71%, 0.47% and 0.1% in 2036 for baseline scenario, scenario '500' and scenario 'all', respectively from 1.04%, 0.82% and 0.31%, respectively for a current access rate and 90% HIV transmission reduction. HIV incidence rate becomes below 0.1% before 2024, a result which is in line with [13]. Therefore achieving high viral suppression (which implies high reduction of risk of infecting others while on ART) and high ART ac-

cess rate are very important to reach elimination stage within less than a decade. Thus, the current ART programs in South Africa should promise higher coverage to achieve the most benefit.

The number of individuals on ART for scenario 'all' breakevens at 2024 and 2027 with the number of individuals on ART for scenario '500' and baseline scenarios (see Figure 4.15 (d)). With similar argument as those above, as ART becomes more accessible to everyone, due to higher ART access rate, and if high reduction of HIV transmission is achieved, then the number of new infections will decline significantly (which is evident by looking at the incidence rate in Figure 4.15(b)). Thus, the number of individuals on ART for scenario 'all' only increases significantly up to 2019 and then has a sharp decline afterwards. This shows the long term impact of early ART with high coverage and effective ARVs.

(a) HIV prevalence

(b) HIV Incidence

(c) HIV death rate

(d) Number of individuals on ART
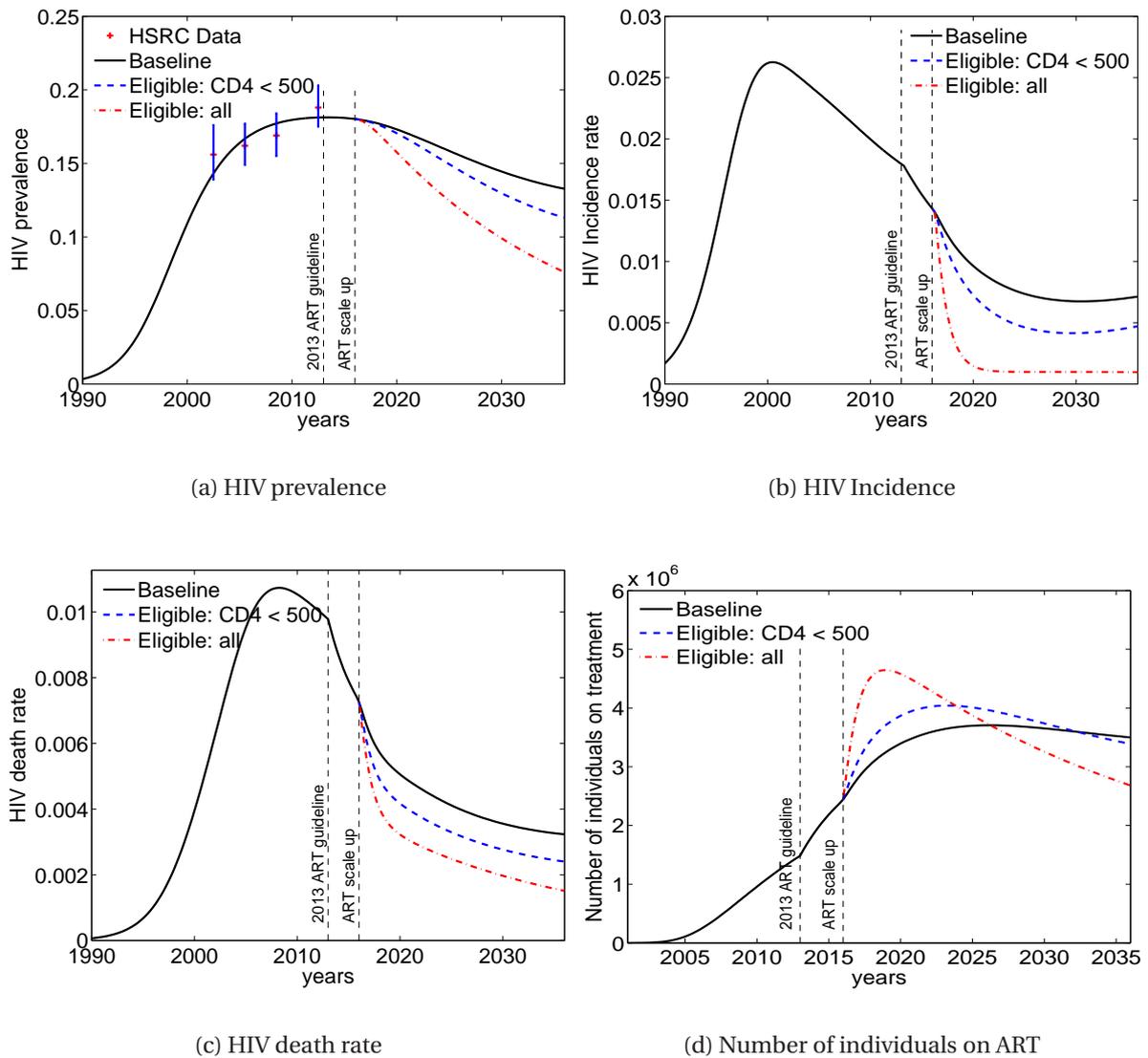
Figure 4.15: Key epidemic results for higher reduction of HIV transmission due to ART and higher ART access rate. Here we considered a 96% reduction of HIV transmission due to ART with the ART access rate of 90% by 2017.

4.5 Discussion

Model structures usually affect predictions, which is why we cannot see similar projected results over the years for elimination of HIV. Models which discuss the impact of TasP, treatment as prevention, in recent years have shown a wide range of optimism about the impact of early ART in the fight against the HIV epidemic. For instance, models discussed in [13, 52] show that elimination of the disease might be possible within less than two decades. But there is substantial uncertainty of projections of the twelve models presented in [52] about

elimination of HIV from the population using ART alone up to 2050. Our results show less optimism about elimination of the disease in such a short period of time. This is because we took, probably, optimistic parameter assumptions; parameters which might tell the reality on the ground. We do not have an intensive ART scale up scenario, which is not the case in the estimates of some other studies [13]. We took an ART access rate which stabilizes around 2013 at 0.52 per year, which can be translated as approximately 40.5% of individuals who become eligible will have started ART every year. Or, that individuals start treatment on average after two and half years of being eligible. The behavioral factors of the patients, managerial aspect in handling the disease, individuals' willingness to be put on treatment and more importantly financial resources limit the scale of the ART scale up. High ART access rate might be achievable in the future but not with the current infrastructure and other challenges which face ART programs in South Africa [152].

It is usually difficult to compare our model analysis with studies which consider CD4 cell count discretization yielding a system of differential equations. For example [128] presented cost-effectiveness strategies of ART provision scenarios from 2004 to present relative to a no ART scenario. For us not only 'no ART scenario', we have even removed a scenario of ART initiation below 200 CD4 cell count. Thus, for a proper comparison between models, one might have to do a similar analysis to [52], a systematic comparison of mathematical models. To do that, it might be very important to design a framework of treatment scenarios having similar time horizon and comparably similar parameter estimation of the key ones, at least. Thus, we mainly presented our results and showed results from other studies for comparison, which of course has different assumptions for the time horizon and other model components.

According to our projection, we could only reach an incidence level of 0.3% after two decades of intervention if individuals start treatment irrespective of their CD4 cell count. Some models presented in the comparison studies by [14, 52], predict complete elimination of HIV early (before 2030) and the rest predict elimination to happen later, that is, 2050. As it was clearly indicated by [14], simple deterministic models predicted very quick elimination of HIV even before 2020, in contrast to our projected results. Moreover, unlike [14] which suggests that elimination of HIV could be possible within 30 years for scale up of ART at CD4

cell count less than 350, our model suggests that even with a high ART access rate the baseline scenario (a threshold of 350 CD4 cell count after 2016) will not lead to HIV elimination within a short period. In another study, the HIV prevalence prediction was projected up to 2050, where it showed HIV prevalence declining to about 5% and 1% in 2030 and 2050, respectively, [53] in contrast to 10% HIV prevalence estimate in 2036, based on our projected results for scenario 'all'. All projected results with current access rate do not lead to HIV elimination within a decade.

Effective viral load suppression (which leads to high reduction of HIV transmission by the patients on ART) and high ART access rate could lead to elimination of HIV within less than a decade. By comparison, we have presented key epidemic outputs for 'ambitious' ART access rate (90% by 2017) and high reduction of HIV transmission reduction (96%). The projections presented for the 'ambitious' strategy show a gradual reduction of HIV prevalence and significant reduction of HIV incidence leading to HIV elimination within a decade. These results are in line with the results in [13]. However, some models discussed in a comparative study [52], showed significant reduction of HIV prevalence, incidence and death rates which might lead to HIV elimination only by 2050.

The potential benefit of ART scale up could be limited due to failure to reach all individuals who become eligible for treatment. Willingness of individuals to start treatment early could be one of the reasons which might impact the effectiveness of ART scale up programs. This has been widely discussed in [81, 82]. Moreover, due to resource limitation especially in developing countries, the target of ART programs might not be achieved [66]. Thus, to achieve high ART coverage and high significant impact of ART, the overall treatment program needs huge effort from governments, stakeholders and community, not forgetting the commitments from the patients themselves to stay adherent to the treatment.

Adopting a policy of ART for all CD4 levels could avert 3.52 million infections and 1.38 million AIDS-attributed deaths over 20 years as compared with the continuation of the baseline scenario. This is a 60.3% decline of new infections to happen over 20 years if we were to keep the current trend. Additionally, there could be 41.0% averted HIV-deaths due to more inclusive CD4 criteria over 20 years. With scenario '500', the percentage declines are less than that of scenario 'all', but still significant. Cumulative numbers of new HIV infections

and deaths could decrease by 17.8% and 17.9% over the next 20 years for a change of ART initiation threshold from 350 (baseline) to 500. Changes of the numbers of different projections were presented in [12] for the above similar scale up scenarios. The number of new infections over 40 years declined from 8.7 million to 6.7 million which is approximately 1.9 million new infections (33%) are being averted due to a shift from 350 to 500 scenario [12]. If the results of our model were run for longer time, we might be able to see similar reduction of new HIV infections over 40 years. In this study, we considered comparison of the actual numbers, changes and percentage changes of the key epidemic outputs of the new strategy with the baseline scenario only. However in [12] the actual numbers, changes and percentage changes of a new strategy were compared with prior ART scale up scenario. Despite the difficulties of comparing most of their results with our projected results, the results of the long term impact of early HIV treatment for higher access rate are similar. That is, early ART averted many cases of new HIV infections and AIDS deaths.

The results of cumulative person years of ART over the time horizon are in line with the projections presented [53] for a delayed versus immediate treatment analysis. Higher ART provision implies that the cumulative person years of ART is a greater number of individuals on ART than with that of a less inclusive CD4 cell count criteria (for instance the baseline or delayed treatment). Our projected results show that over the next 20 years the increase might be by 10.8% and 22.2% for scenarios '500' and 'all', respectively compared with the baseline. However, the annual person years of ART for higher ART provision (immediate ART) does not stay higher but becomes smaller than that of the baseline after about a decade. This means that annual spending for ART becomes smaller in the long term. Even though the cumulative spending might increase at first due to the increase in the cumulative person years of ART, the health benefits are significant. The benefits could mean a 20.8%, and 61.1% reduction in the number of new HIV infections and 17.7% and 38.4% reduction of HIV-related deaths, for scenarios '500' and 'all' respectively.

Universal access for TasP is an ambitious goal, and hence some mathematical models have shown the need of substantial logistical planning across all sectors of HIV field [165]. The logistical planning could include: plan for high linkage to ART care and high retention as we know that poor adherence leads to less chance of unsuppressed viral load [166].

HPTN052 trials show that HIV transmission can be reduced significantly, which is only at individual level. Mathematical models help to design future trials such as a model to estimate the benefit of ART in reducing HIV incidence at a population level. The result shows that the HPTN 071(PoP ART) trial intervention could reduce HIV population level incidence by approximately 60% over three years [167]. With better parameterization using data from trials, this model can also be used to show better projected results of the impact of ART at a population level.

Our analysis nicely links distribution of time since infection and CD4 cell count to analyze the impact of early ART initiation with different scenarios. We know the HIV progression and complications during the late stage of the HIV infection which usually leads to symptomatic stage of the disease. HIV positive individuals show symptoms of sickness at a later stage of time since infection which suggests that health complications increase with time since infection. In our analysis, we showed the distributions of time since infection of individuals who have never been on ART, individuals eligible for treatment and those who newly initiated treatment. Most of the ART naive individuals waiting for ART have smaller τ (recently infected) for higher ART provision (scenario '500' and 'all') as compared to the baseline. If individuals access ART regardless of their CD4 cell count, we would see the majority of individuals start treatment early. Having such kinds of distributions might help us link the quality of health of the population.

In the model assumptions we have included an excess mortality rate due to HIV/AIDS equal to 0.02 for individuals in the treatment class. This means, at any time, a certain proportion of individuals are removed from the population. These individuals do not contribute to the HIV transmission dynamics. If individuals are on a successful treatment program, there is no HIV-related death and individuals have limited risk of infecting others. But in reality we do not have these situation as individuals either fail treatment or dropout [83, 89, 112, 168, 169]. The mortality assumption for the treated class accounts for the modest dropout and treatment failure which we did not consider. However, one could expect that the infection rate of the infected class might be overestimated due to the completely ignored contribution of those who dropout from treatment.

4.6   Conclusion

We have developed an HIV model that is structured with time since infection to evaluate the potential impact of different early HIV treatment scenarios: ART provision scenarios with baseline (CD4 count < 350), CD4 < 500 and regardless of their CD4 cell count were considered as the ART scale up scenarios. Our model confirms what we already know, that as ART provision threshold increases, the reduction in the number of new HIV infections, HIV prevalence and HIV-attributed deaths become more and more significant.

Apart from serving as a confirmation to show the impact of ART, our model also presents the distribution of individuals who are eligible for treatment but yet to be on ART as a function of time since infection. We also presented results for the number of ART naive individuals and number of individuals who are newly initiated to treatment as a function of time since infection. With better clinical and behavioral data for HIV positive individuals as a function of time since infection, one can use the linkage between CD4 cell count distribution and time since infection to estimate the contributions, to the HIV epidemic, by individuals as a function of time since infection. As ART provision is increased (from baseline to scenario '500' and scenario 'all'), individuals waiting for treatment will only be those who are recently infected (or individuals with small τ). This shows that the majority of HIV positive individuals who have been infected for a longer time might be already on treatment and hence the quality of health of the patients is improved significantly, if they are adherent and treatment is successful.

We have shown that, with higher ART use due to more inclusive CD4 cell count criteria, the number of new infections and AIDS-related deaths decrease. But with 'current' ART access, it is difficult to achieve HIV elimination within shorter period. Therefore, South Africa's government and other stakeholders' commitments have to increase significantly to overcome the hindering challenges in the fight to curb the epidemic. As programs run for longer periods, the logistics and management difficulties challenge ART programs. Hence, the proportion of individuals who either fail or dropout from treatment might increase. Thus, it might be very important to study the impact of these factors and understand the level of the

problem, which we aim to discuss in chapter 6.

This work is not without limitations. Despite generating the internally consistent body of evidence on HIV incidence, prevalence and others from the same model under the same set of parameter assumptions, we have faced many challenges with the estimation of some of the time since infection and calendar time dependent parameters. In some cases we used a range of values due to the uncertainties of these parameter values referring estimation from different studies. Better data on parameters such as the acceptability and access rate of early ART initiation are needed for better projections. Lack of long term viral suppression due to ART might bias some of the analysis. Studies have presented a wide range of figures for the reduction of HIV transmission as a result of early HIV treatment. Such assumptions result different projections regarding the period for HIV elimination. Due to these uncertainties, we presented results for different scenarios of HIV transmission reduction. Thus, better data on the impact of early ART at population level might improve the results. Our epidemiological model is not risk and age-structured, so we could not examine targeted strategies. Even if most countries are changing ART initiation guidelines, resource limitation may imply a need for targeted strategies or less ART access rate. For instance, HIV incidence is high in the age group 20-30 years old, prioritizing a specific age group for treatment programs which may bring significant reduction of new HIV infections. Additionally, knowing the age of the individual at infection is also important to have better estimation of HIV death rate which we have not considered. We only considered an average HIV mortality rate for all age by time since infection. The model is already complex and adding age structure would make it even more complex. Additionally, other prevention interventions such as male circumcision were not included. Aspects of treatment failure and dropout were not modeled properly, only modeled using mortality as the way to model the modest treatment failure and dropout rates.

Chapter 5

The cost-effectiveness analysis

5.1   Introduction

In chapter 4, we have developed and discussed a basic mathematical model of HIV, structured by time since infection, which were mainly focused on the clinical and the epidemiological outcomes, such as time trends of HIV prevalence and incidence. Projections of these for the next two decades were presented. Usually with any scale up programs, the initial investment for the program is high. The same is true for ART scale up programs. With the increase of the ART initiation threshold, more individuals will be put on ART causing treatment programs need more funding. Governments, stake holders, NGOs and others are usually interested to know the health outputs of the new intervention scenarios (more inclusive CD4 criteria in our case). They also want to know by how much the cost of the programs will increase? To give an overview and answers to such questions, we present a cost-effectiveness analysis of the different treatment scenarios of the model discussed in the previous chapter. Specifically, we will attempt to calculate ICER ratio for DALYs averted despite the difficulties of estimating parameters of utilities (disability weights) as a function of time since infection. DALY, which measures disease burden, is calculated by adding years of life lost due to premature death and years of life lived with disability. Some researchers have calculated ICER values for DALYs averted and used WHO set metrics to decide whether a new intervention is cost-effective or not.

The three treatment scenarios considered are: the baseline scenario, scenario '500' and

scenario 'all'. Incremental cost-effectiveness ratio values will be represented graphically for each scenario to present the greatest health returns at any given cost. In this chapter, we will only present results for 'current' ART access and 90% reduction of HIV transmission due to ART.

5.2   Model parameter values

In this section we discuss the values of parameters of cost and utilities of the model discussed in chapter 4. In this study, the calculations of the cost and the cost-effectiveness analysis were done using a unit cost of providing ART per patient per year. We have not broken down costs by service cost, drug cost, personnel cost and others, since our goal is to assess the incremental costs and benefits of expanding ART. For the simulation part, we estimated the cost of providing ART per patient per year in South Africa to be 5,151 South African Rands [122] (equivalent to $630 based on the July 2012 exchange rate, $1=8.19 South African Rands). Throughout the thesis we will only use USD (American dollar) for cost-related calculations. Cost of medication and the perspectives adopted here are based on the estimation from the government of South Africa [122]. Sensitivity analysis will be discussed for a range of unit costs of providing ART. Moreover, cost estimations may vary, depending on the discounting rates used. A discounting rate ranging from 1% to 8% is generally recommended in health effects and costs [170]. For this study we used a discounting rate of 3% per annum for the cost and health benefits to bring future costs to the current value [139, 170, 171].

Quality of life weights for HIV positive individuals without ART was assumed to be 0.84 (range: 0.84-1.0), whereas it is 0.91 (range: 0.91-1.0) for those on treatment [124, 172]. For our simulation results we used the same value as [124, 172] for individuals on treatment. But we used a quality of life which varies with time since infection for those individuals who are not on treatment using results from [173] (see Figure 5.1). Lastly, we have assumed a quality of life weight for susceptible individuals to be 0.95, which is a little higher than those individuals on treatment. For susceptible individuals the value we took is greater than that of quality of life for treated and those with out ART, as we were not able to find a reference.

We are not able to find disability weights for individuals who are not on ART as a function

Table 5.1: Summary of the assumptions of utilities: quality of life and disability weights.

	Quality of life	Disability weights
Susceptible	0.95	0.053
Infected	see, Figure 5.1	0.166
Treated	0.91	0.053

of time since infection. However, there are estimations by CD4 categories and/or by stages of HIV. According to the global burden of disease by WHO, disability weights of 0.135 (0.123-0.136), 0.505 (no CI) and 0.167(0.145-0.469) were estimated for HIV cases, AIDS cases not on ART, and AIDS cases on ART, respectively [174]. In other studies, where CD4 category and stages of HIV were used [134, 175], have similar estimations. Untreated HIV positive individuals with CD4 > 350, between 200 and 350 and CD4 < 200 have an estimated disability weight of 0.053, 0.221 and 0.547, whereas HIV positive individuals on ART have disability weight of 0.053 (similar to those with high CD4 count). Since we do not have CD4 categories, we will calculate average disability weights using these results and the proportion of HIV positive individuals who are not on ART by CD4 category. A study presented distribution of CD4 count among those who tested HIV-positive [176]. According to the result, 13.6%(9%, 19.8%), 27.2%(20%, 35%), 25.3%(19% 33%) and 34.0%(27%, 42%), have CD4 counts < 200, $201 - 350, 351 - 500$ and > 500, respectively. Thus, we estimated the average disability weight for individuals who are not on ART to be 0.166. This estimate could, however, vary depending on the proportion of individuals who are not on ART by CD4 counts and hence difficult to give a range for the disability weight assumption for individuals who are not on ART. The values for other parameters are the same as the ones presented in chapter 4. We will discuss the scenario for the assumed range in the simulation results section.

5.3   Simulation results

5.3.1   Annual cost estimation

Projections presented in the previous chapter show that the number of individuals on treatment increases rapidly for higher CD4 threshold just after the start of ART scale up in 2016.
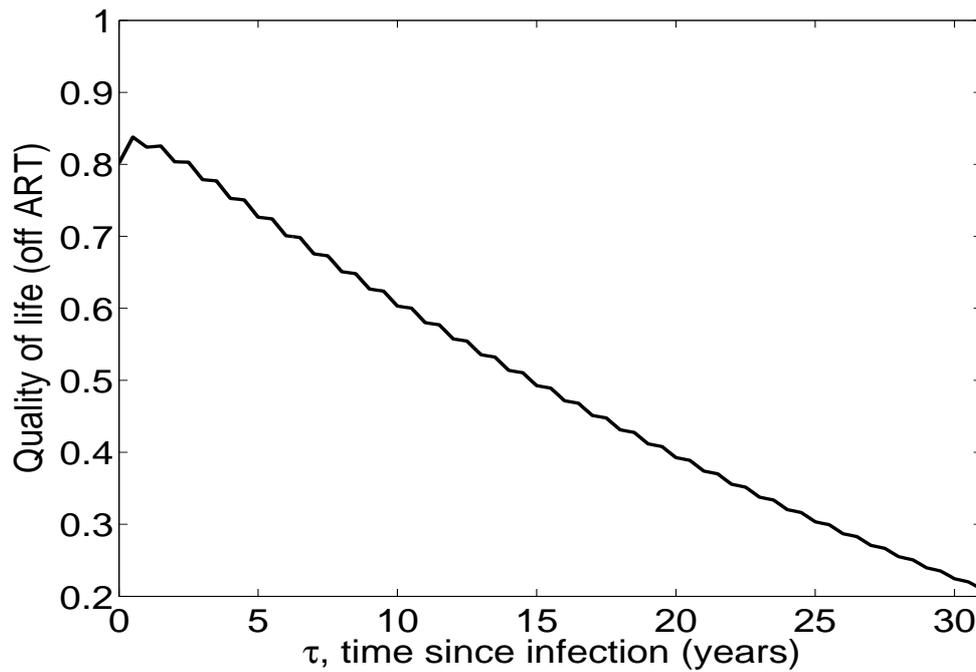
Figure 5.1: Utility for quality of life, [173].

Afterwards the number of individuals on treatment show a steady increase for scenario '500' and for the scenario 'all', the rapid initial increase continues for a short period followed by a gradual decline. This decline could mainly be due to the reduction of the number of HIV infections which we discussed in detail in the previous chapter. Mortality of individuals on ART at a later stage might have a little contribution. As the number of individuals on treatment increases, the annual cost of providing ART increases. Because of this, the government may need an increased investment for treatment especially during the first phase to accommodate the spike in the number of individuals initiating ART due to more inclusive CD4 criteria.

Our model estimates that the government may need up to 2.7 billion USD per year in 2020 (reaching its peak) if ART provision is increased to scenario 'all'. The annual cost will gradually decline after 2020 while it continues to increase for the baseline scenario (see Figure 5.2). The trends of these results agree with published results [12, 13, 14, 177]. In these studies, expanding to CD4 levels (however different model assumption), decreases the annual costs and even breakevens within about 10 years of ART scale up. Since higher provision of ART may significantly reduce costs while reducing HIV burden, we recommend that a large investment for a shorter period of time (for increased ART provision) is preferable to

treating individuals at late stages of the disease. For better understanding of the comparison investment (spending) versus outcome, we present cost-effectiveness ratios in the next section. The summary of the cumulative costs for scenario '500' and 'all' are presented in Table 5.3 which are also used for the calculation of the ICER values.
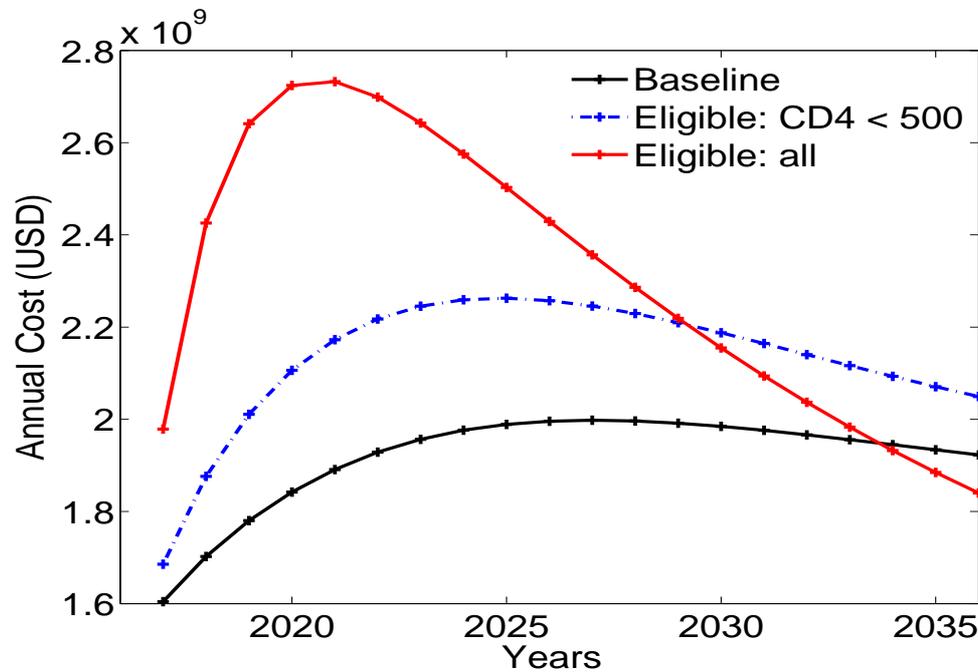
Figure 5.2: Annual cost of providing ART by scenario from 2016-2036.

Table 5.2: Person years of ART and HIV positive individuals over particular period of years.

	Baseline			Scenario '500'			Scenario 'all'		
	5yrs	10yrs	20yrs	5yrs	10yrs	20yrs	5yrs	10yrs	20yrs
PYRS of HIV (millions)	27.37	53.38	105.59	27.29	52.76	102.13	26.50	49.05	87.47
PYRS of ART (millions)	14.89	31.43	66.34	16.57	35.45	73.61	20.86	42.43	79.28
% change of PYRS of ART from prior scenario	-	-	-	11.2	12.8	10.9	25.9	19.7	7.7
% of PYRS of ART from the total PYRS of HIV+ve	54.4	58.9	62.8	60.7	67.2	72.1	78.7	86.5	90.6

Person years of ART over 20 years varies from 66.34 million with baseline to 73.61 million with scenario '500' (10.9% increase from the baseline and about 72.1% of HIV infected) and 79.28 million with scenario 'all' (7.7% increase from scenario '500' and about 90.6% of HIV infected) (see Table 5.2). This pattern reflects the reduction of future cumulative demand for

ART spending as more HIV infections can be averted with expanded ART provision scenarios. The actual spending of ART per year is shown in Figure 5.2. It shows when the annual spending of ART for scenario 'all' breakevens that of the baseline and scenario '500'. The summary Table 5.2 confirms how the cumulative spending varies over time. Cost is directly proportional with the number of individuals on ART. Since PYRS of ART over ten years increases by 10.9% for scenario '500', the future demand of investment for scenario 'all' could be minimized because of fewer HIV infections which leads to fewer individuals on ART (annually). The proportion of person years of ART from the total HIV infected increases with calendar time, with the baseline scenario having the least. Moreover, through high ART provision, more individuals could be on ART over 20 years. About 90.6% of of HIV positives being on ART at the end of 20 years for scenario 'all' as compared to 62% for the baseline scenario.

5.3.2   Incremental cost ratios

In the simulation results we show the incremental cost needed to avert or gain certain health outcomes such as: HIV infections, HIV deaths or DALYs averted and QALYs gained for different scenarios as a function of calendar time. Generally, the ICER for all the scenarios for HIV infections, deaths and DALYs averted and QALYs gained decline with calendar time.

Here we will present the calculation of ICER briefly. Let us see how the ICER value for QALY is calculated.

QALY from an intervention at time t is calculated as follows:

$$\text{QALY}(t) \;=\; \text{QoL}_S * S(t) + \int_0^\infty \text{QoL}_I(\tau) * I(t,\tau) d\tau + \text{QoL}_T * T(t),$$

where QoL_S, QoL_I and QoL_T are quality of life estimates of different states; susceptible, infected and treated, respectively.

The discounted QALY estimate will be obtained multiplying the above value by a discounting factor (3%).

As it is defined in chapter 3, ICER is calculated by dividing the difference of the total cost of two interventions to the difference of the total QALY of the two interventions. For this we need to have a time horizon stated. For our study the period from 2016 to 2036 is considered as the time horizon. Let us present the ICER value for QALY in 2036.

$$\text{ICER} \quad = \quad \frac{\text{Cost of new ART scenario} - \text{Cost of baseline ART scenario}}{\text{QALY of new ART scenario} - \text{QALY of baseline ART scenario}},$$

where:

- Cost of new ART scenario is the total cost needed for the implementation of the new scenario during the time horizon.

- Cost of baseline ART scenario is the total cost needed to provide ART if the current scenario is to continue. The respective QALYs are calculated in a similar way.

The unit of this ICER value will be USD per QALY gained. When the quality of life individuals is improved significantly with small incremental cost then the ICER becomes smaller. Therefore the estimates of the outcomes of interventions influences the cost-effectiveness ratios.

Using the same method, we can calculate the ICER values of the other health outcomes (DALYs averted, new HIV infections and deaths averted).

Our projections suggest that earlier eligibility for antiretroviral therapy is a very cost-effective as the ICER value for DALYs stays less than the GDP per capita of South Africa ($7,592 according to 2012 estimate) [178]. The cost for extending eligibility to all HIV-positive adults ranged from $5575 (in 2016) to $2981 (2036) and hence this strategy is a very cost-effective ART provision scenario (Figure 5.3 a). Similarly, for scenario '500', the ICER value for DALYs decline from $5575 (in 2016) to $5080 (in 2036), which makes this one also a very cost-effective scenario (Figure 5.3 a). Therefore, both ART provision scenarios ('500' and 'all') are very cost-effective intervention scenarios in South Africa, scenario 'all' having the smaller cost per DALYs averted. But these predictions could change depending on the disability of weight assumptions. The baseline parameter for the disability of weight for individuals who are not on ART used here is 0.166. The ICER increases with less disability of weight. Based on the calculation in the parameter values section, the net disability of weight for individuals who are not on ART decreases if the majority of individuals waiting for ART are individuals with a higher CD4 cell count, which becomes achievable with calendar time, with higher access rate and higher ART provision. For such a scenario, cost per DALY could be higher

(a) DALYs

(b) QALYs

(c) Years of life saved
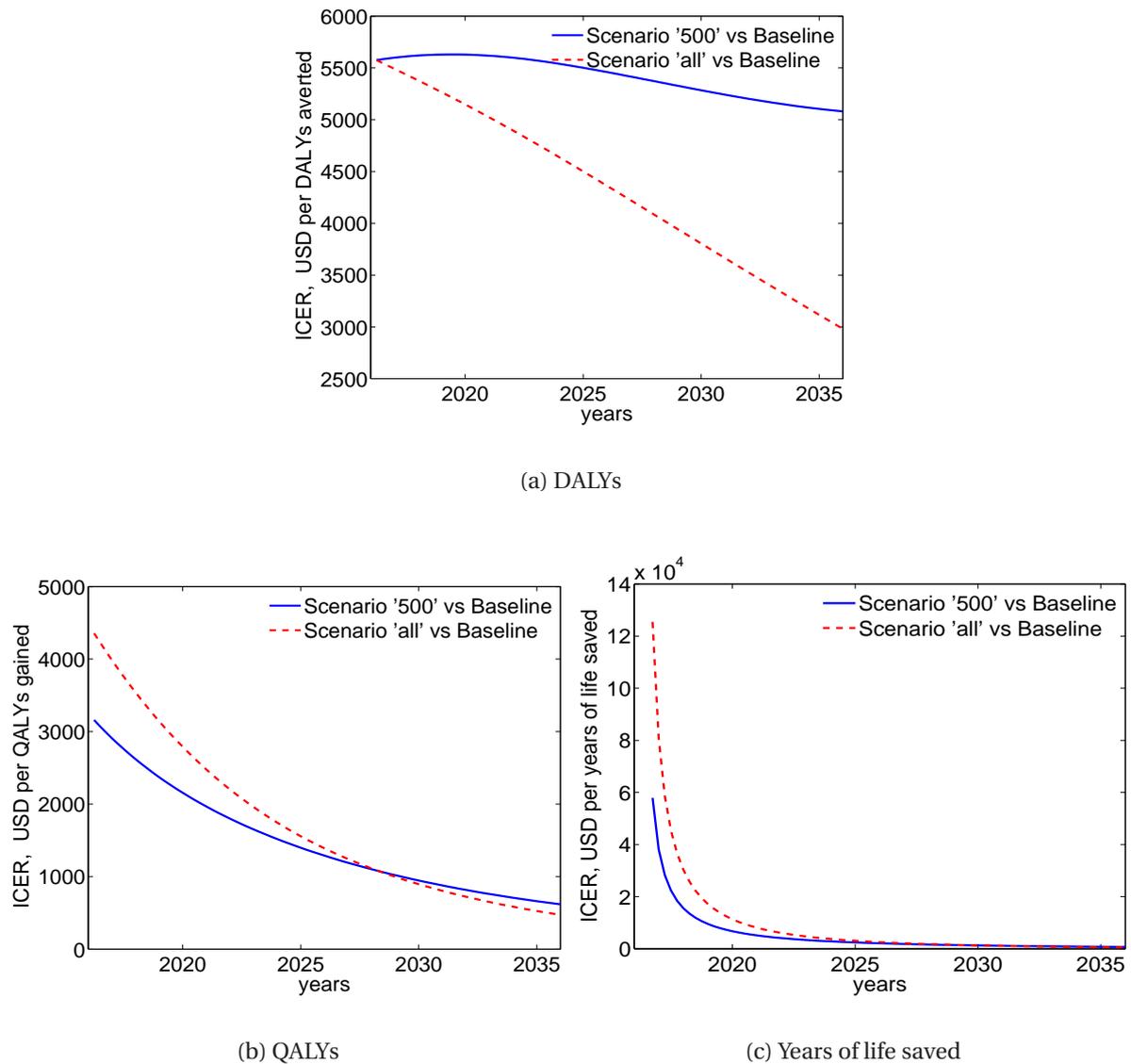
Figure 5.3: Incremental cost per different health outcomes: DALYs, QALYs and years of life saved for expanding eligibility criteria for ART.

than the estimations above but still less than three times the GDP per capita. For instance, if disability of weight for individuals on ART is 0.1, which corresponds to 4%, 16% and 80% of the total individuals without treatment having CD4 < 200, 201-350 and > 350, respectively, then the ICER could be as high as $22,850 and $10,880 for scenarios '500' and 'all', respectively. Still these scenarios become cost-effective but not very cost-effective as the baseline assumption of disability of weight (0.166). The other extreme scenario for the average disability weights of individuals who are not on ART, if the majority of individuals who are not on ART have low CD4 cell count (< 200), example 80%, 10% and 10% of individuals who are not on ART have CD4 cell count < 200, 201-350 and > 350, respectively. Using the same ap-

proach of the weighted average calculation, the disability weight becomes 0.465. For this assumption, cost per DALYs averted stays less than $1600 all the time for both scenario '500' and scenario 'all', which makes both scenarios very cost-effective. We presented maximum and minimum disability weights for individuals who are not on ART in order to have the general picture of the ICER values as we put in uncertainties, where all the disability of weight assumptions show that scenario 'all' is always either cost-effective or very-cost effective.

Figures 5.3, 5.4 and 5.5 show that the incremental ratios for all the scenarios become smaller and smaller with calendar time. For instance, in our model the incremental cost per QALY ranges from $3160 (in 2016) to $620 (in 2036) (Figure 5.3 b) for scenario '500'. The ICER value for scenario 'all' starts at a higher level as compared to scenario '500' and breakevens at about 2028. Additionally, projections show a very sharp decline for the ICER value of years of life saved curve (see Figure 5.3 c). The incremental cost needed to gain years of life saved for all the scenarios; 'all CD4' and '500' become almost similar at 2030. The incremental cost per life years saved declines from $57,900, and $125,600 (respectively scenario '500' and scenario 'all') in 2016 to $730 and $590 in 2036 (respectively scenario '500' and scenario 'all'). Years of life saved are calculated by subtracting the cumulative number of the total population with the baseline scenario from the cumulative number of the total population with the new intervention scenario. The reason why we have large values of ICER for YLS, especially in the first few years, is due to the fact that increased annual spending for the higher ART provision scenario becomes very high while the years of life saved is not large (The total population does not change much at the start of ART scale up). We only see the benefits on the total population increasing at a late stage which is directly linked with life expectancy. A summary of these numbers are presented in a table, see Table 5.3.

Figure 5.4 presents the ICER values for HIV infection averted for different scenarios. The results show that the incremental cost per HIV infection averted declines with calendar time for each ART initiation scenarios. The scenario 'all' has always a smaller incremental cost ratio compared with scenario '500'. The ICER declines from $18,300 (in 2016) to $2,200 (in 2036) per HIV infection averted as compared with the decline from $24,800 to $4,100 for scenario '500'. This means fewer dollars will be spent to avert a single new HIV infection. In Figure 5.4 (b) we showed the phase portrait of the incremental cost from the baseline versus
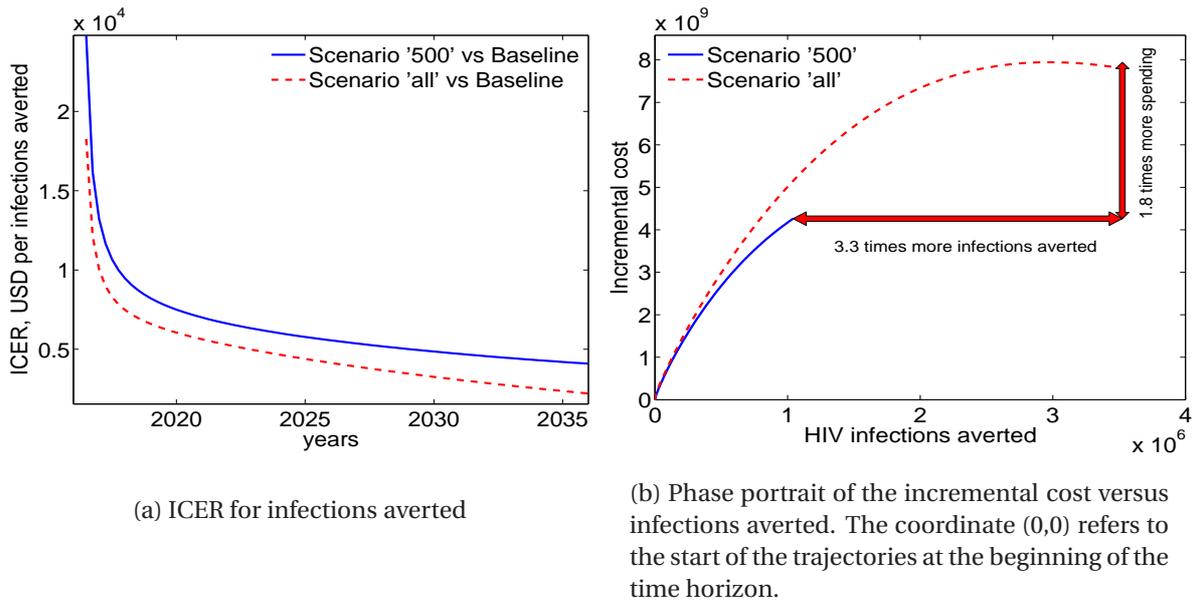
(a) ICER for infections averted

(b) Phase portrait of the incremental cost versus infections averted. The coordinate (0,0) refers to the start of the trajectories at the beginning of the time horizon.

Figure 5.4: Incremental cost per HIV infection averted and phase portrait of the incremental cost and the number of HIV infections averted for different treatment scenarios.

the number of HIV infection averted. Obviously, for more incremental cost, more infections and deaths are averted. For scenario '500', we need over 4 billion USD to avert approximately one million HIV infections over twenty years. Compared with the scenario '500', 1.8 times more spending might avert 3.3 times more HIV infections, if individuals start ART regardless of their CD4 cell count.
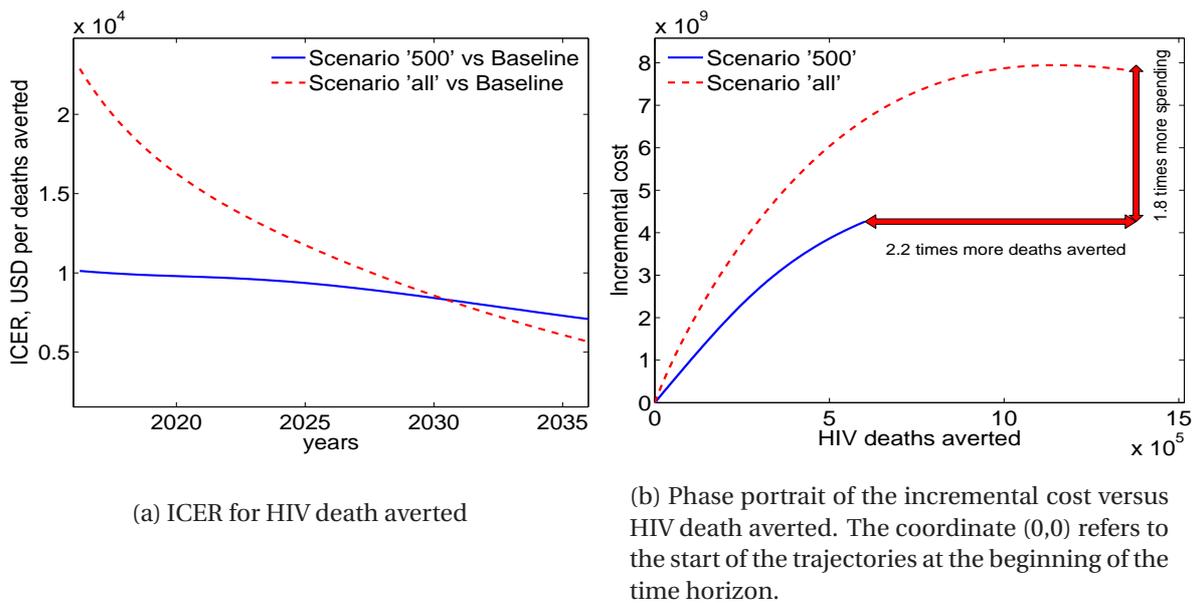

(a) ICER for HIV death averted

(b) Phase portrait of the incremental cost versus HIV death averted. The coordinate (0,0) refers to the start of the trajectories at the beginning of the time horizon.

Figure 5.5: Incremental cost per HIV death averted and phase portrait of the incremental costs and the number of HIV deaths averted for different treatment scenarios.

Unlike the cost per infection averted, we see a different trend of the ICER value for the HIV deaths averted. For scenario 'all' the ratio declines gradually and the value stays almost greater than that of scenario '500' with the exception of after 2030 where we see a breakeven situation (see Figure 5.5 (a)). The ICER for scenario 'all' declines from $22,870 (in 2016) to $5,661 (in 2036) as compared to the decline from $10,130 to $7,087 for scenario '500'. The ICER values for deaths averted are higher than those of the HIV infections averted, for almost all the entire period of the time horizon. This is also explained by the respective subplots in (b) of Figures 5.4 and 5.5. For scenario '500', we need over 4 billion USD to avert approximately 600,000 HIV-related deaths over twenty years, compared to the one million HIV infections which might be averted in the same period. For a similar increase of cumulative ART spending (1.8 times), more HIV infections are averted (3.3 times) as compared to the deaths averted (2.2 times) when we shift scenario '500' to scenario 'all'. The denominator of ICER for HIV deaths averted is smaller than that of HIV infection averted. The difference of the benefits between HIV infections and deaths averted might be due to the fact that HIV treatment has immediate impact in reducing HIV infections as treatment reduces infectiousness of HIV infected individuals due to immediate viral suppression.

Table 5.3: Percentage change of cost and incremental cost-ratios of a new strategy as compared to the baseline ART scenario for the health outcomes; infections and deaths averted, DALYs averted, QALYs gained and years of life saved.

	Scenario '500'			Scenario 'all'		
Time Horizon	5yrs	10yrs	20yrs	5yrs	10yrs	20yrs
Cumulative costs (in Billion USD)	10.23	21.48	42.98	12.89	25.73	46.52
Change of cumulative costs (%)	11.2	12.7	11.7	40.0	35.1	24.1
USD per infection averted	7,002	5,562	4,093	5,628	4,140	2,213
USD per death averted	9,744	9,208	7,087	15,161	11,050	5,661
USD per DALYs averted	5,618	5,460	5,080	5,025	4,363	2,981
USD per QALYs gained	1,967	1,289	618	2,478	1,390	473
USD per years of life saved	5,146	2,130	731	8,093	2,556	585

Table 5.3 shows a summary of the results of the change of the cumulative costs, cost per HIV infection and death averted at 5, 10 and 20 years. For five years of an ART program an increase of ART provision to '500' might require approximately 11.2% increase of the overall program cost. If individuals start treatment regardless of their CD4 cell count, the result

shows that the cumulative cost over five years increases by approximately 40%. Interestingly, for scenario 'all', the percentage changes of the cumulative cost decreases significantly with the time horizon. The percentage changes were 40%, 35.1% and 24.1% of the cumulative cost after 5, 10 and 20 years, respectively. The decreasing trend comes from the decrease of person years of ART due to significant reduction of HIV infections. The percentage changes at 5 years for scenario 'all' was almost four times that of scenario '500' (40% as compared to 11.2%), which reduces to only two times at 20 years of time horizon (24.1% as compared to 11.7%, see Table 5.3). This shows that the benefit of higher ART provision scenario for longer time is significantly higher compared to that of late ART provision scenario. The curves of the impact of ART in averting HIV infections and deaths has been already discussed in chapter 4.

5.4   Annual and cumulative costs as we vary cost estimations

(a) Annual cost   (b) Cumulative cost
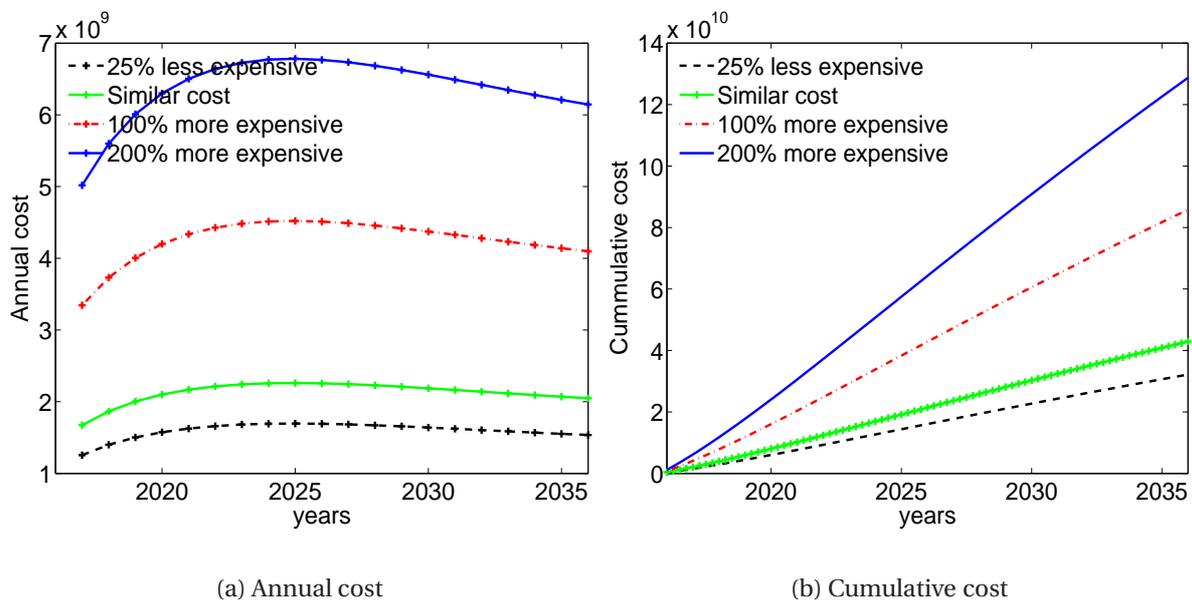
Figure 5.6: Costs as we vary cost assumption for providing ART per patient per year. The baseline cost we assumed is $630 USD per patient per year [122]. The green curve shows annual and cumulative cost estimations of the baseline scenario. All the plots are for scenario '500'.

In this section we performed a sensitivity analysis on the variable: cost of providing ART per patient per year. Input values were varied over specified uncertainty ranges (from 25%

less expensive drug cost to 200% more expensive drug cost). If we assume that the cost of providing ART is 25% less than the baseline assumption ($630), then it becomes $0.75 \times 630 = 472.5. The graphs in Figure 5.6 show that the model projections of the annual costs are very sensitive to the estimation of cost of providing ART per patient per year. Both the annual and cumulative costs increase by the same factor of the increase of the cost of providing ART per patient per year. These results, however, are intuitive as the annual cost of the program is directly proportional to the unit cost of providing ART. Nevertheless, we presented the results in graphs for the readers to clearly visualize the variation of the annual cost as the unit cost of providing ART varies. For instance, the annual cost for an ART program doubles to 4.33 billion USD in 2021 for scenario '500' when the unit cost of providing ART doubles. The same is true for the cumulative cost assumption. For instance, cumulative spending within five years could double from 10.1 billion USD to 20.3 billion USD for scenario '500' if the cost assumption for providing ART is doubled. The ICER values also change with the same factor, due to the fact that the numerator in the ICER formula changes with the same factor. For instance, if the cost of providing ART becomes twice as expensive, then all the ICER values become twice that of the baseline ICER estimates.

The other uncertainty with the cost estimation of providing ART is that the cost of drugs may decrease with calendar time. Here we assumed that the cost of providing ART declines linearly to 50% by 2036, over 20 years, using interpolation. In Figure 5.7, the trends of the annual cost estimations are presented for a fixed cost and a decreasing cost assumption for scenario '500'. The graphs show that there will be a sharp increase of the annual cost projections during the initial phase of the ART scale up. Then both graphs show a decline, even though the decrease for a fixed cost scenario is gradual. The gradual reduction of the annual cost for the fixed cost assumption comes from the gradual decline of the number of person years of ART for scenario '500', (see the graphs of Figure 4.8 in chapter 4). Whereas, the decrease of the annual cost estimation for the decreasing cost scenario, which is significant, is mainly due to the decrease of the cost of providing ART. Working for cheap drugs can of course decrease the annual spending needed and hence pharmaceutical companies need to work on manufacturing cheap nevertheless effective drugs.
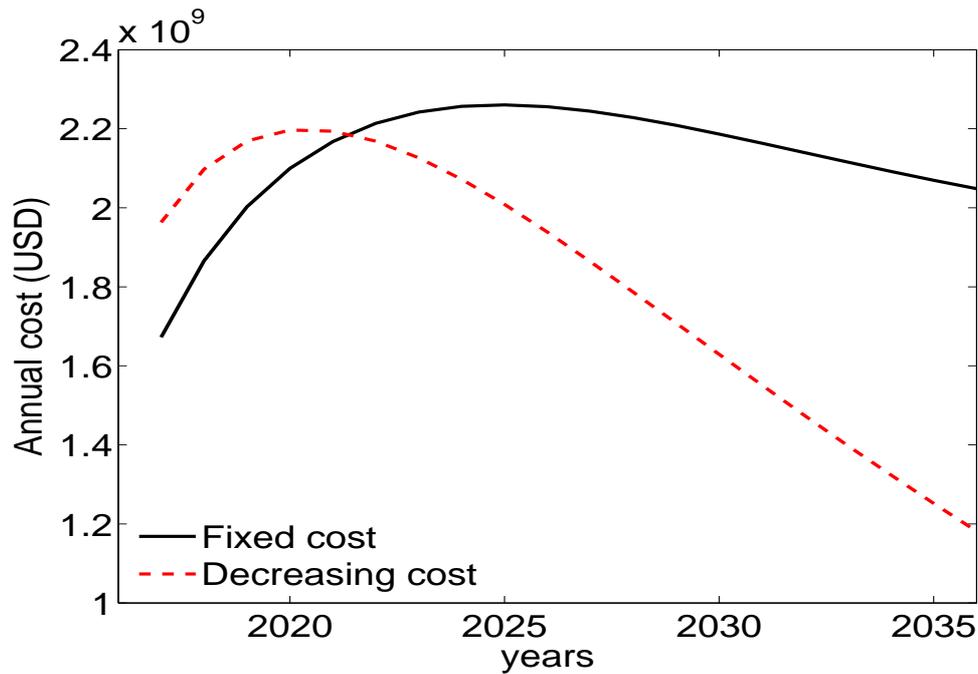
Figure 5.7: Annual cost estimation for a fixed versus a decreasing cost assumption of providing ART. The estimations are done of scenario '500' only.

5.5 Discussion

The total cost of providing ART might increase with personnel costs, resources like building and other factors. For example, if a patient is admitted to a hospital, additional costs for the salaries of the health care staff and the building costs would have to be considered. Some studies have included these components in their modeling work and hence have considered indirect costs (such as building costs), and averted costs from less hospitalization due to early ART roll out [12, 67], which we have not looked at in this work. In a South African study [12], earlier ART initiation was shown to be cost saving with 4 to 12 years of program implementation. Since we did not consider these aspects in this study, our cost estimation to run ART programs might be underestimated. Therefore, with our analysis, cost-benefit analysis is not evident. But we know that ART improves quality of life of the patients which reduces the number of hospital visits, and hence decreases costs for hospital care and staff. Thus, money might even be saved. Moreover, it creates a healthy work force for different sectors and industries.

We know that ART programs are costly, even if the drug cost has shown a gradual decline

in recent years [131, 132], due to the fact that ARVs are taken for the entirety of the patient's life. With more inclusive CD4 criteria, ART programs recruit more HIV infected individuals for treatment which averts many HIV infections, with comparably less incremental cost needed per infection averted. Compared with scenario '500', the scenario 'all' is less costly over the entire period of the projection when HIV infection averted is the intended outcome considered. In this study we showed that the ICER could reach up to 18,260 USD per HIV infection averted if individuals start HIV treatment regardless of their CD4 cell count. Similarly, we see an ICER value of up to 22,870 USD per HIV death averted. Although we found that these cost-effectiveness ratios are high at the start of program implementation of the new ART provision, both of them decrease significantly with calendar time as the program runs for a longer period. The decrease in these cost-effectiveness ratios in 2036 are 2,213 USD per HIV infection averted and 5,661 USD per HIV death averted.

We know that expanding ART to CD4 '500' and 'all' scenarios might be logistically difficult at first phase as programs grow in size very quickly and hence the 'front loaded' investment becomes very high [179]. On average, ART programs in South Africa may be between 1.7 billion and 2.3 billion USD every year in the next 20 years if individuals start at a threshold of 500 CD4 cell count. The investment is always high for earlier intervention. But it saves many things. If individuals were to start ART late, there is a high chance of a need for more resources: clinical staff and sufficient beds for hospital care which also increases the routine of HIV care. In a recent study [180], it was indicated that a new investment framework for the global HIV response might need an HIV program funding scale up from \$16.6 billion in 2011 to \$22.0 billion in 2015. Similarly in South Africa, the national strategic plan estimated a threefold increase for ART (1.588 billion Rand in 2007 to 5.014 billion Rand in 2011) [181]. In another modeling work, it was estimated that an increase of the total cost of ART program by 17% and 32% would be needed for new South African and WHO guidelines, respectively [122]. Clearly we need to increase the investment in ART programs to incorporate the huge influx of newly eligible individuals with new ART provision scenario which have more inclusive CD4 criteria.

5.6   Conclusion

In this chapter we assessed costs and calculated the incremental cost (in USD) per different health outcomes such as QALYs gained, DALYs, infections and deaths averted. Results show that, when the threshold for ART provision is increased, the initial annual spending for providing ART increases greatly. This, however, declines significantly for the scenario 'all' and declines steadily for the baseline and scenario '500'. The incremental cost ratios of different outcomes decrease with time in the horizon time for all the scenarios we considered. The ICER values for infections and deaths averted for scenario 'all' decrease rapidly compared to those of scenario '500'. Moreover, the incremental cost needed to avert one HIV infection was shown to be always less for scenario 'all' compared to those of scenario '500'. This shows that scenario 'all' needs less additional cost for the drug to gain the same health outcome compared to those of scenario '500'. This is because, even if putting individuals on treatment regardless of their CD4 cell count is very expensive, the number of HIV infections averted are many.

In this study we have shown that both scenarios '500' and 'all' are very cost-effective. Moreover, the higher the ART provision scenario, the less incremental cost is needed to avert HIV infections and HIV-attributed deaths. However, achieving the intended access rate of treatment (about 40% have to start treatment in the first year after becoming eligible) is critical to see results over the period of ART program implementations. We clearly see that the person years of ART increases with time and hence commitment for funding by government, non-government organizations is vital especially for the first few years of ART scale up, as the annual spending starts declining later.

In the long term, annual spending could reduce considerably due to significant reduction of new infection over time which might lead to elimination (for high ART access rate and high reduction of HIV transmission). But all of these are true or become evident if, and only if, we have a program which runs effectively, and high retention and high viral suppression is achieved.

This study has the following limitations. In our cost assumption we did not consider

different cost assumptions for first- and second-line regimen separately, as we do not have distinct classes for the two regimens which might underestimate the overall program cost. We rather considered an average unit cost of providing ART per patient per year, but the reality is that some individuals may shift from first-line to second-line regimen, especially when ART programs run for longer periods. We aim to address this by considering treatment failure which we opt to include in an extended model to be discussed in chapters 6 and 7, after we have now a better understanding of the model. Adding components of treatment failure might help us better estimate the cost of ART programs and understand the overall dynamics of HIV. Additionally, limitation of finding better data on the time trend of the cost of ARV might have biased the analysis. What we only presented is analysis for some scenarios of the cost reduction of providing ART. We might need better predictions of cost of ARVs into the future in addition to the past trends of ARVs. The estimation of quality of life for susceptible individuals might also affect the calculation of the incremental cost-effectiveness ratio. Because of the limitation getting data on this, we have just assumed a value closer to 1 (meaning perfect health condition) but at least greater than the estimate for individuals on ART, because those on ART might have some side effects from the ARVs itself.

Chapter 6

Modeling the impact of treatment failure and dropout

6.1   Introduction

In the world, many HIV positive people do not test for HIV before it becomes AIDS (symptomatic). This, however, has changed in recent years. The number of individuals testing for HIV and individuals who access treatment is increasing. Due to this, in the past ten to fifteen years, ART has saved many lives and averted HIV infections. Disease morbidity has also decreased over years. Despite this impact, we have not yet witnessed ART's role in significantly reducing the HIV incidence leading to elimination of HIV in short period. In South Africa, previous studies [182, 183, 184] showed reduction of HIV-attributed deaths. HSRC estimates that HIV incidence in the adult population in 2012 has reduced to 1.72%(1.38%-2.06%) from its peak around 2000, yet we see that as many as 400,000 infections occurred in the same year [27]. Is the impact of ART still only saving lives or are many infections being averted, infections which might in the future lead to the elimination of HIV? Many factors may affect the achievement of a significant decline of new HIV infections to reach HIV elimination. The factors could include increase of treatment failure and dropout. The first challenge in any ART program is linkage to care. Secondly, retention is a big challenge as some continue to adhere (important for minimizing rate of switching) to the drug regimen while others might not show at clinics after ART initiation.

In the previous two chapters, we have worked on a mathematical model which does not include treatment failure and dropout from treatment programs, to first understand the impact of different ART scale up scenarios. Thus, we only presented results of different scenarios where treatment failure and dropout is neglected. In this chapter we add these components as some data show that these are key challenges for a drug regimen which will be taken for the rest of life after onset of HIV infection [84, 185]. Moreover, the increase of the number of individuals who fail first-line treatment and lost to follow up might reduce the impact of early HIV treatment. Studies in [186, 187, 188, 189] have discussed issues of dropout cases from ART programs and drug resistance. Specifically, the number of individuals who might seek second-line treatment may increase with calendar time. Thus, researchers, policy makers and others should ask the question: how fast does the class of second-line treatment grow? Modeling can help produce different scenarios of dropout for a clearer picture. Thus, building on our earlier study of time since infection structured model, we investigate the impact of first-line treatment failure and dropout on the overall HIV dynamics. We therefore extend the model to answer research questions such as: how do the issues of treatment failure and dropout affect the overall effectiveness of ART scale up programs?

Individuals who either stop treatment or are lost from treatment programs are referred as dropouts. Thus, the dropout rate refers to the rate at which individuals who stop or are lost from the treatment program leaves first-line treatment class.

Throughout this chapter and chapter 7, the first model refers to the model discussed in the previous chapters (4 and 5), which is a model without treatment failure and dropout. The second model refers to the model with treatment failure and dropout to be discussed in detail in chapters 6 and 7.

6.2   Model formulation

We considered a mathematical model of HIV structured by time since infection and time since the initiation of HIV treatment by extending the first model. The model has five compartments: susceptible class (S); infected class without HIV treatment (I_1); first-line treatment class (T_1); infected class of those who dropout from first-line HIV treatment (I_2) and

lastly, second-line treatment class (T_2). Susceptible individuals can be infected at a rate ϕ commonly referred as force of HIV infection. HIV infected individuals start HIV treatment at a rate $e(t, \tau)\pi(t)$ and join first-line treatment class. Individuals in first-line treatment may either stop or fail treatment. Those individuals who stop first-line treatment move to class I_2, whereas those who failed the first-line treatment start second-line treatment at a rate f. In [89], has assumed that 50% of individuals who dropout treatment re-initiated ART after new voluntary test. But we do not have data to properly estimate treatment access and HIV transmission probability by individuals who stopped treatment as a function. We thus assume that individuals are less likely to re-initiate ART immediately after they stop treatment, and hence, their seeking treatment depends on how long they have been without treatment. Thus, we assumed that individuals who dropout of treatment can re-initiate ART with similar treatment access rate (as I_1), i.e. $e(t, \tau_3)\pi(t)$. Similarly, the HIV transmission probability of individuals in I_2 is assumed to be the same as that of individuals in I_1 with some scaling factor (σ) to account for a change of behavior which might be seen by individuals who dropout because of the knowledge of their HIV status. HIV/AIDS induced mortality assumption for the treated class (T_2) accounts for the modest dropout and treatment failure, which is a similar argument as in chapter 4 for individuals in the respective treated class (T). Thus, we do not have transitions with in the classes for those individuals who might fail or drop second-line treatment. By doing this we wanted to reduce the complexity of the model.

Similar to the model formulation of chapter 4, to allow for a change of behavior or other external interventions, we let the HIV transmission decrease with HIV/AIDS mortality rate and prevalence. External interventions could result in increased condom use, delayed age of sexual debut and fewer sexual partners. Whatever the reason for the decline of HIV incidence and gradual decrease of prevalence at later stage, we can add an external 'control' which lets the force of HIV infection decline over time. Thus, we have considered an exponential function, $e^{-(\alpha_1 M(t) + \alpha_2 P(t))}$, with α_1 and α_2 as scale parameters and $M(t)$, and $)P(t)$ are HIV mortality rate and HIV prevalence at a calendar time t, respectively. A similar approach for estimating the expression for the infection rate is also considered in [13, 154, 155].

Following these assumptions, we draw the following schematic diagram of the model, Figure 6.1.
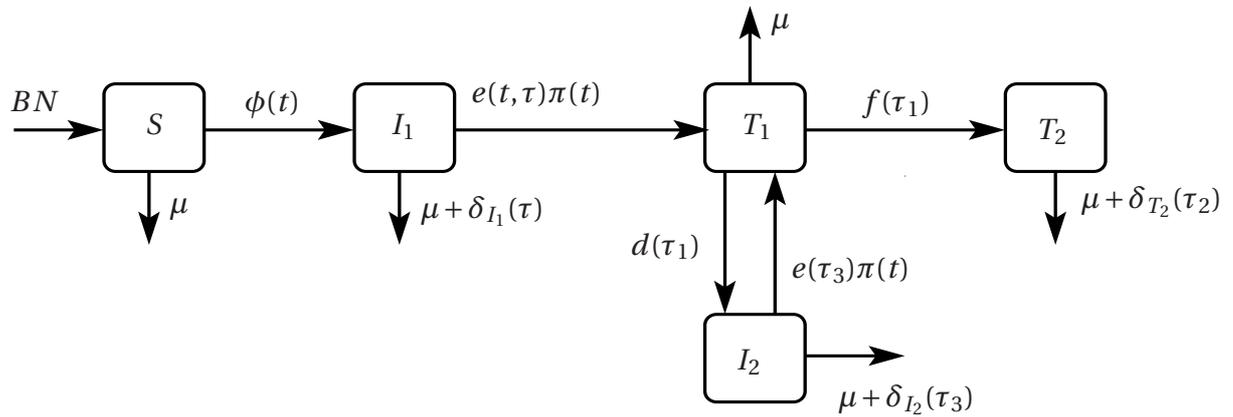
Figure 6.1: Model with treatment failure and dropout.

The model diagram and the model assumptions considered gives us the following system of equations:

$$\frac{d}{dt}S(t) = BN(t) - \big(\phi(t) + \mu\big)S(t),$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right)I_1(t,\tau) = -\big[e(t,\tau)\pi(t) + \mu + \delta_{I_1}(\tau)\big]I_1(t,\tau),$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau} + \frac{\partial}{\partial \tau_1}\right)T_1(t,\tau,\tau_1) = -(d(\tau_1) + \mu + f(\tau_1))T_1(t,\tau,\tau_1), \qquad (6.2.1)$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau_2}\right)T_2(t,\tau_2) = -(\mu + \delta_{T_2}(\tau_2))T_2(t,\tau_2),$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau_3}\right)I_2(t,\tau_3) = -(\mu + \delta_{I_2}(\tau_3) + e(t,\tau)\pi(t))I_2(t,\tau_3).$$

where τ is the time since HIV infection, τ_1 (respectively τ_2) represents the time since the start of first-line (respectively second-line) HIV treatment, while τ_3 is the duration since the interruption of first-line treatment. $e(t,\tau)$ is the proportion of individuals who become eligible to receive ART, which is time since infection and is calendar time dependent. The rate $\pi(t)$ refers to the proportion of individuals who access treatment among those who are eligible. The eligibility function is based on certain ART initiation criteria which was already discussed in chapter 3.

System (6.2.1) has the following boundary conditions:

$$I_1(t,0) = \phi(t)S(t),$$
$$T_1(t,\tau,0) = e(t,\tau)\pi(t)I_1(t,\tau) + e(t,\tau)\pi(t)I_2(t,\tau_3),$$
$$T_1(t,0,\tau_1) = 0, \tag{6.2.2}$$
$$I_2(t,0) = \int_0^\infty \int_0^\infty d(\tau_1)T_1(t,\tau,\tau_1)d\tau d\tau_1,$$
$$T_2(t,0) = \int_0^\infty \int_0^\infty f(\tau_1)T_1(t,\tau,\tau_1)d\tau d\tau_1.$$

Here, the boundary conditions are the number of new individuals who joined the respective class by a transition from another class. For instance, $I_2(t,0) = \int_0^\infty \int_0^\infty d(\tau_1)T_1(t,\tau,\tau_1)d\tau d\tau_1$ is the number of individuals who dropout of treatment at time t. The force of HIV infection is given as:

$$\phi(t) = e^{-(\alpha_1 M(t)+\alpha_2 P(t))}(A+B)/N(t), \tag{6.2.3}$$

where

$$A = \int_0^\infty \beta_I(\tau)I_1(t,\tau)d\tau + \sigma \int_0^\infty \beta_I(\tau_3)I_2(t,\tau_3)d\tau_3$$

is the contribution from individuals who are not currently on ART. And

$$B = \eta \int_0^\infty \int_0^\infty \beta_T(\tau_1)T_1(t,\tau,\tau_1)d\tau d\tau_1 + \rho \int_0^\infty \beta_T(\tau_2)T_2(t,\tau_2)d\tau_2$$

is the contribution from individuals who are currently either on first- or second-line treatment. The definition of the parameters of the rest is given in Table 6.1.

6.3   Model parameter values

As in the previous chapters, the CD4 cell count threshold for eligibility is considered to be 200 cells/mm^3 before 2013 (a year when South African 2013 new ART guideline started implementation) and 350 cells/mm^3 after 2013. We refer this as a baseline ART initiation scenario. We have also two ART provision scenarios; scenario '500' where individuals become eligible when CD4 cell count is less than 500 cells/mm^3, and scenario 'all' where individuals are eligible irrespective of their CD4 cell count. All the new ART scale up scenarios start from 2016. We assume a Weibull function with 2.2 shape parameter and 10 years median survival is used as mortality rate for ART naive individuals (I_1). Other parameter values are described

Table 6.1: Definitions of parameters in the model formulation.

B	per capita adult recruitment rate to the sexual active population
β_I	HIV transmission probability of individuals in the infected classes (both I_1 and I_2)
β_T	HIV transmission probability of individuals in the treated classes (both T_1 and T_2)
η, ρ	the relative reduction in infectiousness of individuals in first and second-line HIV treatment, respectively
σ	relative change of the infectiousness level of individuals in I_2 compared to that of I_1
μ	natural exit rate from the age group 15-49 (either through non AIDS-related death or ageing)
δ_{I_2}	disease induced death rate of infected individuals in I_2 class
$\delta_{T_1}, \delta_{T_2}$	disease induced death rate for individuals in the first- and second-line treatment class
d	the rate at which individuals dropout from first-line HIV treatment
f	first-line HIV treatment failure rate
$e(t, \tau)$	is the proportion of individuals who are eligible to receive ART as a function of time since infection and calendar time
$\pi(t)$	is the rate at which individuals access treatment among those who are eligible as a function of calendar time
N	the number of the total population, $N = S + I_1 + T_1 + I_2 + T_2$.

in Table 6.2, Figure 6.3 and some are already discussed in chapter 4. ART access rate, HIV transmission probability and HIV mortality rate for those individuals who are not on ART have similar functions discussed in chapter 4.

A study assumed a long term dropout rate of 1.5% per year [13], using data from a Malawian ART program which suggests up to 8% dropout rate immediately or soon after initiation of ART and then between 1% and 3% per year. Additionally, another study did cohort analysis among adult patients initiating antiretroviral in South Africa to examine retention of patients on ART from 2002-2007. The results showed an increase of the annual lost to follow up at the first year of ART initiation from 1% (in 2002/2003) to 13%(in 2006) [84]. With each additional year on ART, failure to retain has increased. For this study we assumed a high dropout rate, such as 15% in the first year and declining to a long term dropout rate of 2%. For this we used a survival curve shown in Figure 6.2. Unlike the results suggested by [84], we did not have change of the initial lost to follow up (at the first year of ART initiation) varying with calendar time.
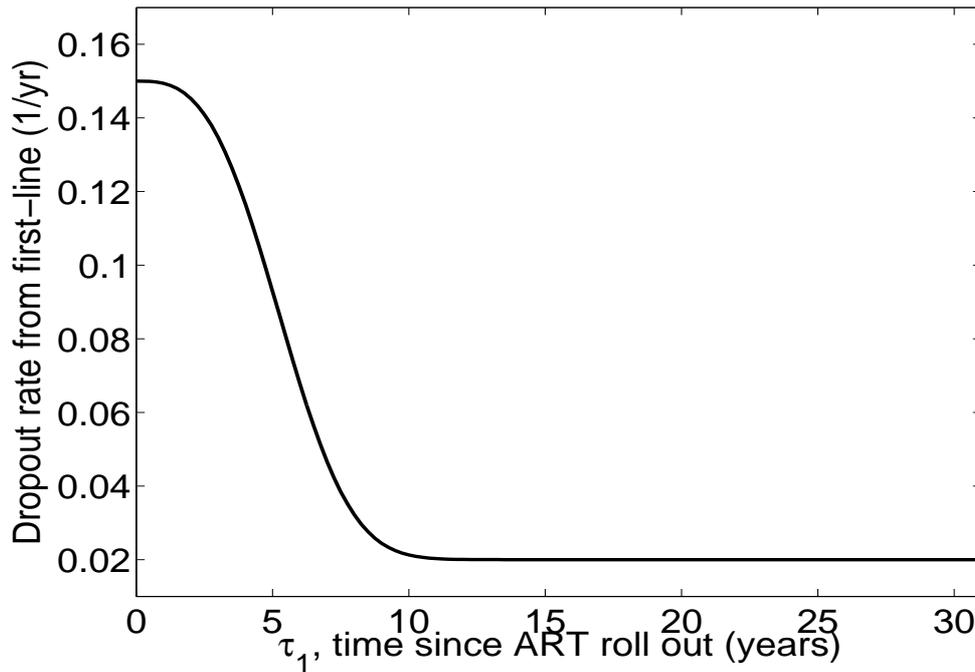
Figure 6.2: Dropout rate for individuals from first-line treatment.

For the dropout we used the following function;

$$d = c + ae^{-(\tau/\lambda)^k},$$

where $c = 0.02, a = 0.13, \lambda = 6,$ and $k = 3.$

According to WHO [109], approximately 3% patients in resource limited settings switched to second-line. A South African study suggests different rates for switching, depending on the drug types: 2.8%(2.1-3.7), 2.4%(2.1-2.7) and 2.9%(2.0-3.9) for Zidovudine, Stavudine and Tenofovir, respectively [110]. For this study we used 3% individuals switching to second-line treatment with a range of 1% to 4% to project different scenarios.

We do not have enough data about the behavior of individuals after stopping treatment. Individuals may be involved in less risky behavior as they at least know their HIV status. But also the same individuals who risked to stop treatment may also get involved in risky behavior. So we do not know exactly how they would behave. Moreover, disease progression in individuals after treatment stops is not clear. As a baseline parameter for σ, we consider that individuals in I_2 class are half as infectious as the individuals in I_1 (i.e. $\sigma = 0.5$).

(a) AIDS mortality rate for individuals in T_2, estimated from [84]

(b) HIV transmission probability
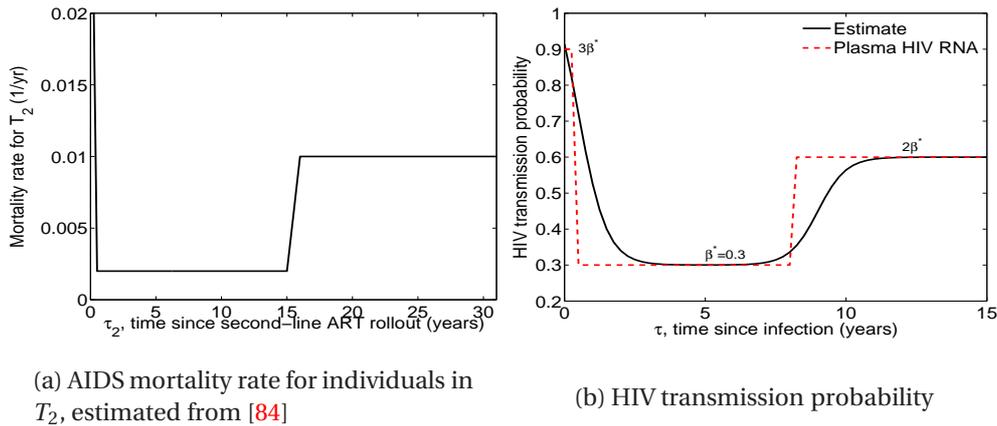
Figure 6.3: Parameter values used in the simulations as a function of time since infection and start of HIV treatment. Transmission probabilities and mortality rates are estimated in the absence of HIV treatment.

Table 6.2: Summary of the parameter values used for the simulation.

parameter	value	remark
B	0.036/yr	explained in chapter 4
μ	0.022/yr	explained in chapter 4
η	0.1	using results from [8, 9]
ρ	0.1	using results from [8, 9]
σ	0.5	assumed
f	0.03/yr	[0.01 0.04] value used from [109, 110]

6.4   Simulation results

In this section, we present simulation results of the time since infection and time since ART roll out structured mathematical model. Similar to the model in chapter 4, for the simulations we took the sexually active population of South Africa. We have the following initial conditions and main inputs for the model simulation. We numerically solved our system of differential equations in the form finite difference scheme solved by Euler's method. We have used smaller step size, $dt = 0.25$ years, to decrease the Euler error. Matlab 2010 version is used for simulating all the results. The following are the initial values, initial time for the

simulation and events with ART scale up scenario.

> t0=1950: the starting year for the simulation
>
> tf=2036: the final year for the simulation
>
> tHIV=1982: the year when HIV is introduced to the population
>
> N0=13,350,000: initial adult population of South Africa (in 1950)
>
> tART=2001: the year when ART roll out started
>
> tART350=2013: is when the 2013 ART guidelines started implementation
>
> tARTScale=2016: year when ART scale up scenarios start

6.4.1   Key epidemic outputs

The plots in Figure 6.4 show rates for the key epidemic outputs. In Figure 6.4(a), the prevalence was fitted to the prevalence of South Africa obtained from HSRC data (2002, 2005, 2008, 2012) [27]. The prevalence is very high even with high ART provision scenario (if all are eligible with current ART access rate). This is increased from the projection of the HIV prevalence presented in chapter 4. The reason why we do not see a declining trend at all is, in addition to the long survival period due to ART, the number of new HIV infections increase with ineffective ART programs (high dropout rates). When individuals dropout from treatment, the risk of infecting others increases, hence more individuals might be infected leading the prevalence to stay fairly at high level. Compared to the results of the first model, even if it is small we see a gradual decline of prevalence only for scenario 'all'. This is a prevalence decline to only 15.8% in 2036, still very high compared to the projections of the first model (i.e. prevalence rate of 10% for scenario 'all' in 2036).

Similar to the results of the model in chapter 4, the incidence rate attains its maximum just before 2000 and declines afterwards 6.4 (b). We see a sharp decline followed by a steady decline and then it stabilizes. A similar trend is observed for the plot of the death rate (Figure 6.4 (c)); however, the curve for the death rate attains its maximum later than the peak of the curve of the incidence rate. Changing the ART provision scenario does not change the

(a) Prevalence

(b) Incidence rate
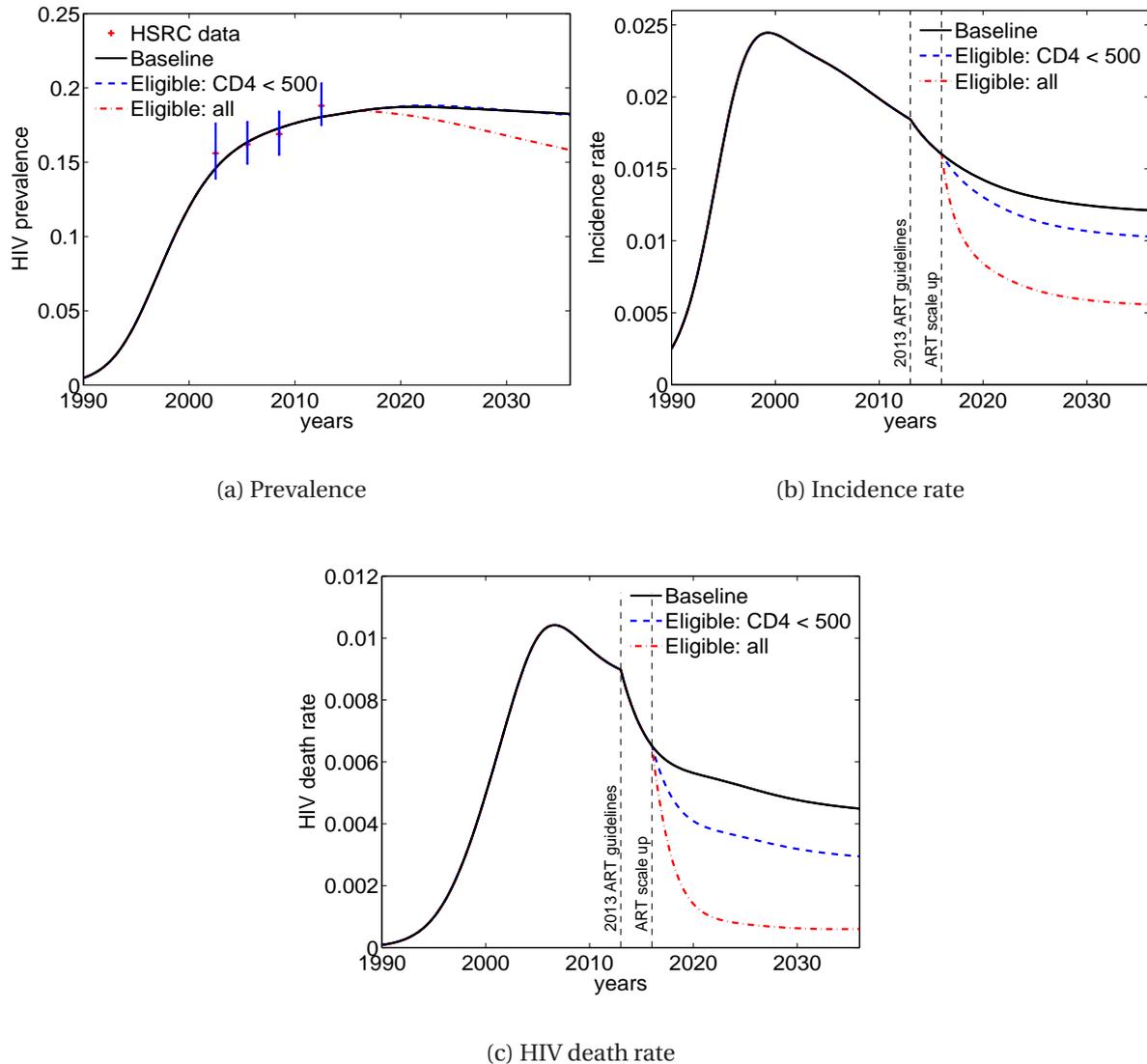
(c) HIV death rate

Figure 6.4: Key epidemic indicators by ART scenario over time; prevalence, the incidence rate and HIV death rates.

prevalence curves much. However, the incidence and death rates significantly decline with the change (increase) of the ART provision. The incidence rate could reduce to 1.03% and 0.56% in 2036 for scenario '500' and 'all', respectively from a projection of 1.21% if we were to continue with the baseline ART scenario. For a shorter time horizon, five years, we see a decline to 1.26% and 0.79% incidence rate level for scenarios '500' and 'all', respectively from a 1.39% incidence rate if we were to continue with the baseline ART scenario. In the plot of the HIV death rate (Figure 6.4 (c)), we see a similar trend of decline for the three ART scenarios. However, the HIV death rate declines significantly for more inclusive CD4 criteria. It might decrease from 0.65% in 2016 (baseline scenario) to 0.45%, 0.29% and 0.06% after

two decades for baseline ART scenario, scenario '500' and scenario 'all', respectively. For a shorter time horizon, after five years of ART scale up implementation we see the HIV death rate declining to 0.55%, 0.39% and 0.11% for baseline, scenario '500' and 'all', respectively.

Compared with the result of the model without treatment failure and dropout, in the model with treatment failure and dropout we see high HIV incidence rate while the HIV-related deaths decline. For scenario 'all', the incidence rate stabilizes at about 0.55% in 2036 as compared to 0.31% (model without treatment failure and dropout, result of chapter 4). This is because individuals who dropout have contributions to HIV transmission as they interrupted ART. We, however, see a different trend for the HIV death rate. The model with treatment failure and dropout suggests that the HIV death rate can be small compared to the projections of the model without treatment failure and dropout. For scenario 'all' in 2036, the death rate becomes 0.06% for the second model as compared to 0.19% for the first model. The death rate of the first model might be over estimated as we used disease induced mortality rate (probably high) for individuals on treatment to compensate for the modest dropout and treatment failure of treatment programs, as we did not have separate classes of first- and second-line treatment. But in the second model when individuals either fail or stop treatment, they join a different class where they live longer with different HIV mortality rate. For individuals who dropout, mortality depends on τ_3 (time since ART dropout). Similarly, individuals in the second-line treatment die at a rate which depends on time since the start of second-line treatment, τ_2. Since these individuals have their own contributions to HIV transmission, we see the number of new infections increasing (for the second model) as compared to the no contribution scenario to HIV transmission by the individuals who might fail or stop ART.

The results presented in Figure 6.5 show the output of different variables of the model. The number of new HIV infections peaks before HIV-attributed deaths, but both decline with calendar time. Whereas, plots for the total number of HIV positive and the number of individuals on treatment keeps increasing for all the scenarios. The increasing trend of the number of total HIV positive individuals (see, Figure 6.5 (c)) is partly due to the fact that people started living longer while on ART. But most importantly, it is contributed while on ART, but a more important contribution is the fact that new HIV infections still occur at higher

(a) New HIV infections

(b) HIV deaths

(c) Total HIV positive

(d) Total individuals on ART
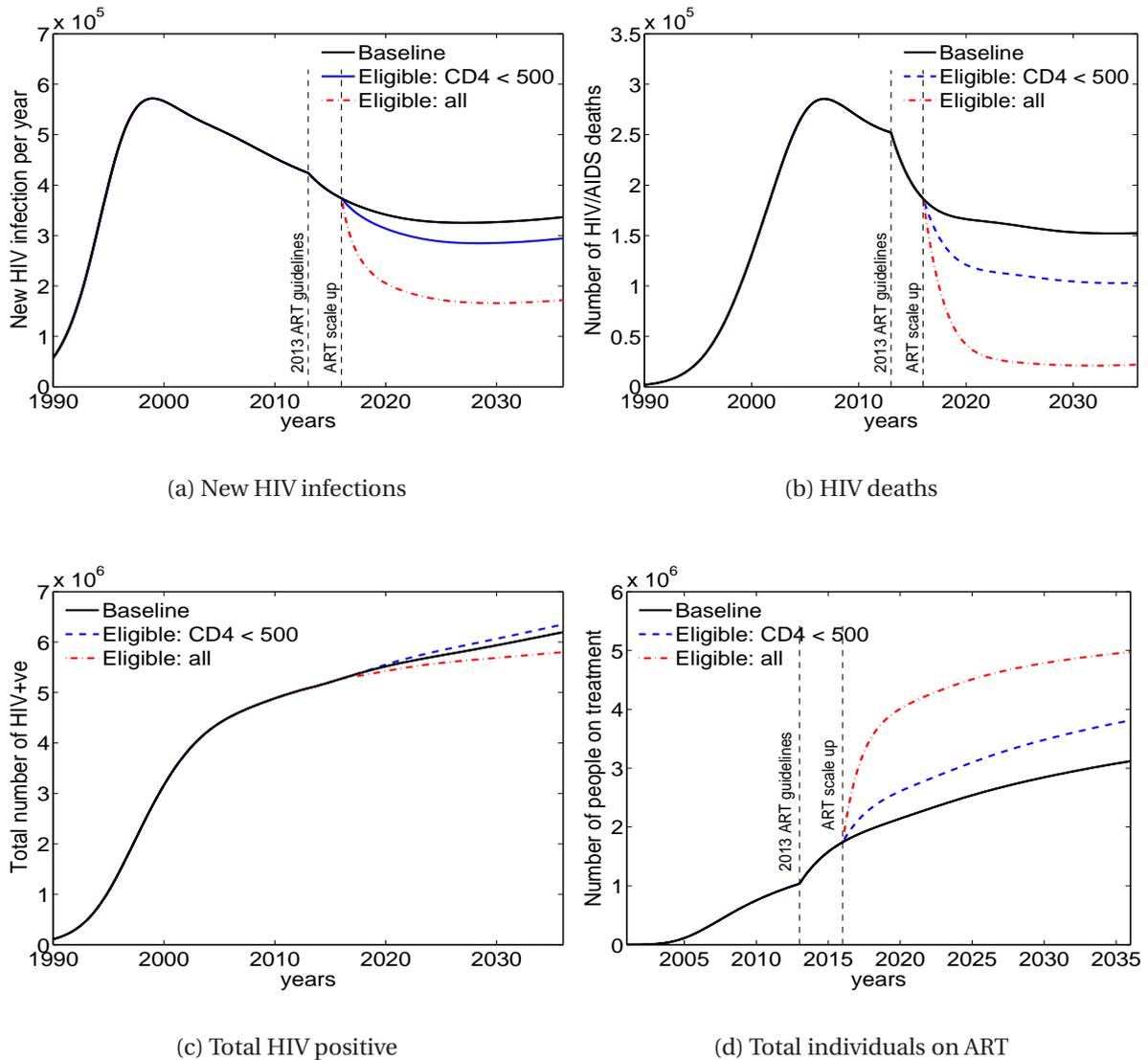
Figure 6.5: This figure presents key epidemic clinical and epidemiological results.

numbers for the second model as compared to the projections of the first model in chapter 4. Figure 6.5 (d) shows the total number of individuals on ART for the three different scenarios. The curves show that more individuals will be in ART on a specific year for higher ART provision scenario (scenario '500' and 'all') as compared to the baseline scenario. Additionally, in contrast to the model projections of the first model, we are not able to see a decline of the number of individuals on ART in any of the three ART scenarios. In the first model, since the number of new HIV infections significantly declined, we see a breakeven situation for the number of individuals on ART for scenario 'all' compared with scenario '500' and the baseline around 2030. But we do not see this kind of breakeven situation for the number

of individuals on ART within two decades (see Figure 6.5 (d)). In the first model, the number of individuals on ART for scenario 'all' in 2036 is approximately 3.4 million as compared to approximately 5 million for the model projections of the second model. Therefore, with individuals failing treatment and dropping out of treatment, the fight against the HIV epidemic becomes more challenging yet with a high ART provision scenario. This continual increase of the number of individuals on ART might indicate the need for the health facility expansion such as treatment provider centers, health care personnel and others continuity for longer period. Unless treatment failure and dropout rates are minimized to the lowest possible level, we will not able to see the annual spending declining. We will discuss the cost analysis of this model in chapter 7.

A study in [27] HSRC estimated that 396,000 (318,000-474,000) new HIV infections occurred in 2012. Our simulation result estimates that approximately 433,200 new HIV infections occurred in 2012, which is in line with the confidence interval of the survey by HSRC. In chapter 4, for scenario '500' we estimated that the number of new infections at the end of the time horizon (2036) will be around 239,700. But, with the same CD4 cell count threshold consideration, the number of new infections becomes higher (approximately 294,500) for the model results of this chapter. This is an increase by approximately 54,800 new HIV infections due to first-line treatment failure and dropout. The difference in the numbers of new HIV infections is mainly contributed by individuals who stop treatment. Comparably the decline of the number of new HIV infections could be more evident if dropout is to be minimized.

Figure 6.6 shows the number of individuals on first-line and second-line treatment for different ART scenarios. In all the scenarios of ART initiation, we generally see an increasing trend. Moreover, as ART provision scenarios increase to scenarios '500' and 'all', the respective number of individuals on both first- and second-line treatment is higher than that of the baseline scenario.

The result in Figure 6.7 shows the proportion of individuals on first- and second-line treatment with calendar time. When the programs run longer, the proportion of individuals who are on second-line treatment increases. It may reach up to 35.9% within two decades with almost a linear increase. From the bar graphs, the proportion of second-line treatment

(a) First-line treatment (b) Second-line treatment
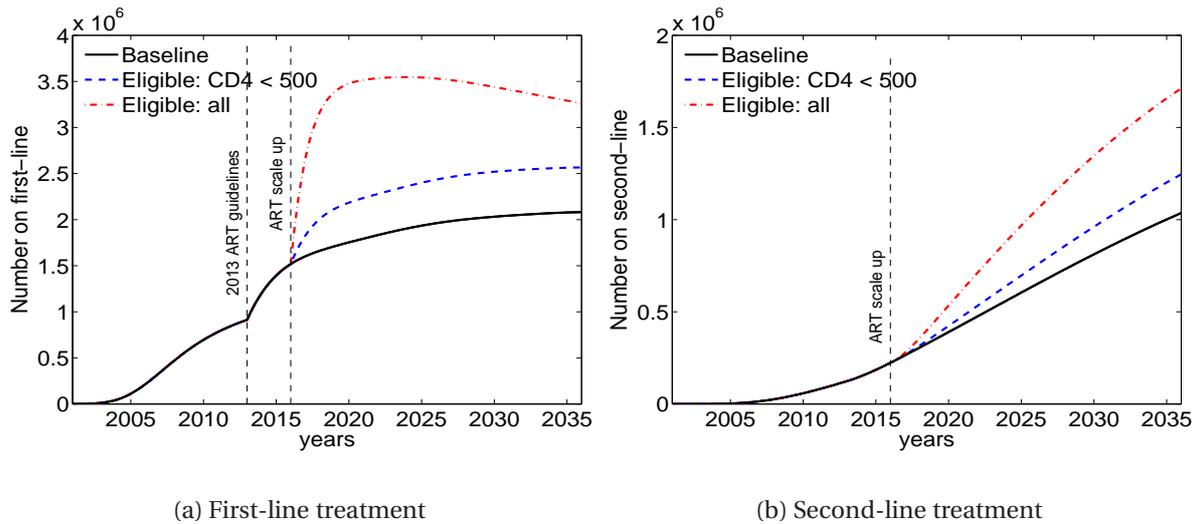
Figure 6.6: Number of individuals on first-line and second-line treatment for different ART scenarios.
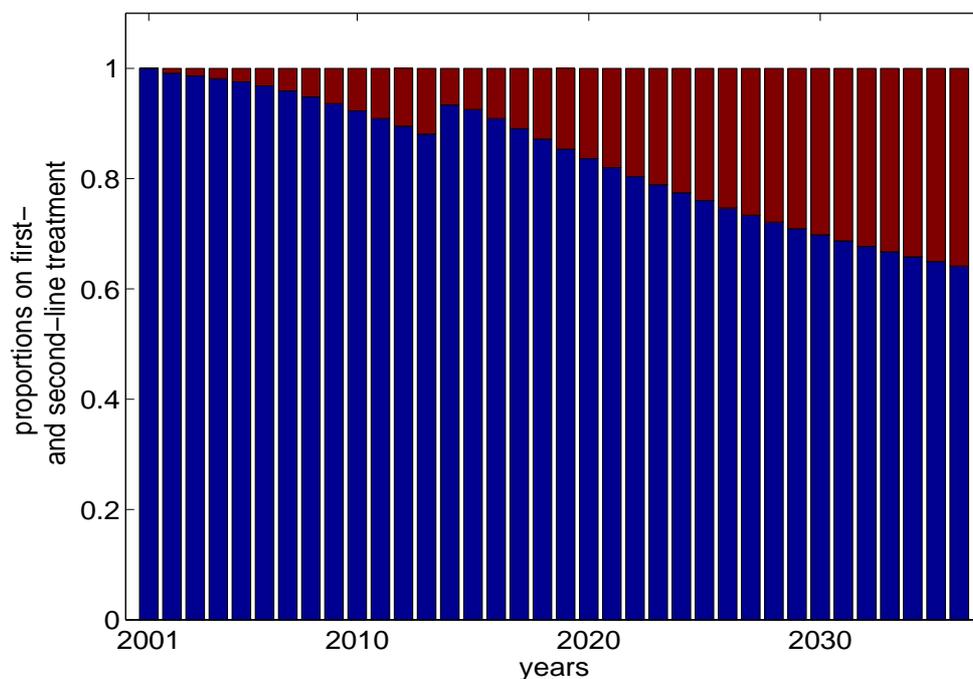
Figure 6.7: Proportion of individuals by treatment category - first-line (Blue) and second-line (Red). With calendar time the proportion of individuals in the second-line treatment grows.

decreased in 2013 from previous years. This is because of the change of treatment guidelines in 2013. Many individuals (most probably with small τ or not showing symptoms) initiated first-line with higher ART provision and most of them do not switch to second-line immediately, as treatment failure rate is dependent on time since first-line ART rollout. Thus, during the first years of implementation of a new eligibility threshold, many individuals initiate first-

line, and hence its proportion increases, making the proportion of the second-line smaller. Usually the cost of the second-line treatment is expensive, which leads to an increase in the overall cost of providing ART at a later stage in the horizon time which we will discuss in detail in chapter 7.

6.4.2   Projections for higher ART access rate and reduction of HIV transmission

In the previous sections, we used the current ART access rate (logistic curve increasing from 0% in 2001 to 52% in 2013 and stays constant) and a 90% reduction of HIV transmission due to HIV treatment. In chapters 4 and 5, we have already discussed the demand by the health sector. The number of individuals who will be on ART increased significantly for the first five years, suggesting increased demand of annual spending only for a short period. But the analysis of this chapter suggests a similarly increased demand of annual spending but continuously for longer periods as the number of individuals on ART continues to increase for the model with treatment failure and dropout. Therefore, in this section we will present a scenario where we achieve a higher ART access rate (90% of all HIV positive individuals who initiate ART every year starting from 2017) and high reduction of HIV transmission (96%) due to HIV treatment. We first present with high HIV transmission reduction and then increase ART access rate.

Assume that the health sectors work effectively to keep individuals adherent to treatment programs leading to long term viral suppression, and hence a higher reduction of HIV transmission by individuals on ART (96% reduction). The results of this scenario are presented in Figure 6.8. The results show that HIV elimination is unlikely to happen within two decades. If HIV+ve individuals become eligible for treatment regardless of their CD4 counts and achieve high reduction of HIV transmission due to ART, the incidence rate could only reduce to just below 0.5% in 2036, which shows that HIV elimination is unlikely to happen soon. Additionally, HIV prevalence stays fairly high around 15% by 2036. The number of individuals on treatment keeps increasing for all ART provision scenarios (see Figure 6.8 (d)). Even though we see reduction in the numbers and rates of the results presented in Figure 6.8, due to high

HIV transmission reduction (96%) as compared to the projections for 90% assumption, it is not sufficient to bring down the incidence level to the threshold of HIV elimination (i.e. 0.1% - one per thousand susceptible individuals). Whether high ART access rate might bring significant declines of incidence rate or not is presented in Figure 6.9 (b).

(a) HIV prevalence

(b) HIV Incidence

(c) HIV death rate

(d) Number of individuals on ART
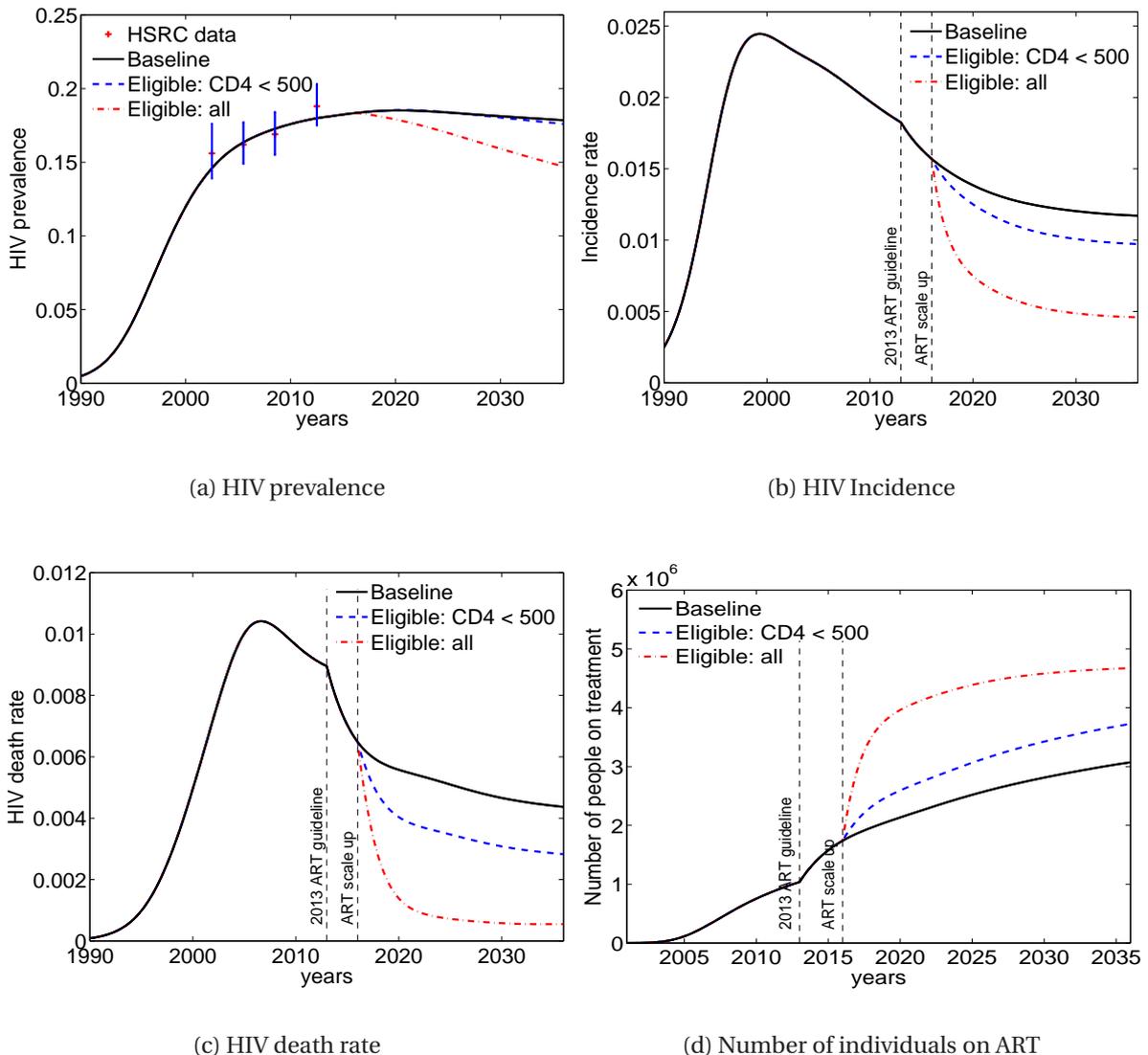
Figure 6.8: Key epidemic results for higher reduction of HIV transmission due to ART. Here we considered a 96% reduction of HIV transmission due to ART with the current ART access rate.

For the simulation results presented in Figure 6.9, we assume high ART access rate and high HIV transmission rate reduction (96%). Even for this scenario, it is difficult to achieve HIV elimination stage within two decades. HIV incidence rate could only be reduced to the level of 0.34% for scenario 'all' in 2036 (see Figure 6.9 (b)). HIV prevalence rate stays fairly

high at about 14% in 2036 (see Figure 6.9 (a)). Therefore, unlike the projection of the first model in chapter 4, the second model does not promise HIV elimination situation. This again suggests the importance of achieving high retention rates and high viral suppression leading to high reduction of HIV transmission.

(a) HIV prevalence

(b) HIV Incidence

(c) HIV death rate

(d) Number of individuals on ART
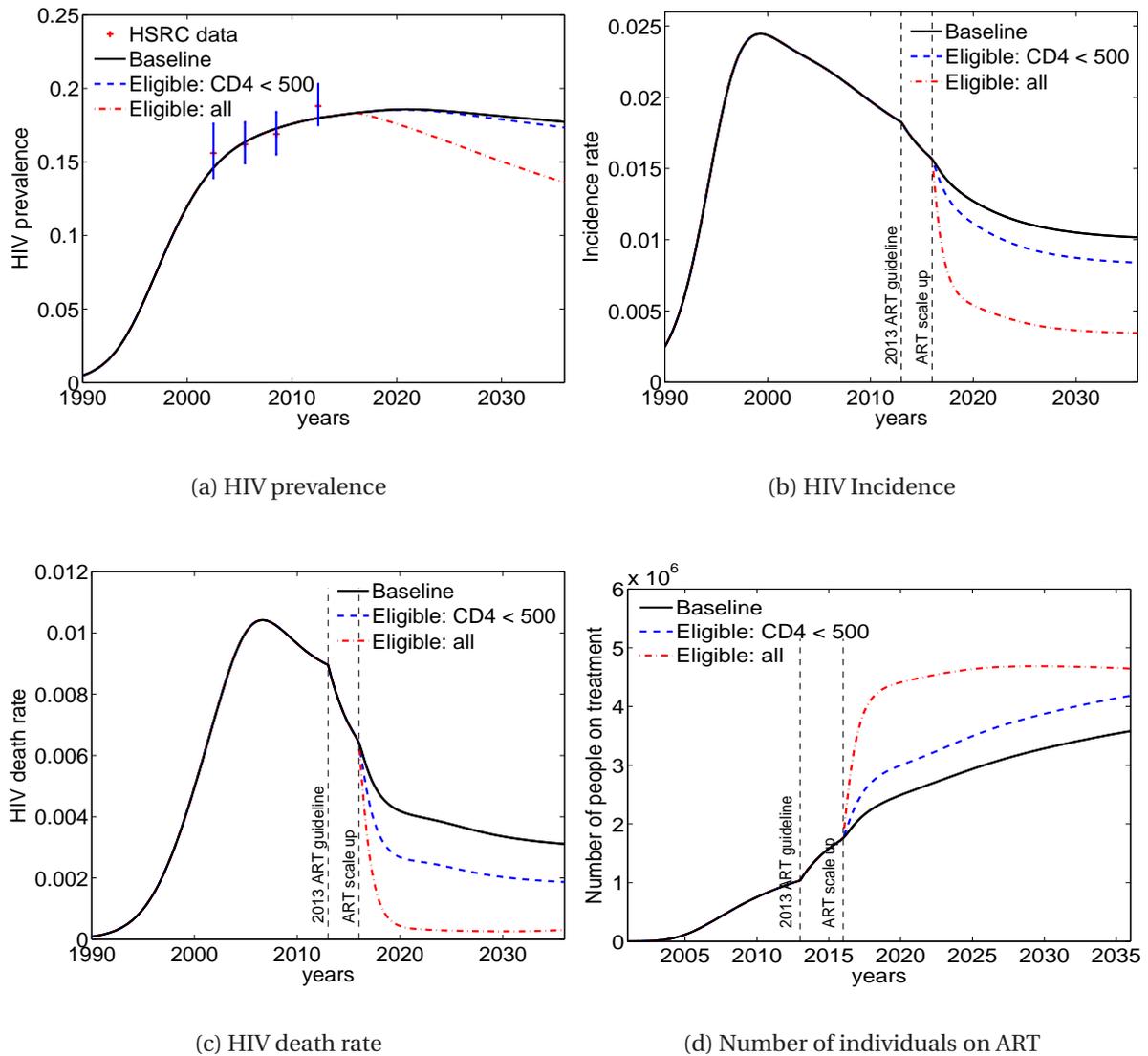
Figure 6.9: Key epidemic results for higher reduction of HIV transmission due to ART and higher ART access rate. Here we considered a 96% reduction of HIV transmission due to ART with the ART access rate of 0.9 by 2017.

Some of the parameters used here have some uncertainty. In the following few sections we will investigate model projections for a range of the parameter values. These includes projections for different relative infectiousness of I_2 as compared to I_1, treatment failure

rate and dropout rates. The projections for different cost estimations will be presented in chapter 7.

6.4.3   The impact of relative infectiousness of I_2

To the best of our knowledge, researchers have not discussed the infectiousness level of individuals who interrupt treatment. The overall infection rate depends on the viral load rebound and sexual contact/risky behavior. It is difficult to precisely estimate because when individuals dropout, it becomes difficult to follow disease progression in the human body and change of behavior. Due to this it is not entirely clear as to whether individuals are involved in more risky behavior or not after quitting ARVs. Since it is difficult to trace ARV defaulters, some studies used structured treatment interruptions to understand HIV dynamics in the patients who stop treatment. The results show that viral rebound happens in the patients who dropout [101, 102]. What is not clear is the long-term effect, as such of studies are done only for short periods. Thus, we assume scenarios from low infectiousness level to high (relatively the same as those who never been on treatment, I_1), i.e $\sigma = 1, 0.75, 0.5, 0.25$. For instance, $\sigma = 1$ refers to a scenario where individuals in I_2 are as infectious as I_1 and $\sigma = 0.25$ refers to a scenario where I_2 becomes 75% less infectious compared to I_1.

It is obvious that when the relative infectiousness level of individuals in I_2 is low, the disease burden reduces. We can see this easily from the plots of the scenarios in Figure 6.10. Here we only considered scenario 'all'. If we assume that individuals who stop treatment are 75% less infectious ($\sigma = 0.25$), the prevalence could be brought to 14% by 2036. But, if we assume that individuals with history of treatment (I_2 individuals) are as infectious as I_1, then the prevalence rate stays above 19%. Therefore, unless individuals who stop treatment change their behavior or agree to other preventive interventions to minimize the dropout rate, the effectiveness and benefits of ART scale up programs will be limited. But we know that it is challenging and very difficult to control sexual behavior of individuals. However, programs could strive for high retention rate leading to a minimal dropout and hence, high viral suppression can be achieved at the population level. This suggests that increasing the retention rates of ART programs is critical to improve the effectiveness and benefits of ART.

(a) Prevalence

(b) Incidence rate

(c) HIV death rate
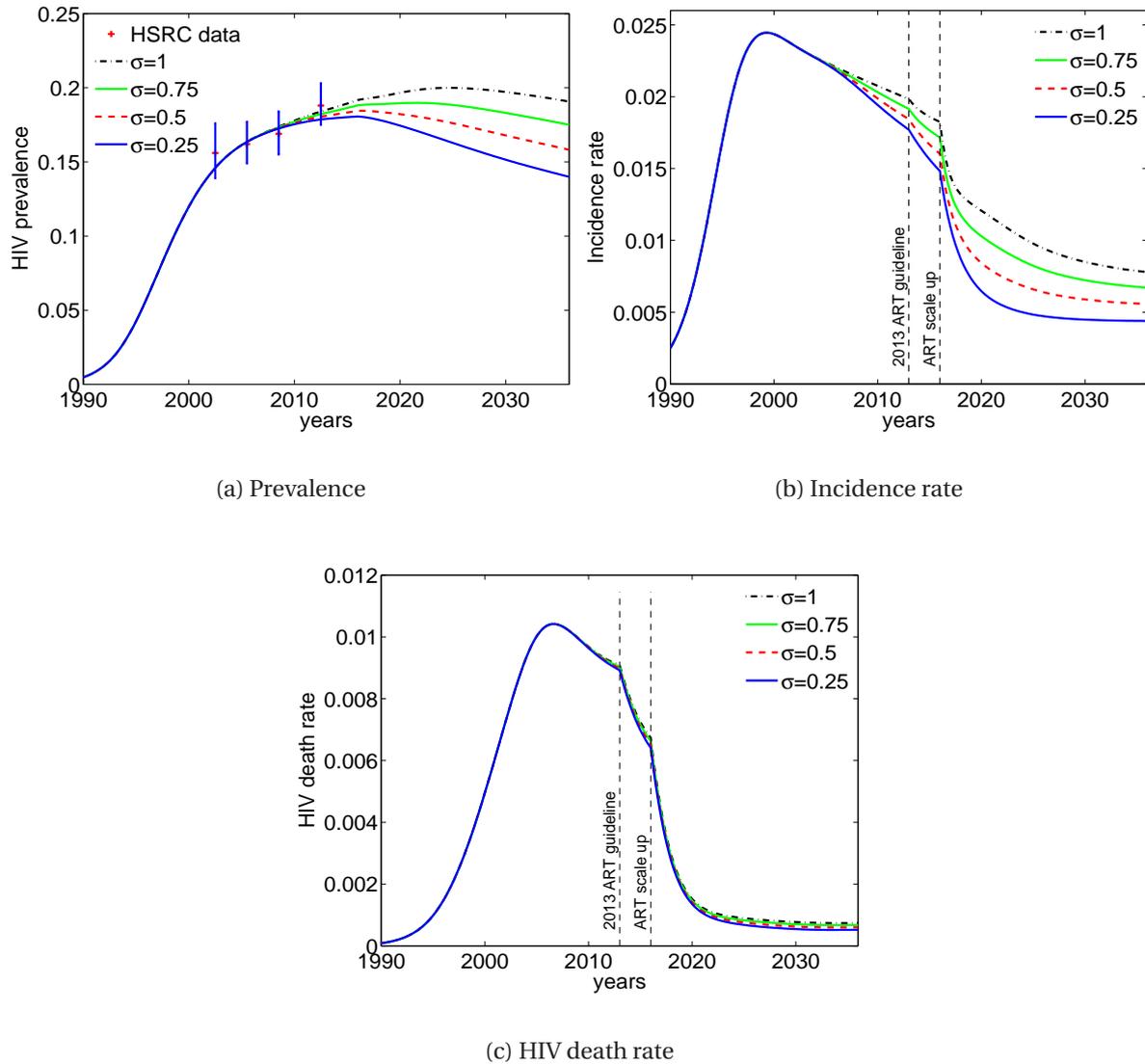
Figure 6.10: Plots for key epidemic results. All rates decline faster when we assume individuals who stop treatment are less infectiousness. All the curves are for scenario 'all'. The red - - - line represents the baseline parameter value for σ, relative infectiousness level.

As in Figure 6.10, we also present different scenario plots for $\sigma = 1, 0.75, 0.5, 0.25$ in Figure 6.11. When infectiousness level of I_2 is the same as I_1, the total number of HIV positive individuals becomes greater than that of the case where the infectiousness level is assumed to be low. We can clearly see that, if individuals show some sort of change of behavior after stopping treatment, then the increase of the total number of HIV positive individuals becomes gradual as compared with high relative infectiousness. This is due to the reduced contribution of individuals in I_2 in infecting new individuals. In other words, the only (majority of) new infections which occur could be from the contacts with individuals in I_1 class.

(a) Total infected

(b) Individuals on treatment

(c) First-line only

(d) Second-line only
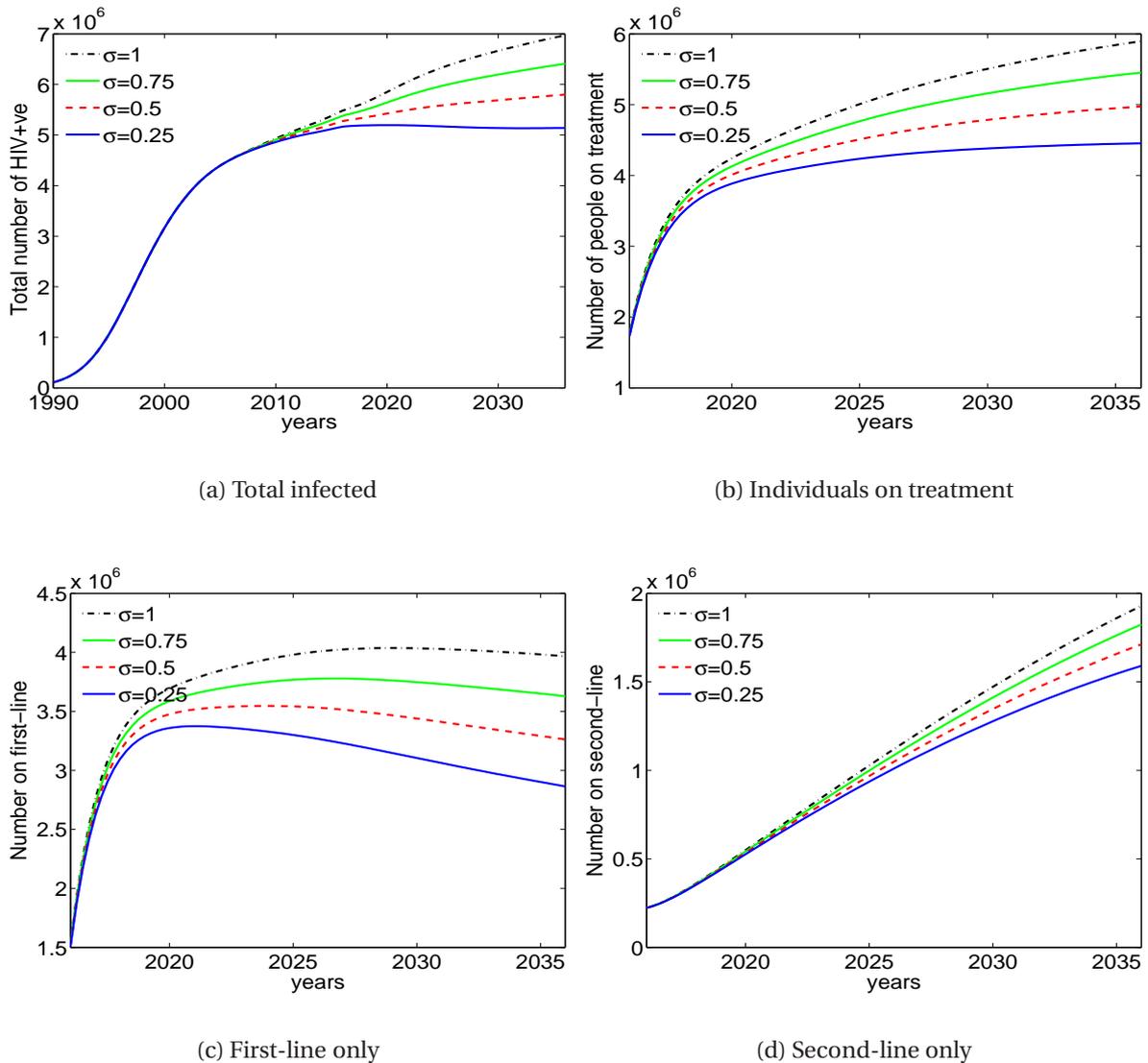
Figure 6.11: Plots showing the number of total infected people, number of individuals on treatment, and the bottom two shows the number of people on those two drug regimen separately. The red - - - line represents the baseline parameter value for σ, relative infectiousness level.

Additionally, we have presented the number of individuals on first-line and second-line treatments, (see Figure 6.11 (c) and (d)). The smaller the relative infectiousness level, the smaller number of individuals on first-line and second-line treatment, which is another intuitive result. Moreover, the longer individuals stay on first-line treatment, the higher chance of switching to the second-line treatment. Due to these, curves for the first-line treatment become asymptote to certain value, while the number of individuals on the second-line treatment keeps increasing which goes in line with the bar plot of the proportion of first-line and second-line treatment, Figure 6.7. When programs grow and run longer, management and

Table 6.3: Summary results of the impact of the relative infectiousness level of those who stop HIV treatment compared to ART naive (I_1). All the numbers are percentage changes of the numbers of infection and deaths and the cost when infectiousness levels vary and are compared with similar infectiousness levels of I_1 and I_2.

	HIV infectiousness level of I_2 as compared to I_1								
	$\sigma = 0.75$			$\sigma = 0.5$			$\sigma = 0.25$		
Relative reduction	5yrs	10yrs	20yrs	5yrs	10yrs	20yrs	5yrs	10yrs	20yrs
New HIV infections	10.44	12.31	12.68	21.55	25.60	26.47	33.40	40	41.47
HIV-related deaths	2.86	4.05	5.72	5.86	8.34	11.85	9.01	12.90	18.45

monitoring of first-line and second-line might get complex.

In a summary result presented in Table 6.3, we present projections at 5, 10 and 20 years of the impact of ART on the key epidemic outputs by varying σ. If individuals in I_2 class are 25% less infectious as compared to I_1, a 10.44%, 12.31% and 12.68% reduction in new infections might occur within 5, 10 and 20 years in the time horizon, respectively. Similarly, we see approximately a 2.86%, 4.05% and 5.72% reduction in HIV-attributed deaths, respectively. See the table for other results of the percentage reductions.

6.4.4   The impact of treatment failure

(a) New HIV infections   (b) HIV-related deaths
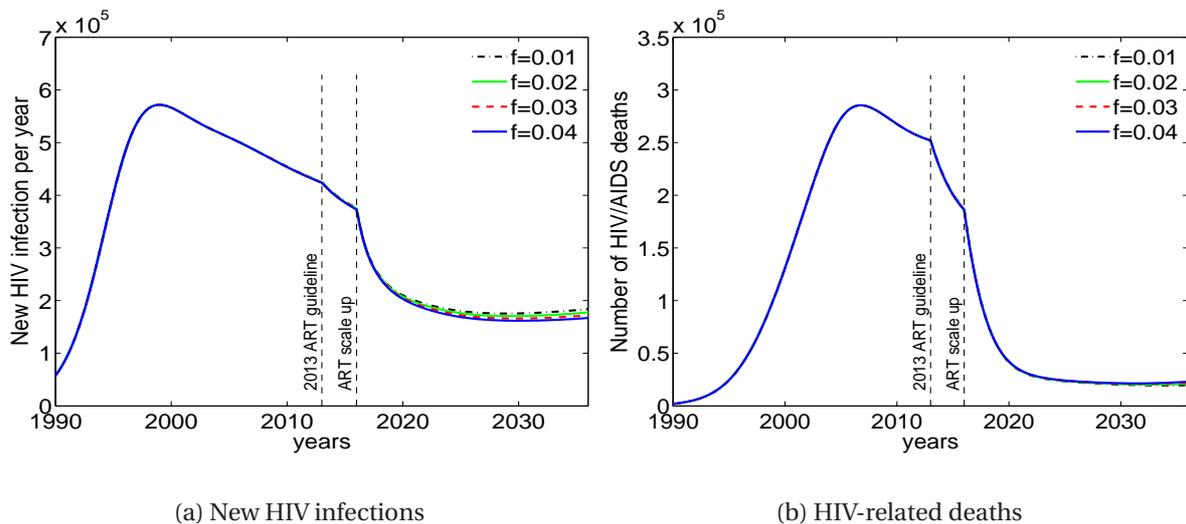
Figure 6.12: The number of new HIV infections and HIV-related deaths as we vary treatment failure rate. The red - - - line represents the baseline parameter value for the treatment rate, i.e. $f = 0.03$/yr.

Treatment failure of first-line therapy might usually lead to a switch to second-line ther-

apy. But because of resource limitation such as virological monitoring, and testing for drug resistance, individuals might not switch immediately. In our analysis we have not considered a scenario where individuals stay on or wait for a switch to a second-line treatment. After failing individuals may continue on first-line treatment. Based on these assumptions, we have presented simulation results of the impact of treatment failure in Figure 6.12. The increase of the impact of treatment failure rate did not change the overall dynamics of HIV; however it impacts the cost of treatment programs. It is because we are just moving them from a less infectious class to another and still less infectious class (due to HIV treatment) as we assume both first- and second-line treatment benefit a similar level of viral suppression resulting in a high reduction of HIV transmission. Figure 6.12 (a) and (b) show that both the number of new HIV infections and HIV/AIDS deaths did not change much. But the number of individuals on second-line treatment increased significantly for higher treatment failure rate as many individuals switch therapies which we presented in Figure 6.13.

Figure 6.13 shows simulation results of different scenarios of treatment failure. The baseline parameter for treatment failure considered was 0.03/yr(0.01-0.04); here we explore the projections for a tenth of baseline treatment failure rate to 15 times. Like the results before, change of treatment failure rates did not bring much change on the incidence rate and death rates (Figure 6.13(a) and (b)). But the number of individuals on first-line treatment declines with high treatment failure, leading to the number of individuals on second-line to increase significantly. This has health implications as there are testing and procedures to be followed by individuals to switch therapies. The higher the treatment failure rate, the increased challenges with logistics/management. We, however, did not go into the detail of these analyses, but presented the cost aspect in chapter 7.

6.4.5   The impact of dropout

Individuals dropout from HIV treatment due to many reasons: side effects of the drug, transportation cost because of inaccessibility of the ART care clinics, and long waiting times at the clinics were among the reasons [190]. Here, we are only interested to study the impact of dropout rates on the HIV dynamics. Thus, we will try to present results of different scenarios

(a) HIV incidence rate

(b) HIV death rate

(c) First-line treatment

(d) First-line treatment
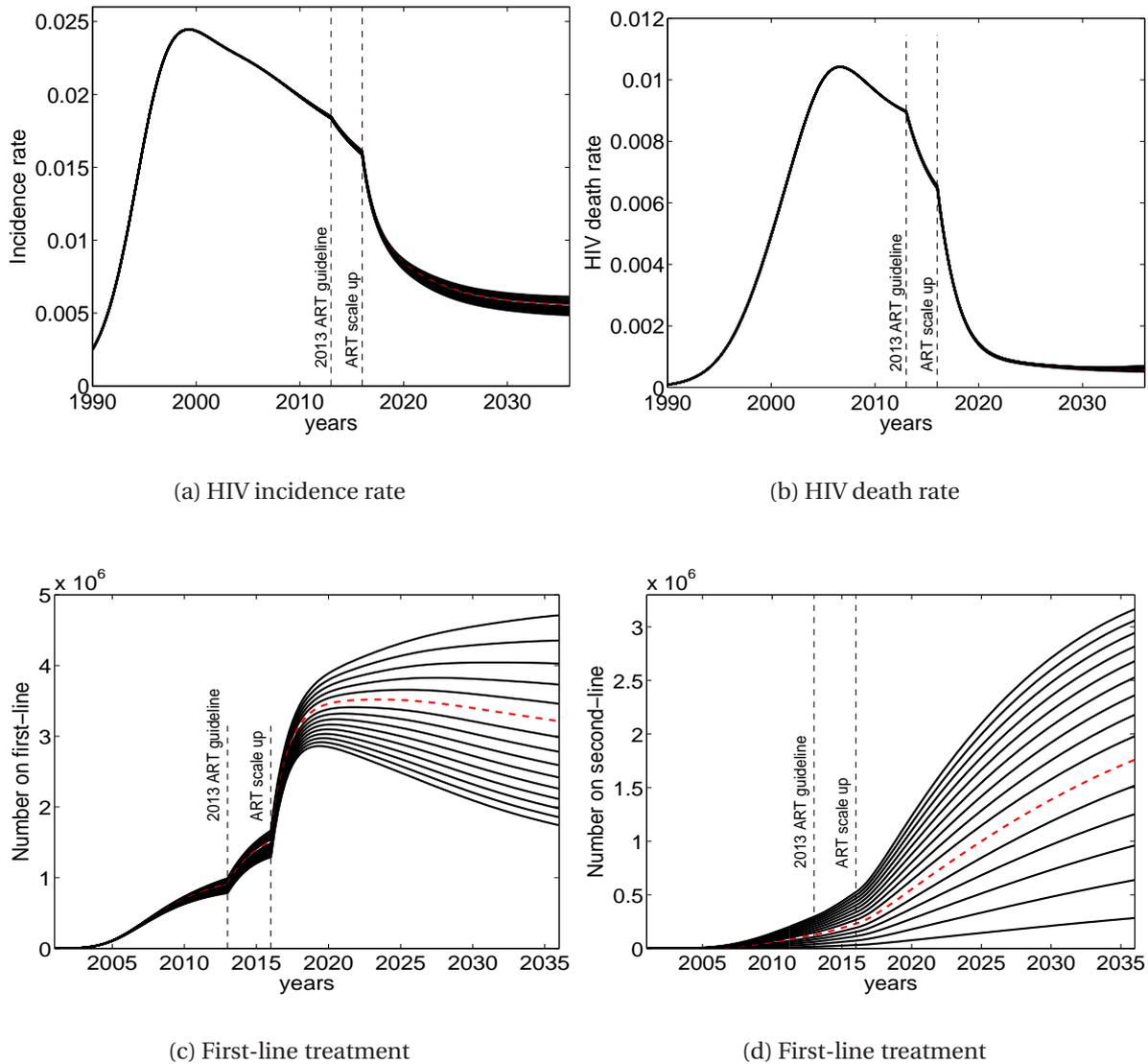
Figure 6.13: Different projections as we vary the treatment failure rate. HIV incidence and death rate, and Number of individuals on first- and second-line treatment. The red - - - line represents the simulation results of the baseline parameter value of treatment failure i.e. f=0.03/yr.

of dropout rates. The baseline parameter value for the dropout rate is an asymptotic exponential function (see the section for model parameter values). Since we considered a time since infection dependent dropout rate, it will be difficult to present different scenarios using different shape and scale parameters. Rather than changing the shape and scale parameters, we scaled the whole baseline function of the dropout rate by multiplying with a scalar. For instance, a 25% less dropout scenario indicates that the baseline parameter of the dropout rate is multiplied by 0.75, and for a 50% increase the baseline parameter is multiplied by 1.5.

Unlike the results for treatment failure rates, change of the dropout rates affect the HIV

(a) New HIV infections

(b) HIV-related death

(c) Individuals who are not on ART
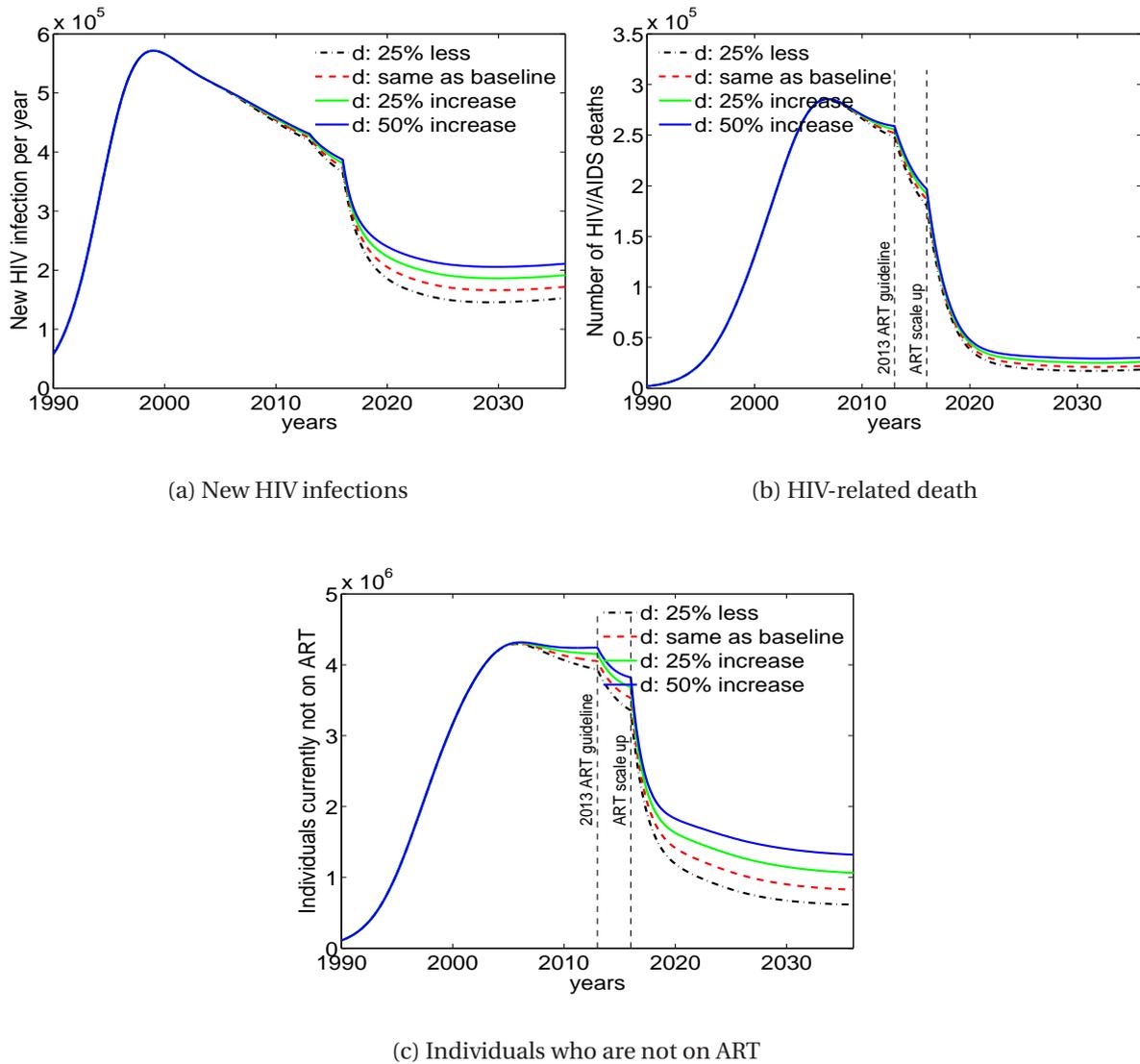
Figure 6.14: Number of new HIV infections, HIV-related deaths and individuals who are not on ART as we vary the dropout rate. The red - - - line represents the baseline parameter value for the dropout rate.

dynamics. The number of new HIV infections grow with higher assumption of the dropout rate. For example, in 2021 and 2026, the number of new HIV infections for the scenario of a 50% increase of dropout rate are 231,100 and 208,800 respectively, which showed an increase from the scenario of the baseline projection results: 194,900 and 169,900, respectively (Figure 6.14 (a)). We see a similar trend for the number of HIV deaths. The number of HIV deaths, as well, increase for the assumption of a 50% increase of dropout rates. The number of HIV deaths increase to 40,400 and 31,200 in 2021 and 2026, respectively from 33,900 and 23,200 for the baseline assumptions, respectively.

We have also presented the projection of the number of individuals who are not on ART, Figure 6.14 (c). The assumption we considered for ART initiation is similar to the ART uptake for individuals in I_1. Another intuitive result is that as the dropout rate increases, the number of individuals who are not on ART increases. The result shows that the increase is significant. The number of individuals who are not on ART in 2021 and 2026 are 1.76 million and 1.52 million for a 50% increase scenario, as compared to 1.33 million and 1.03 million for the baseline dropout rate parameter. This shows that the pool of individuals with risk of infecting others increases with higher dropout rates. This is the main reason why we see increase in the number of new HIV infections in Figure 6.14 (a).

In Figure 6.15, we presented simulation results of different variables for a range of scenarios of dropout rates to understand the sensitivity of the results. The graphs clearly show that the projected results are sensitive to the assumption of the dropout rates. The incidence and death rates change significantly, see Figure 6.15 (a) and (b). The range of the parameter values used is from a tenth of the baseline dropout parameter to to a 15 times higher dropout rate, while keeping the baseline parameter values for the other parameters. Earlier we have high treatment failure rate results to significant increase in the number of individuals on second-line treatment. Similarly, the number of individuals on second-line treatment increases with high dropout rates (see Figure 6.15 (c) and (d)). The increase of the number of individuals on second-line treatment usually results in the increase of annual spending. Moreover, in management of treatment linkage, re-initiation is also a challenge. Generally, both treatment failure and dropout create an additional burden on the health system, probably for longer period as we will not be able to see significant reduction of HIV infections. These results suggest a need for further studies on the elimination of dropout rates so that we have better and more precise projections.

6.5 Discussion

Early ART initiation may be advantageous for both clinical care and prevention. Individuals stay alive longer with minimal health complications, if the drugs are effective and administered properly. Moreover, it reduces the risk of transmitting the disease to others.

(a) HIV incidence rate

(b) HIV death rate

(c) First-line treatment

(d) First-line treatment
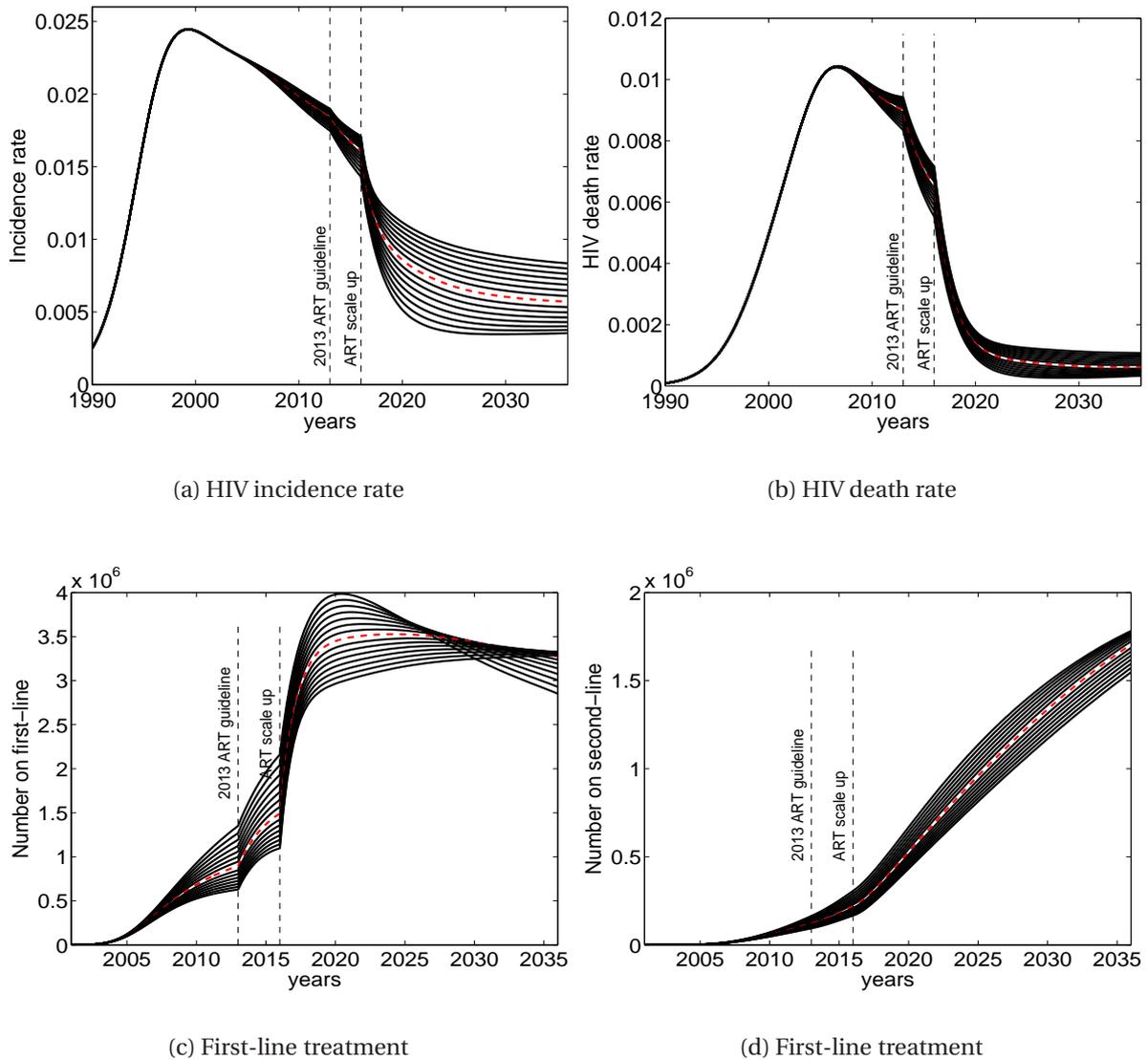
Figure 6.15: Different projections as we vary the dropout rates. HIV incidence and death rate, and the number of individuals on first- and second-line treatment. The red - - - line represents the baseline parameter value for the dropout rate.

With the current trend of dropout rate of first-line treatment, unless the contribution to new HIV infections by these groups is minimal, the benefit of ART scale up will be limited. In this study we showed that an incidence rate which could be brought to 0.31% by 2036 might stay at higher level, about 0.55%, due to treatment failure and dropout rates. Similarly, due to high dropout we do not see the gradual decline of HIV prevalence which we see from the results discussed in chapter 4. The HIV prevalence might stay very high, at around 15%, even after two decades of ART scale up implementation as compared to a 10% HIV prevalence if we do not have treatment failure and dropout. HIV prevalence does not decline

faster for two main reasons. Firstly, when individuals are on ART they survive for a longer period (same for both the first and second models). Secondly, because new HIV infections still occur at reasonably higher rates for the second model. Unlike the results of chapter 4, the latter significantly contributes to the HIV prevalence staying higher. Therefore, work has to be done to reduce the contributions of those who stop treatment to the HIV epidemic. This could be achieved by either a change of behavior by individuals to get involved in less risky sexual contact or achieve high retention and adherence rate. We believe that increasing retention and adherence level are theoretically possible, compared to changing the behavior of individuals who are already lost from the programs.

6.6 Conclusion

We have developed a mathematical model of HIV structured by time since HIV infection and time since the start of HIV treatment to understand the impact of treatment failure and dropout. Using the compartmental model with five stages, we have simulated key epidemic results such as prevalence, incidence and HIV death rate. The prevalence plot was fitted to data from South African HSRC data. Sensitivity analysis were performed for some input values to assess the impact of the uncertainty on the results.

The long term behavioral implications of HIV patients receiving ART is not clearly known. Moreover, having a large cohort of people who are on ART is by itself a challenge where the behavioral implications are unknown. Due to these and additional reasons, individuals either stop treatment (dropout) or fail first-line treatment because of weak attrition or other drug complication issues. Therefore, to achieve the anticipated benefit from ART scale up programs, programs must achieve high retention and adherence within ART.

This work is not without limitations. Defining the dynamics of HIV disease progression in I_2 class was a challenge. Whether individuals show change of behavior or not after stopping treatment is not entirely known. In other words, what could be the infectiousness level of individuals who stop treatment compared to those who have never been on treatment? This is in addition to the challenge of estimating the parameter value of the dropout rate. Another limitation is finding data on the treatment dropout rate. We found only short- and long-

term estimates of the dropout rate and we used those values to estimate a function using a survival function. Moreover, there was limitation in estimating the treatment failure rate as a function of time since infection. Drug resistance is the the main cause for individuals to fail treatment, which usually leads to switching the drug regimen. The causes and other properties of drug resistance are not discussed in this thesis. In this thesis, we have not also done a proper sensitivity analysis on some of the parameters; treatment failure and dropout rates, and relative infectiousness level of individuals who dropout ART. We rather showed scenario plots by varying only one parameter, leaving the rest fixed, as we face difficulties in randomly varying time since HIV infection, ART initiation, dropout and treatment failure dependent parameters. Similarly, sensitivity analysis on time since ART initiation dependent mortality rate parameter was not discussed for the same limitations as above. Additionally, we have only assumed that individuals who fail treatment switch therapy at certain rate. But in some settings after treatment failure individuals might not switch therapies immediately, which we did not precisely modeled. Therefore, estimations of the long term effect of treatment programs due to treatment failure and dropout might not be captured properly. Lack of long term viral suppression due ART might affect the estimation of the risk of infecting other individuals due to ART. Thus, better data of individual's long term viral suppression is vital to have better projections of the impact of early ART.

In conclusion, the results presented here gave us more insight, and hence further studies are of great importance to clearly understand the scale of the problem of dropout and switching to a second-line regimen. Model predictions could be improved, when more data comes from different trials and ART programs which show long term impact of ART at population level. Therefore, ART scale up programs should focus on retaining patients on ART, as many studies have shown that retention is currently a challenge [96, 99, 191]. Only scaling up the ART initiation threshold is not enough. In line with this question the focus of TasP (treatment as prevention) could switch from making ART available to providing support and care to those receiving ART with high retention.

Chapter 7

The cost-effectiveness analysis

7.1   Introduction

In this chapter, we will discuss cost and cost-effectiveness analysis of the treatment scenarios of the second model discussed earlier in chapter 6. The treatment scenarios considered are: the baseline scenario, scenario '500' and scenario 'all'. Incremental cost-effectiveness ratio values will be represented graphically for each scenario to present the greatest health returns at any given cost. All cost related and utility dependent parameter values are the same as the parameter values discussed in chapter 5. In this chapter, we will only present results for 'current' ART access and 90% reduction of HIV transmission due to ART.

7.2   Simulation results

In this section we present simulation results of the second model. Specifically, we will discuss annual and cumulative costs, and incremental cost per different health outcomes.

7.2.1   Annual cost estimation

Projections presented in the previous chapter show that the number of individuals on treatment increase for all CD4 threshold just after the start of ART scale up in 2016, which continually increases the annual spending of ART even for higher ART provision. Our model estimates that the government may need up to 1.34, 1.63 and 2.49 billion USD per year in

2021 for baseline, scenario '500' and scenario 'all'. In all the scenarios there is a gradual increase of the annual cost estimation from the respective estimations in 2016 (see Figure 7.1). For the first model we see a breakeven situation of the annual cost for higher ART provision which is not the case for the simulation results of the second model. Always the estimation of the annual spending for scenario 'all' is greater than that of the scenario '500' and the baseline ART scenario. In chapter 6 we presented the number of individuals on ART which shows the increasing trend for all the scenarios. This is why we see an increasing trend for the annual costs too. When individuals dropout from HIV treatment, new HIV infections occur at higher numbers compared to a scenario where there is no dropout.
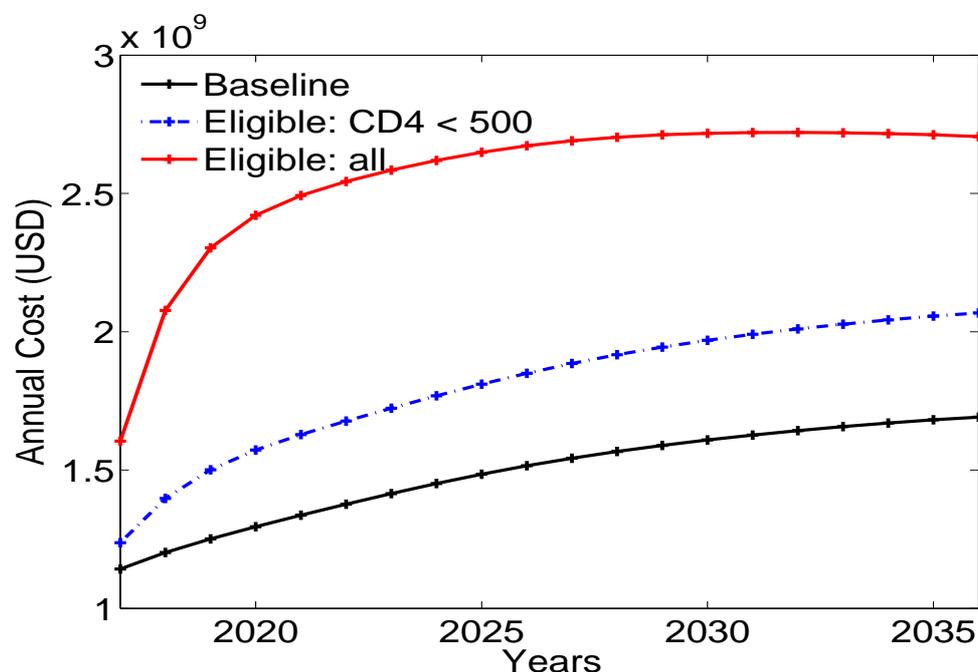
Figure 7.1: Annual cost of providing ART.

Table 7.1: The variation of the annual cost of estimation of providing ART between the projections of the first and the second models. All the costs are given in billions of USD.

		first model, chapter 4			second model, chapter 6	
Scenario	2016	peak year, cost estimates	2036	2016	peak year, cost estimates	2036
'all'	1.98	2020, 2.72	1.84	1.60	increasing trend	2.71
'500'	1.69	2025, 2.26	2.05	1.24	increasing trend	2.07
baseline	1.64	2025, fairly stable afterwards	1.92	1.14	increasing trend	1.69

The reason why we see smaller annual cost assumption (compared to the results of the first model) during the initial phase of ART scale up scenarios for the second model is due to the fact that many individuals who initiated ART already dropout from treatment (see Table 7.1 and Figure 7.2) and hence smaller annual cost estimation. Note that we have included the treatment failure and dropout aspects starting from the year when ART roll out is started, i.e. in 2001 years. The reason for doing so is to capture the actual trend of these components of treatment program challenges from the starting of ART roll out. Due to this the person of years on ART is lower than that of the scenario where there is no dropout. With time, more individuals who dropout re-initiate ART and additionally, the increasing number of dropout increases the number of new HIV infections and hence many new individuals initiate ART every year making the number of individuals to keep increasing. As a result, the annual costs of ART programs will have increasing trend for all ART provision scenarios. In 2036, for scenarios '500' and 'all', the annual cost spending increases from 1.84 and 2.05 billion USD (for the first model) to 2.71 and 2.07 billion USD (for the second model) due to the dropout effect.
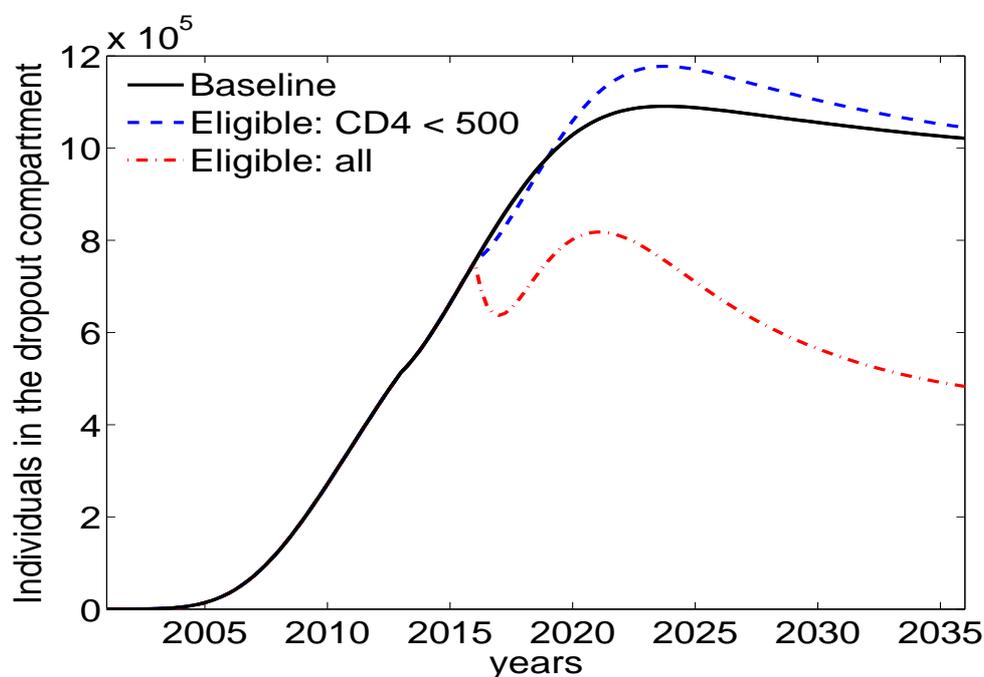

Figure 7.2: The number of individuals who are in the dropout compartment.

In Figure 7.2, the reason why we see a decline in the number of individuals of those who

are in the dropout class for scenario 'all' is because for scenario 'all', after dropout they immediately become eligible and can re-initiate ART (of course, depending on the ART access rate). But for the baseline scenario and scenario '500', after dropout, individuals become eligible as a function of time since dropout from treatment. It is, however, challenging to properly parametrize this parameter. But it is clear that if all HIV positive individuals are eligible for treatment then the possibility of individuals who dropout from treatment, only to re-initiate treatment might be high, if ART programs run effectively.
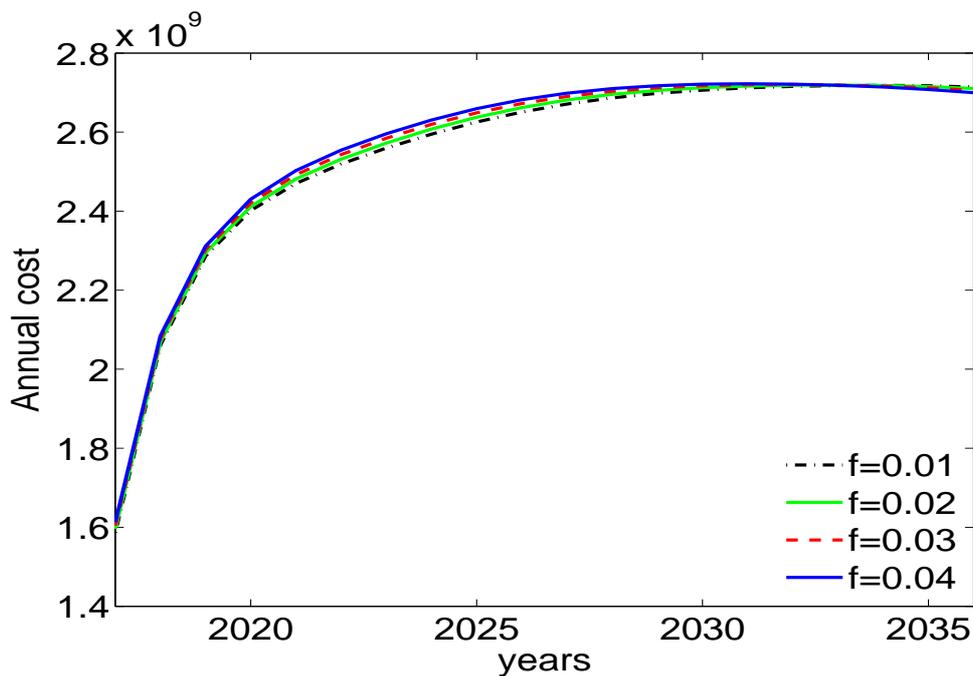
Figure 7.3: Annual cost for different values of treatment failure. Because of the scale of the y-axes the difference is really significant. The difference of the annual cost could be in millions of USD.

The sub-Saharan Africa region might face widespread antiretroviral drug resistance in the coming decades [52, 192], which leads to the spread of transmitted drug resistance and hence probably a need to put them on a new drug regimen [193, 194]. The increment of the annual cost for a treatment failure rate equal to 0.04 might be 2.50 and 2.68 billion USD, at the five and ten years, respectively. This is an increase from 2.49 billion and 2.67 billion USD, for the baseline assumption of treatment failure rate (i.e. $f = 0.03$/yr). On the other hand, the annual cost could decrease to 2.48 USD billion and 2.66 billion USD at the five and ten years, respectively, if $f = 0.02$/yr. In Figure 7.3, even if the difference of the annual cost seems to be small, because of the scale of the y-axis, the actual differences are in millions,

which we presented the summary results in Table 7.2. For instance, the annual spending might increase by 11.3, 22.1 and 32.5 million USD in 2021 (within five years of ART scale up) for treatment rates $f = 0.02, 0.03$ and $0.04/\text{yr}$, respectively when compared with the scenario of $f = 0.01/\text{yr}$. These results show that more investment cost will be needed for ART programs, if treatment failure rates are high. In our cost assumptions we have not considered cost for virological monitoring to confirm treatment failure or drug resistance, thus our estimates might be underestimated. Therefore, it is very important to minimize the number of individuals who fail first-line treatment to the lowest possible number.

Table 7.2: Annual cost and changes for different treatment failure rate at 5 and 10 years of the time horizon. All the numbers are given in millions.

Treatment failure rate, f (1/yr)	5 years		10 years	
	Annual cost	change of cost from prior f value	Annual cost	change of cost from prior f value
0.01	2,470	–	2,650	–
0.02	2,481	11.3	2,662	11.1
0.03	2,492	22.1	2,672	21.4
0.04	2,503	32.5	2,682	30.9

In the previous paragraph we presented the impact of treatment failure on the annual cost estimation. Here we will see the impact of treatment failure and dropout (fixed parameter values) if the cost ratio between second- and first-line varies. First-line treatment failure which leads to a switch to a more expensive second-line treatment scheme might become a big challenge to the long-term costs and effectiveness of treatment as prevention strategies. With the assumption that the second-line drugs cost twice the first-line drug, the increase of the overall cost of providing ART, due to the switch from the first-line to the second-line treatment. Since the proportion of individuals on the second-line might increase over time by 18.0%, 25.3% and 35.9%, respectively, at 2021, 2026 and 2036 (see the bar plot in Figure 6.7 from chapter 6), we see an increased need for annual spending. Our model results for scenario 'all' estimates that by 2021 an approximately 26.4% increase in the cost might not have been needed if all individuals on treatment were only on first-line. Similarly, we see a need of approximately a 32.0% and 39.3% increase in the annual cost estimation by 2026

Table 7.3: Annual cost and cumulative cost percentage increase as the cost ratio between second-line and first-line treatment varies. All relative increases are in comparison to the reference cost estimation, which is: we assume that both first- and second-line treatments have similar cost.

	Cost of providing second-line treatment as compared to first-line								
	50% more exp			100% more exp			200% more exp		
Relative increase (%)	5yrs	10yrs	20yrs	5yrs	10yrs	20yrs	5yrs	10yrs	20yrs
Annual cost	13.2	16.0	19.7	26.4	32.0	39.3	52.8	63.9	78.6
Cumulative cost	11.8	13.3	15.7	23.6	26.7	31.4	47.2	53.3	62.9

and 2036 (10 and 20 years in the horizon time), respectively. Additionally, the cumulative investment needed for ART program within 5, 10 and 20 years should increase by 23.6%, 26.7% and 31.4%, respectively, be due to only the higher price tag for the second-line drug. For the assumption that the second-line drug is thrice that of the first-line drug, the cumulative investment needed to have an increase of approximately 47.2%, 53.3% and 62.9%, respectively. See Figure 7.4 and Table 7.3 for other estimates of the annual cost and the cumulative cost estimation variations.

(a) Annual cost   (b) Cumulative cost
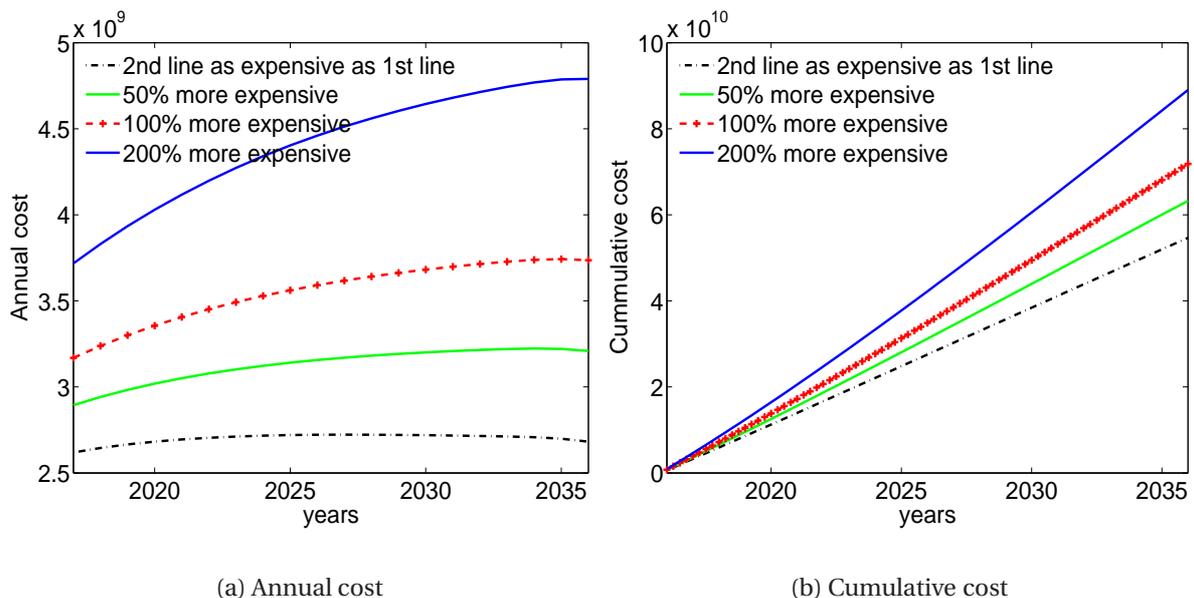
Figure 7.4: Costs as we vary cost assumption for providing ART per patient per year. The baseline cost we assumed is 630 USD per patient per year. The black curve shows annual and cumulative cost estimations of the baseline scenario. All the plots are for scenario 'all'.

The other uncertainty with the cost estimation of providing ART is that the cost of drugs may decrease with calendar time. For a decreasing cost of providing ART per patient per year, we assumed that the cost declines linearly to 50% by 2036 (using interpolation). In Figure

7.5, the trend of the annual cost estimation is presented for a fixed cost and a decreasing cost assumption. The graphs show that there will be a sharp increase in the annual cost projection during the initial phase of the ART scale up. Then the estimation for the fixed cost scenario continues to increase while the annual cost assumption for a decreasing cost of HIV drug might decline starting from 2023. Unlike the results of the first model we do not see the annual cost declining for an assumption of a fixed cost of the drug. This is because we see an increasing trend for the number of individuals on ART for the second model. But results of the first and second models suggest that cheaper drugs (a decreasing cost of drug with calendar time) might be important to decrease the burden on the annual spending for treatment programs.
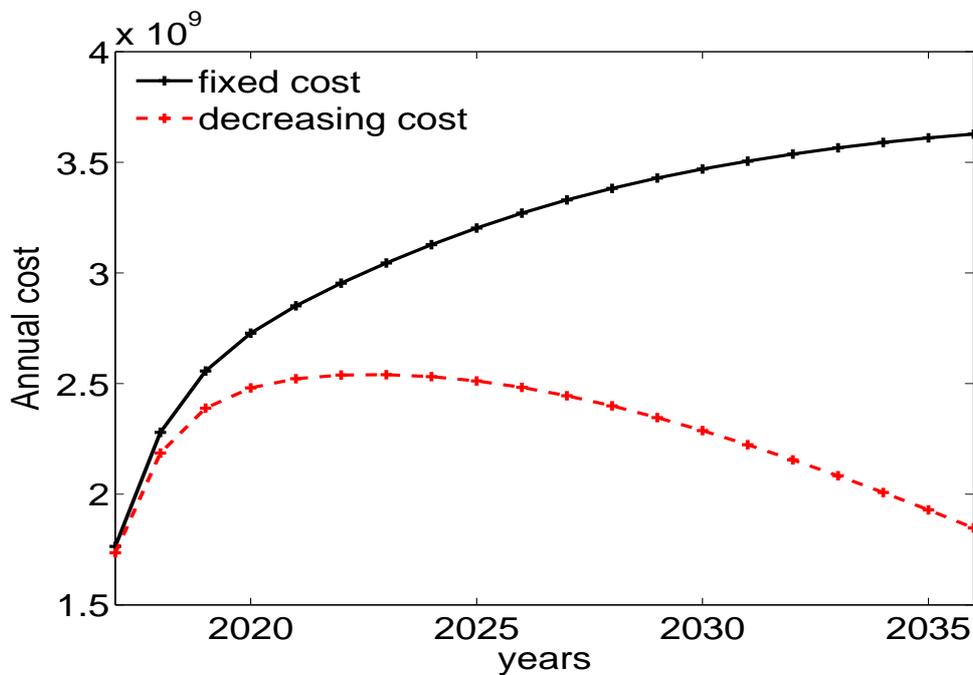
Figure 7.5: Annual cost estimation for a fixed versus a decreasing cost assumption of providing ART. The estimations are done of scenario 'all' only.

Annual cost estimations could also vary with infectiousness level assumption of individuals who dropout from treatment. When both individuals without HIV treatment (I_1) and with a history of HIV treatment (dropouts I_2) are equally infectious, then the annual spending becomes 2.65, 2.98 and 3.20 billion USD in 2021, 2026 and 2036, respectively. Assume that individuals who dropout from treatment show some sort of behavior change as they know their HIV status. This leads to a reduction of risky sexual contacts and hence these

individuals might be less infectious compared to individuals in I_1 class who have never been on ART and do not know their HIV status. In this case we see a reduction of the number of new infections which, in turn, decreases the total number of individuals who are on ART. Therefore, the annual spending declines with infectiousness level reduction of individuals in I_2. If individuals are 75% less infectious, then the annual cost estimation at 5, 10 and 20 years of the time horizon decline to 2.41, 2.5 and 2.43 billion USD, respectively.
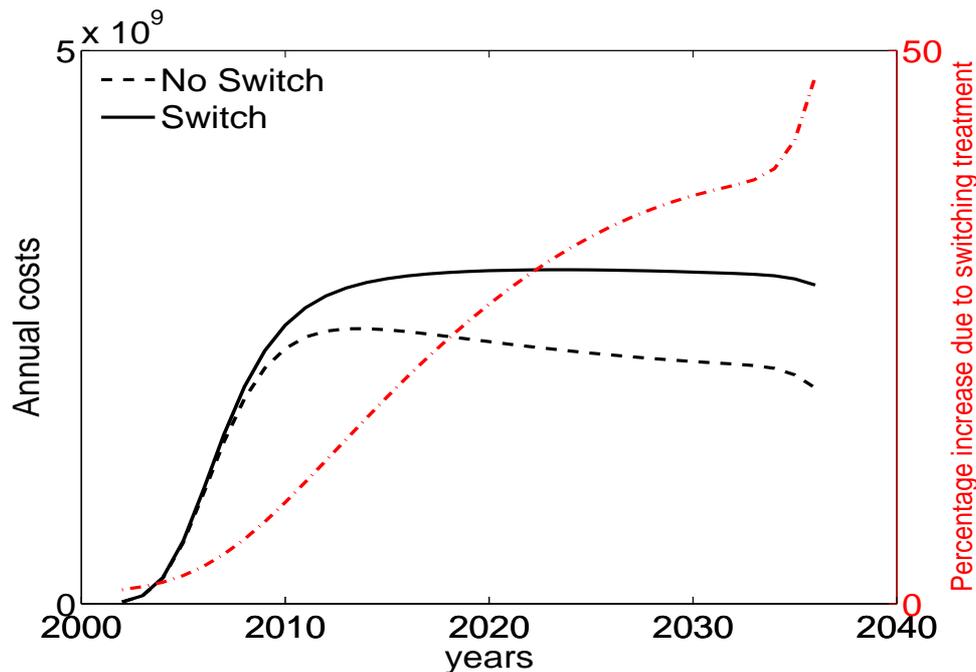
Figure 7.6: The percentage increase of the annual cost of providing ART due to switching treatment when we consider no treatment dropout. Here we only plotted for scenario 'all' from the ART provision scenarios.

In Figure 7.6 we presented the annual cost of providing due to switching treatment and without treatment. We assumed no treatment dropout scenario to clearly understand the increment of the annual cost due to switching treatment. For this analysis, we took scenario 'all' and assumed that second-line is twice as expensive compared to first-line treatment. The results show that the annual cost at 2016, 2021, 2026, and 2036 might increase by 25.3%, 28.5%, 34.1%, and 47.7%, respectively, due to a switch from first-line treatment (see the right y-axis in Figure 7.6). In the previous chapter we have shown that treatment failure does not change the HIV dynamics this much, it only affects the cost estimation. In a resource limited setting it is very important to minimize drug regimen change.

7.2.2   Incremental cost ratios

In this section we will present the incremental cost needed to avert or gain certain health outcomes: infections or deaths averted or QALYs gained, for different scenarios as a function of calendar time. Generally, the ICER values for QALYs gained, infections and deaths averted decline with calendar time with the exception of DALYs averted, which showed a gradual increase, see Figures 7.7, 7.8 and 7.9.
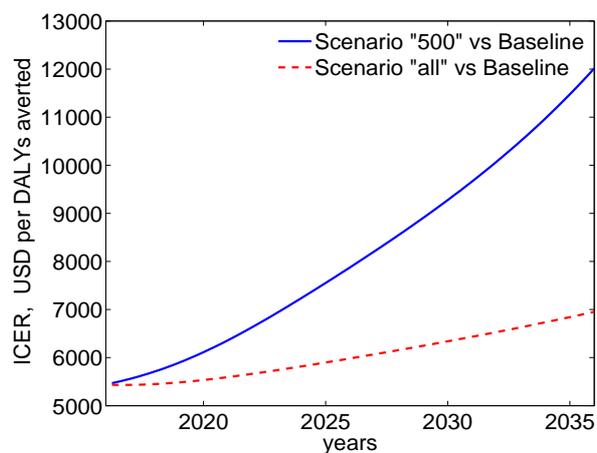
(a) DALYs
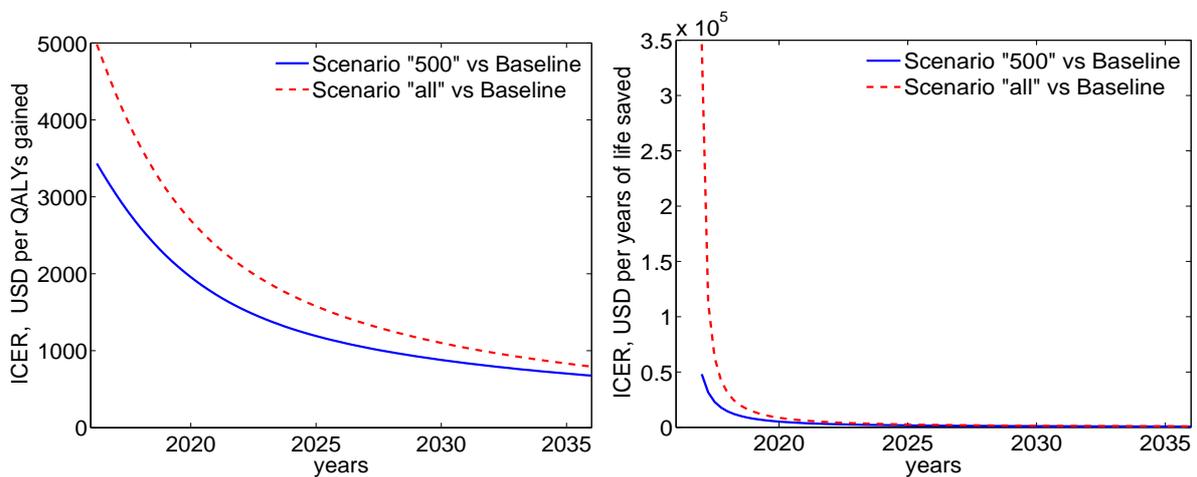
(b) QALYs

(c) Years of life saved

Figure 7.7: Incremental cost per different health outcomes: DALYs, QALYs and years of life saved for expanding eligibility criteria for ART.

In our model the incremental cost per QALY ranges from $3,433 (in 2017) to $675 (in

2036) (Figure 7.7 b) for scenario '500'. The ICER value for scenario 'all' start at higher level as compared to scenario '500' and have a similar declining trend by which both ICER values become almost the same at the end of the 20 years of time horizon. Additionally, projections show a very sharp decline for the ICER value of years of life saved curve (see Figure 7.7 c). The incremental cost needed to gain years of life lost for both scenarios, '500' and 'all' become almost similar after a decade. The incremental cost per life years saved declines from $48,050, and $346,400 (respectively scenario '500' and scenario 'all') in 2017 to $719 and $889 in 2036 (respectively scenario '500' and scenario 'all'). However, the trend of the incremental cost per DALYs averted is different. For scenario '500' it may increase from $5,468 (in 2017) to $12,010 (in 2036) and for scenario 'all' it may increase from $5,434 (in 2017) to $6,953 (in 2036) (see Figure 7.7 a). Scenario '500' is cost-effective, whereas scenario 'all' is a very cost-effective scenario as the ICER is always less than the GDP per capita of South Africa (see Figure 7.7 a). Additionally, the ICER for scenario 'all' is always less than that of scenario '500'. This indicates the cost-effectiveness of high ART provision scenarios.
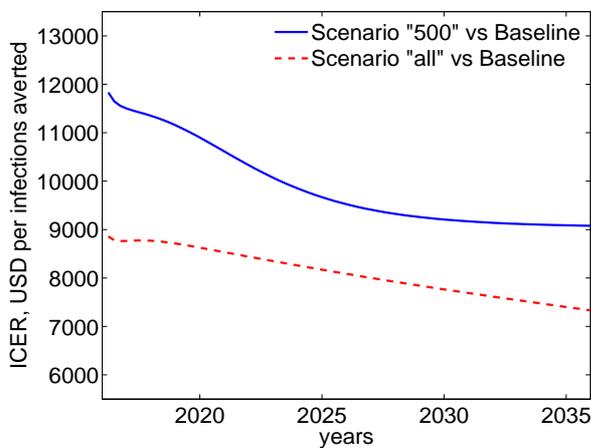
(a) ICER for infections averted
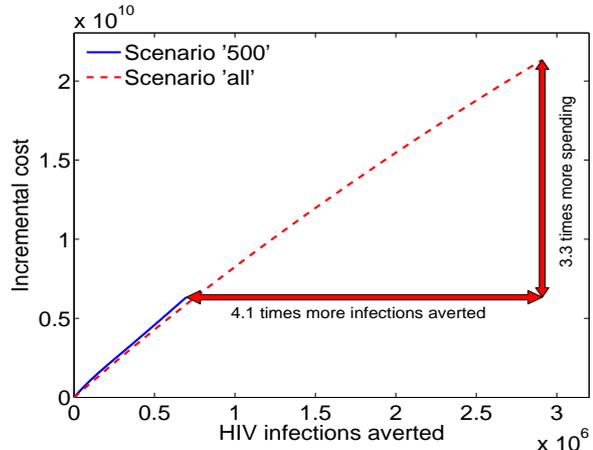
(b) Phase portrait of the incremental cost versus infections averted. The coordinate (0,0) refers to the start of the trajectories at the beginning of the time horizon.

Figure 7.8: Incremental cost per HIV infections averted and phase portrait of the incremental cost and the number HIV infection averted for different treatment scenarios.

Figure 7.8 presents the ICER values for HIV infections averted for different scenarios. The results show that the incremental cost per HIV infection declines with calendar time for both ART initiation scenarios ('500' and 'all'). When the number of HIV infections averted

is considered as the outcome of measure, the scenario 'all' has always smaller incremental ratio compared to scenario '500'. The ratio declines from $8,859 (in 2017) to $7,332 (in 2036) as compared to the decline from $11,830 (in 2017) to $9,079 (in 2036) for scenario '500'. This shows that fewer dollars will be spent to avert a single new HIV infection if individuals access treatment regardless of their CD4 cell count. In Figure 7.8 (b) we presented the phase portrait of the incremental cost (from the baseline ART scenario) versus the number of HIV infections averted. For scenario '500', we need over 6 billion USD to avert approximately 700,000 HIV infections over twenty years. For approximately 3.3 times more spending for scenario 'all' when compared with that of scenario '500', we might avert 4.1 times more HIV infections.

(a) ICER for HIV death averted

(b) Phase portrait of incremental cost versus HIV death averted. The coordinate (0,0) refers to the start of the trajectories at the beginning of the time horizon.
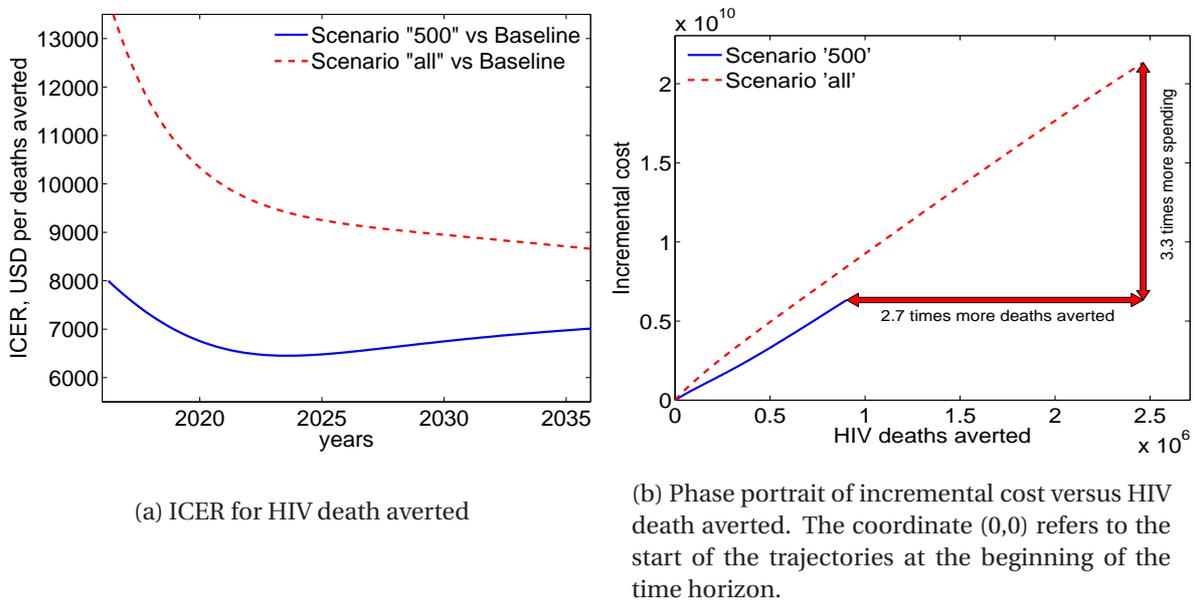
**Figure 7.9:** Incremental cost per HIV death averted and phase portrait of the incremental costs and the number of HIV death averted for different treatment scenarios.

Unlike ICER values for HIV infections averted, we see a different trend of the ICER value for the deaths averted. For scenario 'all' the ICER is always greater than that of scenario '500' throughout the horizon time (see Figure 7.9). The difference of the trends we see here might be due to the fact that HIV treatment has immediate impact in reducing new HIV infections as treatment reduces infectiousness of HIV infected individuals, due to immediate viral suppression after initiation of ART. The incremental cost per deaths averted declines from $13,810 (in 2017) to $8,660 (in 2036) for scenario 'all' as compared to the decline from $7,997 (in 2017) to $7,012 (in 2036) for scenario '500'. In Figure 7.9 (b) we presented the

Table 7.4: Percentage change of cost and incremental cost-ratios of a new strategy as compared with the baseline.

	Scenario '500'			Scenario 'all'		
Time Horizon	5yrs	10yrs	20yrs	5yrs	10yrs	20yrs
Cumulative costs (in Billion USD)	7.61	16.44	36.35	11.72	24.24	51.35
Change of cumulative cost (%)	17.1	19.6	21.1	71.8	76.4	71.1
USD per infection averted	10,614	9,523	9,079	8,533	8,086	7,332
USD per death averted	6,596	6,523	7,011	9,958	9,170	8,659
USD per DALYs averted	6,361	7,877	12,014	5,594	5,982	6,953
USD per QALYs gained	1,730	1,109	675	2,367	1,454	793
USD per years of life saved	3,802	1,156	719	6,086	2,234	889

phase portrait of the incremental cost (from baseline ART scenario) versus the number of HIV-related deaths averted. For scenario '500', we need over 6 billion USD to avert approximately 900,000 HIV-related deaths over twenty years. For approximately 3.3 times more ART spending for scenario 'all' when compared with that of scenario '500', we might avert 2.7 times more HIV-related deaths (4.1 times more for infections). For higher ART provision scenario, number of HIV infections can be averted as compared to the number of HIV-related deaths which can be averted for the same increment of cost due to ART initiation threshold initiation shift.

Table 7.4 shows the summary of the results. The change of the cumulative cost in percentages was calculated with reference to the baseline ART scenario for the corresponding 5, 10 and 20 years of time horizon. For five years of ART program, an increase of ART provision to 500 CD4 count might require approximately 17.1% increase in the overall program cost. If individuals start treatment regardless of their CD4 cell count, the result shows that the cumulative cost might increase by approximately 71.8% compared to the 'baseline' cost within five years. The percentage change for scenario 'all' decreases with a longer time horizon. This shows that the benefit of the higher ART provision scenario in longer time is significantly higher compared to that of late ART provision scenarios. The impact of ART in averting new infections and deaths has been discussed in chapter 6 and presented with graphs to show the return benefits of ART scale up investments.

Figure 7.10 shows the incremental cost needed to avert DALYs. For this we considered switch and no switch scenarios of first-line treatment when all HIV positive individuals ac-
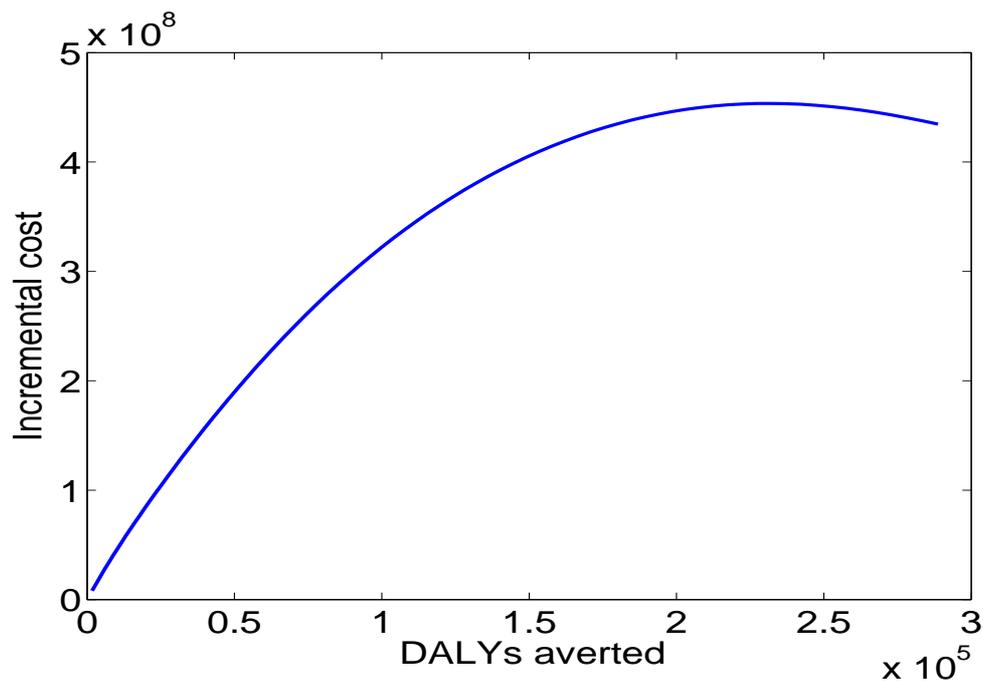
Figure 7.10: Phase portrait of the incremental cost and the number of DALYs averted compared to no switch of first-line treatment for scenario 'all'. The coordinate (0,0) refers to the start of the trajectory at the beginning of the time horizon.

cess ART regardless of their CD4 cell count. If there is a switch of the second-line drug, then due to the expensiveness of the second-line drug the incremental cost becomes higher. But over time the incremental cost might show a decline at a later stage in the time horizon. This might be because of the decline of person years of individuals with higher disability weights over time as many individuals will be on ART with either of the scenarios.

The ICER values (whether for DALYs, QALYs, infections or deaths averted) for the second model are always greater than the respective ICER values presented for the first model in chapter 5. This is because for similar incremental cost we see different health returns. For instance, the number of HIV infections averted for a similar amount of an incremental cost (due to ART scale up) for the second model is smaller than the first model. This clearly shows that treatment failure and dropout minimizes the benefits of ART scale up programs.

7.3 Discussion

The annual spending estimations are improved in this chapter compared to the previous one by considering separate cost for classes for first- and second-line treatment. In the first

model, all the individuals on treatment are on a similar kind of drug regimen and hence the cost estimations of the first model were underestimated. Moreover, the trend was not accurate as it suggests that the annual spending might breakeven the cost estimation of the baseline ART scenario. The results of the second model show that the proportion of individuals, on second-line treatment grows as programs run for a longer period. Thus, unlike the model without treatment failure and dropout, the annual cost estimations continue to increase. The increasing trend of the number of individuals who are on treatment is the main reason for the continual increase of the cost. Additionally, treatment dropout increases the pool of infectious individuals and hence keeps the rate of infection at a higher level, which was shown in Figure 6.14 in chapter 6. Therefore, whenever we have treatment failure and dropout, the annual spending over the time horizon shows an increasing trend. This suggests the urgency to work on reducing treatment failure rate and hence reduce the rate at which individuals switch to second-line regimen. And also reduce the rate at which individuals dropout from HIV treatment.

Moreover, we have shown that as we have more individuals who have stopped treatment, the expected outcome of early HIV treatment in the fight against HIV might be limited. More incremental cost might be needed to avert HIV infections and HIV deaths. Without treatment failure and dropout, after a decade the longterm incremental cost to avert a single HIV infection might be around $2,000 for scenario 'all', as compared to $7,000 if individuals switch drug regimen and also dropout from treatment programs. A study presented an incremental cost of HIV drug resistance test versus DALYs averted in a low-income setting [195] for switch versus no treatment switch scenario. With time the incremental cost increased to avert many DALYs. The result we presented here has also a similar trend of incremental cost even though the cost considered in our case is only the cost of providing ART. The incremental cost increased due to a switch to second-line drug regimen over time to avert DALYs.

7.4   Conclusion

A mathematical model of HIV structured by time since infection and time since ART rollout is considered in this chapter. The first model discussed in chapters 4 and 5 was extended to incorporate treatment failure and dropout. In this chapter, we have presented the annual, cumulative cost and incremental cost per different health outcomes. Annual spending of ART continues to increase even for high ART provision in contrast to the excepted decline of ART spending with time due to early ART. This is due to treatment failure and dropout.

The results suggest that treatment failure and dropout can significantly affect the benefits of ART. The hope of eliminating HIV within less than a decade, as suggested by some, is unlikely to happen. It may even take more than two decades if the situation of treatment failure and dropout continue with the 'current' trend. Despite these, ART scale up scenario '500' is a cost-effective treatment scenario for South Africa, while treatment of HIV positive individuals regardless of their CD4 cell count is a very cost-effective. The higher the ART provision scenario, the more benefit there will be concerning health outcomes, with less incremental cost.

Similar to the cost-effectiveness analysis of chapter 5, we have also limitations in this chapter. The time trend of the cost of first- and second-line ARV might bias the analysis in capturing the past trend and predict into the future. What we only presented is analysis for some scenarios of the cost reduction of providing ART. Thus, we might need better predictions of cost of ARVs into the future in addition to the past trends of ARVs. The estimation of the parameter value for the treatment failure affects the cost estimations, especially due to high price of second-line drugs. If the failure rate is underestimated, then the total cost of programs might be underestimated. The same analogy goes for an overestimated treatment failure rate. Therefore, more data on treatment failure and dropout is of great importance to improve the results of the second model. As a result, our understanding of the impact on the overall ART programs could be improved. Future studies should also focus on understanding the contribution to the HIV dynamics by individuals who dropout from treatment by studying the sexual behavior and disease progression. The estimation of quality of life for

susceptible individuals might also affect the incremental cost-effectiveness ratio. Because of the limitation of getting data on this, we have just assumed a value closer to 1 (meaning perfect health condition) but greater than the estimate for individuals on ART, which might have some side effects from the ARVs itself. Estimates of utilities for the two infected classes I_1 and I_2 are assumed to be similar as we have limitation on data. Similarly, assumptions of utilities for T_1 and T_2 might bias the calculation of the incremental cost-effectiveness ratios. Thus, we need more data on utilities which depend on different variables such as disease state and time since infection and ART roll out for those who are on ART.

Chapter 8

Conclusions and recommendations

8.1 Conclusions

In this thesis we have developed mathematical models for the dynamics of HIV. The models were developed to simulate the hyper endemic HIV dynamics in South Africa. We studied the impact of early HIV treatment using a time since infection structured model, which was discussed in chapters 4 and 5. In chapters 6 and 7, we discussed an extended model by incorporating components of treatment dropout and treatment failure leading to a switch to a new drug regimen, second-line treatment. In both models, we have linked CD4 cell count with the distribution of time since infection to determine the proportion of individuals who become eligible for treatment for certain ART scenarios as a function of time since infection. For both models we have simulated projection of HIV prevalence, incidence and death rate for 20 years into the future. We also calculated the cost, and cost effectiveness analysis was done by calculating the incremental cost per certain health outcomes, such as: HIV infections and deaths averted, QALYs gained and DALYs averted.

As far as our knowledge is considered, we have not seen a modeling work which incorporates dropout and switching from first-line to second-line regimen components by linking distribution of CD4 cell count with time since infection. The inclusion of these components in chapters 6 and 7 might give us better insights into the overall impact of early HIV treatment. The first model which was discussed in chapters 4 and 5 has three classes: susceptible, infected and treatment. Two more classes: a class for individuals who stop treatment and a

class for individuals on second-line treatment were added in the extended model discussed in chapters 6 and 7.

ART scale up programs might face some challenges, such as: limitation of financial resource and continual commitment of funding. The need for huge investment usually increases during the initiation phase and hence the commitment to continue the support in funding the programs for longer period is important. Suppose we do have every resource, still other challenges such as individuals stopping treatment and treatment failure might face ART programs. Since treatment is a life-time treatment, unless and otherwise we have a miraculous drug in the near future which cures HIV/AIDS, we can not be sure of the patients' commitment for fifteen years or even longer, to take pills every day. Thus, individuals stop HIV treatment, because they are feeling better, others may stop from a change in their life style (such as being drunk and forgetting the taking of pills) and others due to complications from the drug. Even though support groups might help in reducing such problems, we believe that the efforts are not yet enough. We actually see that, the number of individuals who stop treatment is increasing with calendar time. Hence, in this thesis we have shown that the impact of early HIV treatment to fight against the epidemic could be limited as a result of the increase in the number of individuals who stop treatment. But the predictions might vary as we are not entirely clear about the change in behavior of those groups and the rate of disease progression after treatment interruption. Whether individuals will be involved in risky sexual activity or not is not clear. We, however, have presented projections for different scenarios of infectiousness level of individuals who stop ART.

In this thesis we have also shown the impact of early HIV treatment confirming previously published results. If individuals initiate ART regardless of their CD4 cell count, on average after two and half years, then the HIV incidence and death rates reduce significantly. But it might still be difficult to see HIV elimination (or an HIV infection free state). The incidence rate might not decline below 0.1% in a short period, a threshold used as HIV elimination stage. For scenario 'all', if dropout and treatment failure are minimized, HIV incidence stabilizes at around 0.3% within two decades for 'current' ART access rate and reduction of HIV transmission by 90% scenario, in contrast to 0.55% HIV incidence, if we have treatment dropout and failure. Due to a high dropout rate, new HIV infections occur at a higher rate.

For scenario 'all', we might see the number of new HIV infections increasing from 99,890 to 172,000 in 2036, if treatment failure and dropout is not minimized, where dropouts are the main reason for the continual increase of new HIV infections.

Like treatment dropout, treatment failure is also a big challenge. When first-line treatment fails to suppress the viral load, individuals need new drug regimen. And new drug regimen (second-line treatment) is usually expensive; as a result the overall program cost grows. In this thesis we have shown that the percentage of the cost increases for different second-line treatment cost. As programs run for a longer period, the proportion of individuals in the second-line increases. Approximately 18.0%, 25.3% and 35.9% of individuals on treatment will be on second-line treatment in 2021, 2026 and 2036, respectively. This might lead to the increase of the annual cost of providing ART by 26.4%, 32% and 39.3% in 2021, 2026 and 2036, respectively. Similarly, the cumulative cost might increase by 23.6%, 26.7% and 31.4% in 2021, 2026 and 2036, respectively.

We have discussed in detail the uncertainties which lie on some of the parameter estimations. ART access rate, and the reduction of HIV transmission as a result of being on ART, are a few of the parameters we struggled to precisely estimate. Despite this, the model projections have interesting results and provide some insights as we have provided different scenarios of those parameters. For instance, if ART access rate of South Africa increases from the 'current' value to 90% by 2017, and high reduction of HIV transmission by patients is achieved, then the HIV incidence in 20 years can be reduced to 0.34% for a scenario with dropout and treatment failure. In contrast, if we minimize dropout and treatment failure, HIV incidence rate can be brought to 0.1%, leading to HIV elimination stage within less than a decade. These results show that ART programs with high ART access rate and high reduction of HIV transmission can minimize the HIV incidence significantly.

It is obvious that the initial phases of ART scale up programs are accompanied by a need for huge investment. But the yearly investment afterwards start declining within a few years, specially for scenario 'all'. The cost may breakeven with the cost estimation of the baseline ART scenario if the programs run longer. But all of these are true only if dropout and treatment failure rates are minimized, as we have shown that the annual spending of ART might continue to increase if individuals continue dropout from treatment.

In all increased ART provision scenarios, the investment return is high. Many lives are saved and the number of new infections decrease with time. The impact increases with increasing ART provision scenario from the baseline to scenarios '500' and 'all'. The cost effectiveness analysis discussed in this thesis helps to suggest the scenario, among the scenarios considered, with less incremental cost needed to avert a health outcome. Scenario 'all' is a scenario with less incremental cost per HIV infections averted throughout the horizon time as compared to scenario '500'. The respective ICER value for infections averted for scenario 'all' is always less than that of scenario '500'. This meets one of the motivations of starting ART early, as fewer dollars are needed to avert a single HIV infection for higher ART provision scenario.

Both ART scale up scenarios, '500' and 'all', are very cost-effective scenarios in South Africa if individuals are prevented from dropout and failure from first-line treatment. For scenario 'all', we have shown that the incremental cost per DALYs averted becomes below $5,580, which is less than the GDP per capita estimate of South Africa in 2012, i.e. $7,592. For scenario 'all', the ICER for DALYs averted might decline from $5,580 (in 2016) to $2,980 (in 2036) for no treatment dropout and failure assumption. In contrast, the ICER value for DALYs averted become higher when individuals dropout and fail treatment with an increasing trend. It might increase from $5,400 (in 2016) to $6,950 (in 2036).

In conclusion, our results confirm that early initiation of ART contributes to a steep decline in the number of new HIV infections and HIV deaths, but also show that the benefit of ART might be limited due to the impact of dropout and treatment failure. Despite the uncertainties associated with some of the models' parameters such as ART induced sexual behavioral change, with the current access rate our simulations show that HIV elimination is not possible to achieve within a decade. To achieve HIV elimination soon, ART access rate must substantially increase, and the dropout and treatment failure rates must also substantially reduce.

8.2   Recommendations

In the last decade, we have witnessed many improvements and commitments by different authorities: governments, non-governmental organizations and others, for the fight against the biggest health challenge, the HIV/AIDS epidemic. Most countries are moving towards early HIV treatment, where some have started recommending ART initiation regardless of CD4 cell count. The numbers of new HIV infections and HIV-attributed deaths have declined significantly due to ART roll out over the last decade. Each and everyone should continue the efforts to see an HIV free generation in the near future. Below are a few recommendations and future research insights for a better understanding of the dynamics of HIV and a better usage of the limited resources collectively.

Future studies

The disease progression after individuals stop HIV treatment is not entirely clear. Thus, the impact of this group of individuals on the HIV dynamics at a population level is not very clear. Future studies should focus on understanding the disease progression dynamics after treatment stops as we know that with treatment programs running for a longer period more and more individuals might stop treatment. In this thesis, we only attempted to study different scenarios of HIV infectiousness of those individuals who stop treatment. The results show that if individuals who stop treatment are involved in risky sexual contacts, despite the knowledge of their HIV status, new HIV infections occur at a higher rate every year.

In this study we have shown that treatment failure might contribute to the increasing demand of the annual cost of providing ART. Better data on treatment failure as a function of different variables such as time since ART initiation is important for better parameterization of some of the parameters. Thus, future studies should also show focus on collecting data on treatment failure and design different strategies to minimize the rate at which individuals fail first-line treatment. Manufacturing of cheaper and effective second-line regimen should also be given priority by pharmaceutical companies.

Policy makers and health workers

Mathematical modelers have shown the impact of early HIV treatment. Thus, from the evidence currently available, we have seen many progress in the ART scale up programs. Many lives have been saved and the number of new HIV infections has declined. However, the impact might be limited due to the increase of the number of individuals who stop treatment and treatment failure leading to a continual demand for high annual spending. Therefore, health care workers and policy makers should design different strategies to achieve high retention rate so that treatment dropout and failure rate can be minimized to the lowest possible rates.

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