

Novel Approaches in Antiretroviral Therapies Retention and Demand Estimation for AIDS patients in Zimbabwe

Master in Business Administration Thesis

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Lastly, I hope that someone will take advantage of the information produced in this work, and that this will contribute to improve the life condition of someone.

Abstract

Currently, Zimbabwe is one of the most HIV-affected countries of the world, presenting an average prevalence of about 13-15% of the population living with the virus. The Zimbabwe government has implemented a framework focused on HIV between 2012 and 2015. The program has been completed and data are currently still being collected. Improvements have been made but the pandemic is far from being beaten.

This work is focused on the challenges encountered while determining improvement in health status, retention and factors associated with attrition among HIV-infected patients within the latest HIV programs. According to these challenges, possible solutions based on literature are proposed. Moreover, the data collected from national and international reports have been used in a stochastic model to complement the comparative analysis of policies. An initial estimate of costs and effects is reported.

The stochastic model defined an horizon of equilibrium for the pandemic in more than 40 years, unless large investments are made and policies on prevention are extended. While the current success in terms of decentralization of life-saving treatments is acknowledged, there is still a need to improve and decentralize testing and monitoring of patients. Confidently, the costs associated to anti-retroviral therapies will continue to drop, but in this context it is relevant to identify the emergence of medication toxicities or failure, to act a change from first to second line therapy promptly. All these observations lead to the general suggestions of increasing the domestic financing in the fight against HIV, and of improving the rural HIV-testing.

Abbreviations

In the following list, acronyms are explained indicating the used letters of a multipart name with capital letters:

AIDS Acquired Immune Deficiency Syndrome

ART Anti-Retroviral therapy

ANC Ante-Natal Care

CHEERS Consolidated Health Economic Evaluation Reporting Standards

DBS Dried Blood Spots

EDTA Ethylene-Diamine-Tetraacetic Acid

HIV Human Immunodeficiency Virus

LTFU Lost To Follow-Up

M&E Monitoring & Evaluation

MOH Ministry Of Health

MOHCC Ministry of Health and Child Care

MSF Médecins Sans Frontières

MTCT Mother-To-Child Transmission of HIV

NNRTI Non-Nucleoside Reverse Transcriptase Inhibitor

NRTI Nucleoside Reverse Transcriptase Inhibitors

PICT Provider-Initiated Counseling and Testing

PLHA People living with HIV or AIDS

PCR Polymerase Chain Reaction

PrEP Pre-Exposure Prophylaxis

QALY Quality Adjusted Life Year

RDS Respondent-Driven Sampling

ROOT Routine Opt-Out HIV Testing

SAPPH-IRe Sisters ART Programme Prevention HIV, Integrated Response

SMS Short Message Services

TB Tuberculosis

UN United Nations

UNAIDS Joint United Nations Programme on HIV and AIDS

UNDP United Nations Development Program

WHO World Health Organization

Zim ASSET Zimbabwe Agenda for Sustainable Socio-Economic Transformation

ZNASP Zimbabwe National HIV and AIDS Strategic Plan

ZUNDAF Zimbabwe United Nations Development Assistance Framework

Table of Contents

Acknowledgments	ii
Abstract	iii
Abbreviations	iv
1 Introduction	1
1.1 Country background	3
1.1.1 Targeting the 90-90-90	6
1.2 Study purpose	7
1.2.1 Study questions and objectives	8
1.2.2 Structure of the thesis	8
1.2.3 Ethical issues	8
1.2.4 Statement regarding conflict of interest	9
2 Novel Possible Solutions and Opportunities	10
2.1 Tracing Mother-Child pairs Lost to Follow-Up	10
2.2 Routine Opt-Out HIV Testing in Children	12
2.3 Sex-workers interventions	12
2.4 Co-occurrence of Tuberculosis	14
2.5 CD4+ Testing	15
2.6 Food insecurity	16
2.7 Funding Gap	17
2.8 Conclusions	18
3 Factors Influencing Data Collection	19
3.1 Non-responder bias	20
3.2 Respondent-driven sampling	21

3.3	Back-calculation methods	21
3.4	Serial prevalence surveys	22
3.5	Conclusions	23
4	Epidemiological Impact Predicted by Mathematical Models	24
4.1	Markov Models in Economic Evaluation and Epidemiological Disease Progression	25
4.1.1	Asymptomatic-HIV-AIDS Transition Model	26
4.1.2	Healthy-HIV-AIDS-Death Transition Model	26
4.1.3	CD4+ Counting Transitions Model	28
4.1.4	Virus Load and Lost To Follow Up Model	29
4.2	Conclusions	31
5	Proposed Model for Impact of ART Policies	32
5.1	The proposed Markov chain	32
5.1.1	Non-responder bias evaluation	35
5.1.2	Serial prevalence	36
5.2	Results	37
5.2.1	Probabilistic sensitivity analysis	37
5.3	Costs and QALYs estimation	39
5.3.1	Costs	41
5.3.2	QALYs	44
5.4	Comparison with Avenir-health Spectrum	46
5.4.1	Results	47
5.5	User point of view	48
5.6	Drummond Checklist	50
6	Discussions	55
	Bibliography	59
	Appendix A Appendix	76
A.1	Settings tables for Avenir-health Spectrum	76
	Declaration on Scientific Integrity	81

1

Introduction

The acquired immune deficiency syndrome (AIDS) is an immune system pathology induced by the infection with the human immunodeficiency virus (HIV) virus. After a subject is contaminated by the HIV-virus, a brief influenza-like period occurs, followed by a long period of latency (generally up to 8 years, but in some cases even up to 12 years) [1]. Then, the infection manifests itself slowly, and while it progresses, it interferes increasingly with the immune system, leading easily to infections and tumors [1].

HIV is transmitted by using body fluids as vectors. In practice it spreads during risk behaviors such as unprotected sex, blood transfusion, injection with re-used needles, and from mother to child interaction (during pregnancy, delivery, or breastfeeding) [1]. Disease progression can be evaluated by counting CD4+ cells [2], moreover the World Health Organization (WHO) proposed a staging system for the HIV infection and disease [3] which can be summarized in the following stages:

1. The HIV-virus is present but asymptotically, this is not categorized as AIDS.
2. Minor mucocutaneous manifestations and recurrent respiratory tract infections occur.
3. Unexplained chronic diarrhea (more than a month), severe bacterial infections or pulmonary tuberculosis (TB) are experienced.
4. Infections as acute toxoplasmosis, candidiasis of the esophagus/ trachea/ bronchi/ lungs and Kaposi's sarcoma occur.

Currently, there is no effective cure for AIDS or vaccine for the HIV-virus. However, antiretroviral therapies (ART) can slow the disease progress and may lead to a quasi-normal life expectancy [4]. To be more effective, ART should be initiated as soon as possible [5]. Otherwise if no treatment is initiated, in healthy adult the survival time after infection is in average 11 years [6], while perinatal HIV-infected infants experience higher mortality with shorter lifespan [7]. Studies suggest that children aged 5-10 years, which initiate ART and then abandon the program, are not able to follow a normal growth process [9]. Patient retention in ART programs for children showed a correlation to reduced risk of TB [10]. All these observations highlight the importance of early and uninterrupted ART therapies.

The purpose of ART is to contrast the enzymes that are crucial in the replication of HIV [11]. CD4+ cell count is crucial for identifying HIV patients and to assess disease progression. In fact, apart from being a leading marker of disease progression, CD4+ counts are used as an indicator of suitable ART administration [11]. One of the challenges related to HIV is its genetic variability, in fact there are two major types called HIV-1 and HIV-2 which are further divided in other subgroups complicating the planning of ART programs [8]. The presence of a new virus infection can be detected after a window period which varies from 9 days to 3 months, depending on the person's body and the used test.

- Antibody tests - also know as *rapid tests* - give a positive result based on the presence antibodies to HIV. They are relatively easy to be used even by community health workers. However, they might be inaccurate due to the need up to 3 months for the body to produce these antibodies at levels that can be detected by these tests with an accuracy of 99.97%.
- RNA tests detect HIV-virus by using a process called polymerase chain reaction (PCR). Those tests are precise and they can detect the virus already after 9-14 days after infection, but are more costly and require highly trained personnel.
- HIV combination tests, which detect antibodies against the subtypes HIV-1 or HIV-2 as well as a protein called p24, can detect the virus in average after 16 days with an accuracy of 95%. This is possible because the p24 protein forms part of the core of the virus and it can be detected before the antibodies formation.

In children younger than 18 months, antibody tests are inaccurate due to the presence of maternal antibodies in their blood [12]. Therefore, the infection would be better diagnosed by PCR testing for HIV. Unfortunately, the presence of PCR testing in Subsahran countries is limited [12].

1.1 Country background

Zimbabwe remains one of the most affected countries by the HIV infection. In the country there is a generalized HIV epidemic with an estimated prevalence of about 13-15% (quantifiable in about 1,500,000 people living with HIV) and an incidence of 0.85% [13]. In average, there are estimated 70,000 annual AIDS deaths, leaving about 1.000.000 orphans related to the HIV epidemic [13]. The first AIDS case was reported in Zimbabwe in 1985. From 1985 to the late 90s the HIV prevalence rose sharply to reach a peak of 27.7% in 1997 as shown in Figure 1.1, from 1997 there has been a decline of infection probably due to behavioral changes [14]. The country has experienced a deep socioeconomic crisis between 2001 and 2009 with extreme recession and hyperinflation affecting significantly the health care system in terms of workforces and supplies [15].

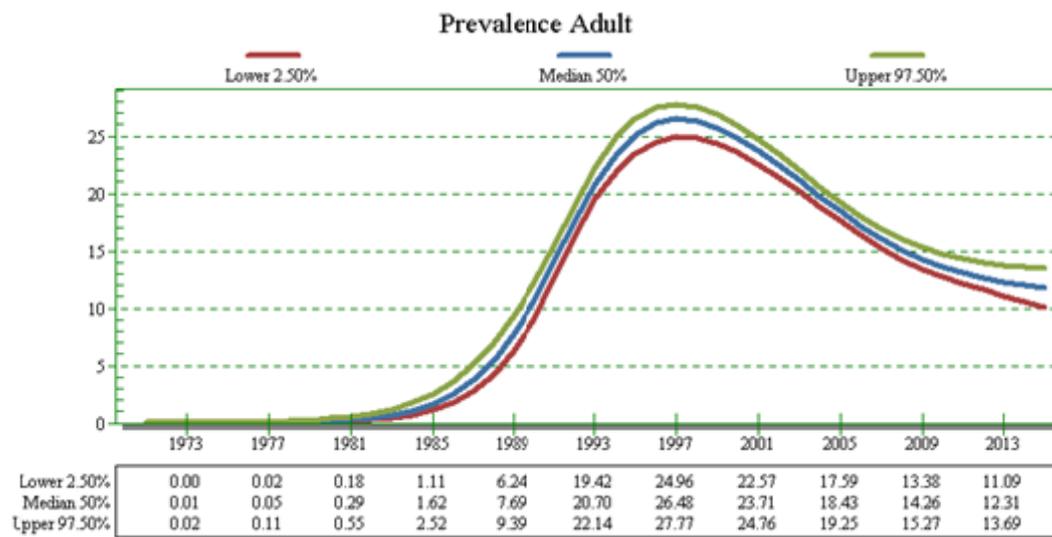


Figure 1.1: Previous prevalence per year, image taken from [16].

At country level, HIV-infected adults are eligible for ART if they are diagnosed at WHO clinical stage IV irrespectively of CD4+ count; at WHO stage

III with CD4+ cell count < 350 cells μL ; or WHO stage I or II with CD4+ cell count < 200 cells μL . Cotrimoxazole preventive therapy is suggested to all symptomatic HIV-infected patients, and therapy adherence is assessed by health workers through pill counting in health facilities [17]. Recommended first-line ARTs currently comprise Tenofovir-based regimens for adults and Zidovudine-based regimens for children, Nevirapine as non-nucleoside reverse transcriptase inhibitors and Lopinavir/Ritonavir as protease inhibitors. The second line comprises the alternative Zidovudine also for adults and Efavirenz non-nucleoside reverse transcriptase inhibitors and Atazanavir/Ritonavir as protease inhibitors in case of adverse drug events [18]. A retrospective review conducted on a representative sample of 3,919 patients showed a higher attrition (death or stopped treatment) in patients who did not receive Cotrimoxazole compared to the other approaches [17]. In the country the virus is spread mostly through sexual contact and mother-infant transmission. Participation to ART programs is free of charge, though patients are supposed to pay consultation fees and laboratory costs for CD4+ cell counts.

The Government of Zimbabwe has introduced a national HIV policy and a National AIDS council, with the goal of no new infections, no HIV related deaths, and no HIV stigma and discrimination. More specifically, the Zimbabwe National HIV and AIDS Strategic Plan (ZNASP) provided both policies and strategic guidance to all HIV and AIDS interventions. Goals were set within the ZNASP to be achieved within the 2011-2015 time frame with a midterm review conducted in 2013. Those data have been used in a stochastic model to estimate ART demand in Chapter 5.

Given the limited domestic resources to fight the epidemic in the country, the United Nations (UN) system in Zimbabwe has been supporting the government and its partners in developing and implementing an HIV response plan in several sectors called ZUNDAF (Zimbabwe United Nations Development Assistance Framework). The plan had three main goals [19]:

1. To improve access and uptake of HIV prevention services.
2. To improve access and uptake of HIV treatment, care and support.
3. To improve leadership, coordination and management of multi-sectoral HIV responses.

The first point focuses on prevention, this includes prevention of mother to

child transmission (MTCT), safe male circumcision and other services preventing virus transmission, and promotion of safer sexual behaviors. The second point is in agreement with the new WHO guidelines on efficacious treatment, while the last point concerns the enhancement of capacities and operations of national management and coordination, in particular regards monitoring and evaluation (M&E) practices ensuring data collection and presentation. Results related to these points have been summarized in the matrix shown in Figure 1.2.

Year	2007	2009	2012	2013	2014
Percentage of HIV-positive pregnant women who receive antiretroviral to reduce the risk of mother-to-child transmission.	22%	59%	85%	82%	
Number of Adults 15-49 who were tested and received results	579,767	1,108,264	2,240,344	2,274,328	1,465,289
Number of males circumcised according to national standards		2,801	40,775	112,084	400,235
Percentage of eligible adults and children currently receiving antiretroviral therapy.	Adults - 31.3%, Chn - 9.7%	Adults - 62%, Chn - 22.2%	Adults- 85% Chn- 43%	Adults - 76.9%, Chn - 40.5%	Adults - 63.4%, Chn - 54.8%
Percentage of adults and children with HIV known to be on treatment 12 months after initiation of antiretroviral therapy.	93.1%	75.0%	85% (Adults - 85.4%, Chn - 82.8) ;	85.7% (Adults- 87.1% Chn - 85.6%)	89.5% (Adults- 89.7% Chn- 88.3)

Figure 1.2: ZUNDAF summary matrix, image taken from [20].

Moreover, the national response has been also guided by the following policies:

- National AIDS Council Act.
- Income Tax Act.
- National HIV Policy 1999.
- National Health Policy.

- Zimbabwe Agenda for Sustainable Socio-Economic Transformation (ZIMASSET).
- National Health Strategy 2011 - 2015.

These key policies took also into consideration the need to develop a data dictionary to harmonize AIDS and TB data collection and analysis, to standardize manual data storage system, and to move toward electronic databases.

Buzdugan et al. [21] surveyed 8,568 mother-infant pairs in 156 health facilities randomly selected from 5 provinces in Zimbabwe in 2012 before the introduction of any peri-natal programs. The survey identified 1,107 HIV-infected women, and the 10% of these having an infected child (though 66% of them were still breastfeeding). This highlighted the need of more effective programs related to mother-infant pairs. Since January 2014, the Ministry of Health and Child Care (MOHCC) has introduced the Option B+ approach where all HIV-positive pregnant women are on ART for life independently from the CD4+ count, which has been shown to be effective in other countries (e.g. Malawi) to increase ART coverage among HIV-infected pregnant women [22, 23]. Before the introduction of Option B+, only women with low CD4+ counts or being in an advanced WHO clinical disease stage were included into ART programs [23].

The Zimbabwe country report 2014 showed promising improvements as part of the ZUNDAF evaluation [20]:

- The annual HIV related deaths decreased from 115,117 in 2011 to 54,994 in 2014 with decreasing trend in the years in between.
- The MTCT rate reduced from 18% in 2011 to 6.6% in 2014.
- Coverage of ART has increased from 5% in 2004 to 77% in 2014.

Despite these achievements, the ART coverage for children and adolescents is still disproportionately low as shown in Figure 1.3.

1.1.1 Targeting the 90-90-90

At the end of 2014, UNAIDS launched the ambitious "90-90-90" target [24], where by 2020, 90% of people living with HIV will be diagnosed, 90% of those diagnosed will be followed adequately with ART therapies, with 90% of viral

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Percentage of eligible adults and children currently receiving antiretroviral therapy.	Adults -31.3%, Chn – 9.7%	Adults - 62%, Chn -22.2%	Adults- 85% Chn- 43%	Adults– 76.9%, Chn – 46.12%	Adults - 63.4% Chn- 55%

Figure 1.3: Results related to children and adolescents, image taken from [20].

suppression of those in ART. The benchmark figures for Zimbabwe are those reported in Figure 1.4

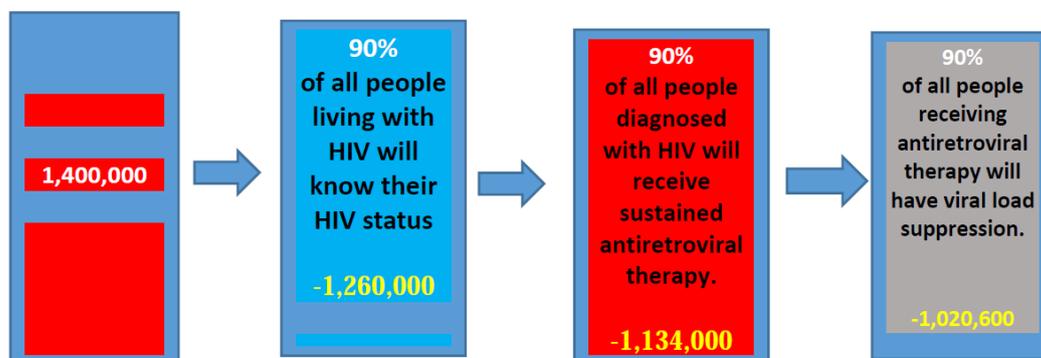


Figure 1.4: 90-90-90 benchmark figures for Zimbabwe, image from [20].

1.2 Study purpose

In this thesis, first the most common HIV-related challenges experienced in Zimbabwe are reviewed mentioning possible state-of-art solutions used in other countries. Second, from national and international reports representative multi-stage data are identified and gathered. In particular, information about individuals, such as being recorded as alive-continued ART, died for AIDS or lost to follow-up are collected. These will then be used to compute probabilities of transition away from alive on treatment and the other instances aforementioned, feeding a stochastic model used for simulation on the next years. The purpose of the model is to define future ART demands, costs and perspectives for the country of Zimbabwe.

1.2.1 Study questions and objectives

This thesis reports the opportunities and challenges encountered by the Ministry of Health (MOH) in Zimbabwe and GlobalFund.

The detected challenges and the stochastic models will be used to cover important and general issues about the overall design, and interpretation of health economic evaluations. Drummond checklist [25] is used in Chapter 5 to review the whole analysis. The questions and answers are posed from the point of view of policy makers as members of the MOH, MOHCC and partners as UNDP and GlobalFund staff.

The study questions can be here summarized:

- What are the delicate circumstances encountered during improvement of health-care in HIV-related issues, data collection, and ART patient retention?
- Can we suggest ideas which can be translated into national policies to help HIV-infection reduction, data collection, and patient retention on ART programs?
- Can a stochastic model [26] be designed to improve the estimate of ART demands, HIV-related deaths and people living with the HIV-virus?

1.2.2 Structure of the thesis

This first chapter gives a first brief background on HIV/AIDS and Zimbabwe. Chapter 2 focuses on current opportunities and possible new policies. The third chapter mentions issues related to data collection. Chapter 4 reviews the used of Markov model in HIV/AIDS studies while Chapter 5 proposes a Markov model suitable to the available data from Zimbabwe. The last chapter comprises the final discussions.

1.2.3 Ethical issues

The study was carried out jointly with personnel of the Global Fund to Fight AIDS, Tuberculosis and Malaria, which in turns operates with UNAIDS and UNDP in Zimbabwe. The data were extrapolated from routine reports for which ethical approvals have already been granted by the local committees, and therefore no further ethical approval was required.

1.2.4 Statement regarding conflict of interest

The author of the thesis has no conflict of interest with the GlobalFund, UNDP in Zimbabwe, or any pharmaceutical company working on ART or other therapies about HIV.

2

Novel Possible Solutions and Opportunities

Before delving into the model for predicting the future ART needs, other issues related to the health-care system that can improve the life of the overall HIV-infected cohorts should be reviewed. These are tuberculosis co-occurrence, stigmatization, inadequate testing infrastructures, and others.

2.1 Tracing Mother-Child pairs Lost to Follow-Up

High retention rate is crucial to reduce HIV-infections especially in MTCT prevention programmes which remains low in many Sub-Saharan countries. Option B+ is currently the state of art policy to reduce MTCT [27], but loss to follow-up and inadequate or missing documentation represent the major threats to the existing programs. Option B+ includes life-long ART therapies for HIV-infected pregnant women, recommends testing in all children born to HIV-positive mothers at four to six weeks postpartum using PCR technology [27], and use of Cotrimoxazole prophylaxis to prevent *Pneumocystis carinii* pneumonia. All these steps are often referred as "MTCT prevention cascade" [28]. Despite some countries are able to perform all steps of the cascade, many experience high loss to follow-up across the steps. In Malawi, the first country using the Option B+ approach, despite the increased ART coverage, lost to follow-up (LTFU) was five times higher than the previous policies with women initiating with low CD4 count [29].

Médecins sans Frontières (MSF) is also involved in MTCT prevention in the

country. They started decentralized projects in the semi-rural settings in the arid Tsholotsho district. A pilot study [28] conducted in the same district involving health workers, showed a lower number of LTFU mothers or infants in particular after the delivery, though no significant decrease in HIV transmission was noted. Therefore the introduction of community health worker could be useful to reduce LTFUs but other policies should also be sought.

A recent qualitative study conducted in Malawi highlighted some determinants for refusals and stopping ART in pregnant women [30]. The barriers to the therapy initiation included pressure from the partner and feeling relatively healthy, in addition reasons to stop also included side effects. Conversely, reasons to start or re-start the participation to ART, included encouragement from community health workers, becoming comfortable to side effects, tangible decline in health, and change in partner. The authors also designed a visual framework to understand all barriers depicted in Figure 2.1, and most likely these barriers are also present in Zimbabwe and should be taken into consideration.

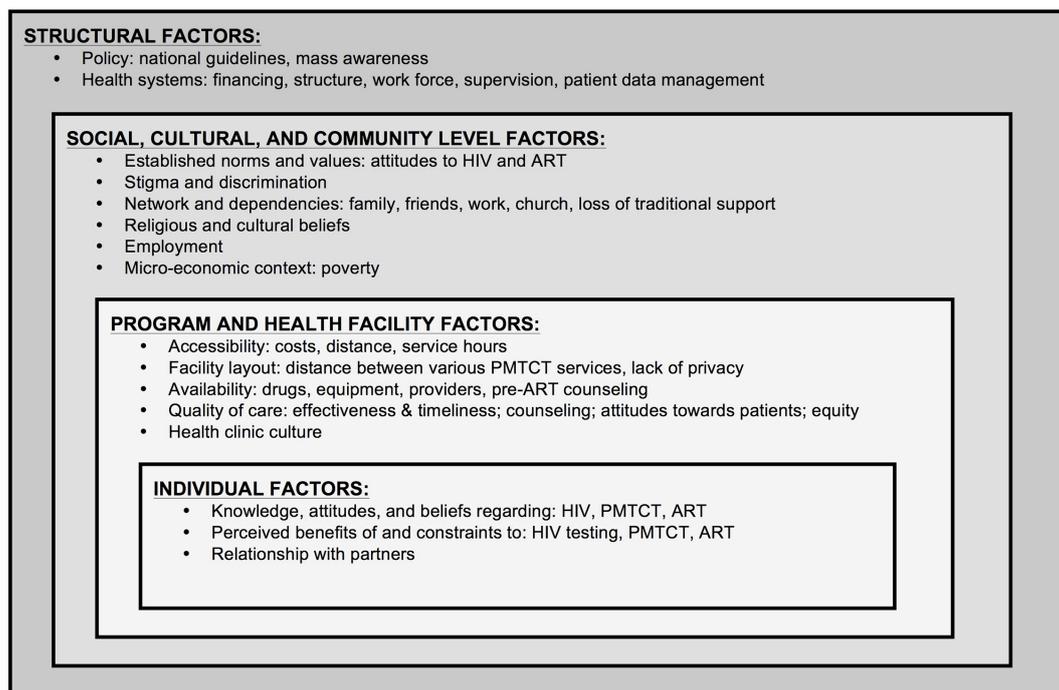


Figure 2.1: Socio-ecological framework of the barriers and facilitators in the Option B+ MTCT program cascade, image taken from [30] which in turn was adapted from [31].

2.2 Routine Opt-Out HIV Testing in Children

Along with the adherence of HIV-infected pregnant women to ART programs, testing potential children for HIV is also crucial. In fact, mortality is high among HIV-infected infants in their first year of life. In fact, approximately 30% of HIV-positive children do not survive up to their first birthday, and more than 50% die before the second [32]. In Zimbabwe, mother-to-child transmission of HIV (MTCT) is, at the time of writing this document, the most common way for children to become HIV-infected [33]. Certain interventions can reduce MTCT to less than 5% if effective testing is carried out promptly [34]. However, the coverage of HIV testing in infancy remains low with only 20% of HIV-exposed infants accessing early diagnosis [35].

According to the national guidelines introduced in Zimbabwe in 2007, HIV-testing is given in the form of opt-in provider-initiated counseling and testing (PICT) [36], where people visiting a clinic or hospital are tested pro-actively upon decision of a health-worker but independently from the presentation reason [37]. Despite the goal is to reach as much as infected people as possible, the infant HIV testing coverage remains incomplete. A possible explanation is that the procedure is entrusted to health workers which are relatively ineffective in identifying cases who need testing [36]. An alternative testing approach that limit the influence of health workers is the routine opt-out HIV testing (ROOT) [36]. In this approach the health-workers take no decision and the judgment to carry out the test relies only on the person attending the health facility. A pilot carried out in 6 primary health-care facilities in Harare (Zimbabwe's capital) showed an increase of test uptake from 71% to 95% if ROOT was used instead of PICT [36]. Therefore, ROOT can be considered as an alternative approach to reduce missed HIV diagnosis in infancy, since the bias of health-workers who do not estimate properly HIV risk is removed.

2.3 Sex-workers interventions

The expression 'sex worker' refers to anybody engaged in activities related to exchange of money or valuable goods for sexual services. It is preferred to "prostitution" since it gives a less derogatory and sexist connotation.

Sex-workers are among the groups at more risks of infections. This occurs since sex-workers are exposed to constant physical contact with people and to a series of factors impeding them the access to services within global re-

sponses of HIV [38]. Beyond national laws which may criminalize sex-workers, in some cases they are not properly involved into HIV response programs [39]. Violence against sex-workers is common, and in some cases is also accepted by many, including police authorities and clients. This includes rape, forceful acceptance of condom-less sex, and sex with policemen to avoid arrest [40]. In 2012, the Zimbabwe's national sex-worker HIV Prevention Programme reported 50% HIV prevalence among sex-workers attending their clinics; the most recent UNAIDS country report also estimated 50% prevalence among sex-workers, compared to 15% among the general adult population [41]. The first step to address such a high prevalence is testing and then management. The hurdles that sex-workers encounter in testing are similar to those of the common people, as the opportunity costs, the poor awareness of services, geographical distances and related poor infrastructures, time constraints, and fear of being HIV-infected with subsequent stigmatization. In addition, sex-workers have further disadvantages as fear of authorities related to the criminalization of prostitution, and fear of status disclosure to other sex-workers or potential clients with consequent loss of income [42, 43].

Community mobilization among female sex-workers has emerged as an effective HIV prevention strategy. Community-based prevention programs in southeast Asia, Africa, and South America confirmed that HIV can be controlled both by sex-workers and relative communities [44]. In particular, if those focus mainly on condom-less sex, violence, and discrimination [45].

The evidence suggested that by encouraging sex-workers to be identified as part of the community, better quality of life and health for the sex-workers is reached [46]. In fact, community empowerment is associated with reduction of HIV and other sexual infections prevalence and increased condom use [47]. Pre-exposure prophylaxis (PrEP) is the use of some ART medicines by HIV-negative people to reduce the risk of new HIV acquisition [48]. Case-control analyses about PrEP suggested that those using PrEP consistently had a bigger reduction of HIV risk, and it can be useful to sex-workers, since PrEP is a tool in their control [49]. However, this is seen as a dangerous approach by the majority of pharmacists in Zimbabwe who believe that the availability of PrEP could lead people to abandon safer sex practices (e.g. condoms) [50]. PrEP use of ART is also related to concerns about developing drug resistance [51], and considered a poor cost-effective approach compared to other solutions [52]. Therefore, it remains still unclear whether the use of PrEP is the best

solution compared to other policies.

Mtsetwa et al. conducted a qualitative analysis on communities in Zimbabwe where the community mobilization seems promising [41]. Moreover, Zimbabwe has approved a community mobilization project initiated in April 2014 called the SAPPH-IRe trial ('Sisters Antiretroviral Programme for Prevention of HIV – an Integrated Response') [53]. The program provides free condoms, HIV testing, PrEP, counseling, and legal services. All services are supported by a network of peer educators, as part of a larger programme called *Voice*. It is believed that this campaign will lead positive results for the sex-workers and for other people.

Summarizing, sex-worker interventions should integrate social justice and health-care strengthening. As for the the SAPPH-IRe program, this community mobilization advocates good health and legal practices, but it is important to promote even more responses against violence and discrimination and sensitization to authorities which might abuse of their power.

2.4 Co-occurrence of Tuberculosis

The increase of TB cases in Sub-Saharan Africa has been largely attributed to HIV [54]. Despite the lives saved, TB is still present and associated with high mortality and related to HIV. The reasons are the neglected TB diagnosis in HIV-infected patients and delay of presentation to health facility [54].

The level of co-infection in Zimbabwe is high. In the country the TB prevalence was estimated by WHO as 409 cases per 100,000 people, while mortality - including HIV/TB related mortality - as 153 cases per 100,000 people [54]. The TB treatment infrastructures in Zimbabwe are included into the general services in all health facilities of the country. At those facilities, suspected cases are managed by examining their collected sputum on a microscope with acid-fast staining techniques (as the Ziehl-Neelsen method). For smear-negative cases and extra-pulmonary TB, the diagnosis can be extended by a radiographic examination. In Zimbabwe, similarly for the diagnosis of HIV-infection in infants, the use of PCR analysis is not so common, although it has been recently recommended particularly for the GeneXpert devices [55]. Sputum smear microscopy and chest radiography is time consuming, costly for the patients who need to make multiple journeys to the lab or health facility, while the GeneXpert approach is more sensitive and rapid, but still needs to

be scaled up across the country [56].

A recent survey conducted in 47 randomly selected health facilities in Zimbabwe, investigated whether the larger delay in diagnosis was attributable to patients delay and health-care system delay [57]. The interval between TB symptoms onset - with symptoms as cough, fever, unintentional weight loss, fatigue, sweats during sleep - and patient presentation to a health facility was measured. The study showed that the average patient delay was greater than 30 days while the health-care delay was greater 4 days. Patient delay was more pronounced in rural settings compared to urban areas where district or mission hospitals were present. Being patient delay the weakest ring of the chain, it appears clear the need to increase social mobilization and not only infrastructure strengthening, to make people more dynamic at the first symptoms TB-related.

2.5 CD4+ Testing

Suitable ART therapy design and monitoring are given by differentiation of CD4+ cells/ μ L levels in the blood, which is currently the most used diagnostic approach to choose treatment and monitoring [58]. However, as many Subsahran African countries, CD4+ testing capacity has not kept up with the ART decentralization process carried out by the government to strengthen the peripheral or rural health facilities [59]. In 2009 the available CD4+ machines across the country were only 46 [60].

The reasons of this delay is related to the costs of diagnostic equipment, the need of more advanced facility infrastructure and lack of skilled staff compared to ART distribution [61]. The consequence of this gap is the limitation to urban laboratories performing the test, where the samples need to be transported [59]. Samples collection in Zimbabwe is carried out by using Ethylene-Diamine-Tetraacetic Acid (EDTA) tubes, which after collection must be examined within 24 hours. This requires an urgent transportation performed the same day from rural to central facilities, which is challenging and not always managed. In a pilot project in the Beitbridge district, MSF has compared the CD4+ testing access among HIV patients from rural and urban areas, by comparing 2,145 HIV positive adults in a retrospective cohort analysis at ART initiation, at six and at twelve months follow-up after treatment initiation [58]. MSF noted that the risk of missing CD4+ testing

after six months and twelve months was respectively 9.2 times higher and 7.6 times higher for rural patients compared to urban patients at ART initiation, as shown in Figure 2.2. The difference was probably related to material and human resources constraints. This pilot highlighted the lower access to CD4+

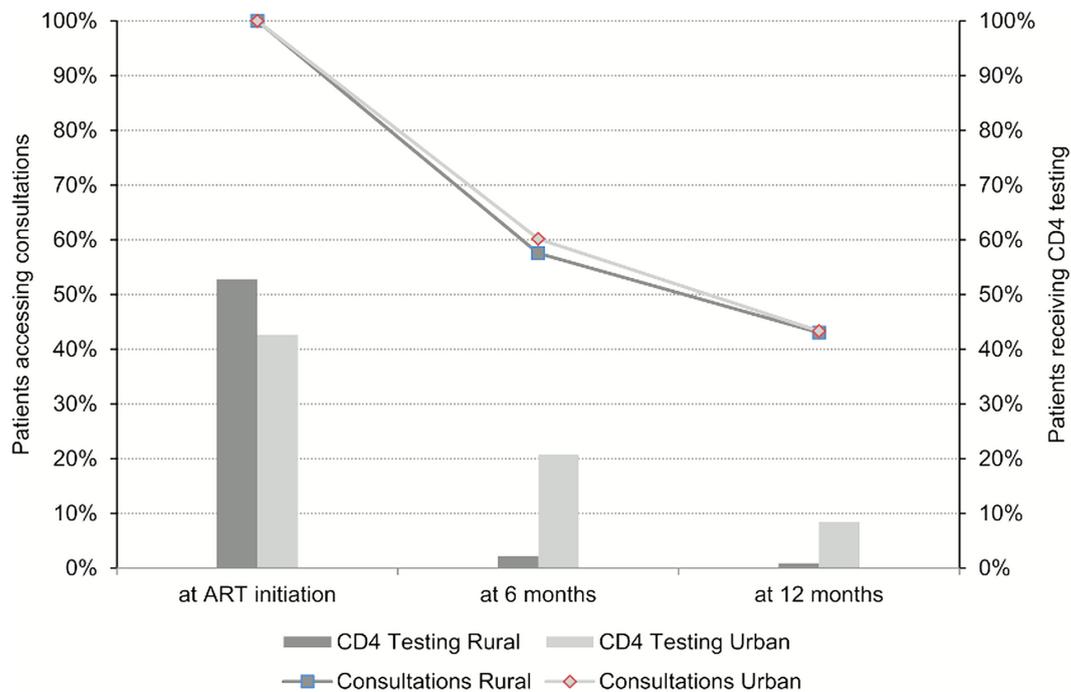


Figure 2.2: Proportion of rural vs urban patients accessing consultations and CD4+ testing, image taken from [58].

testing in rural areas. Despite it has to be confirmed by national investigation, changes in health care delivery and investment in new diagnostic technologies, such as use of dried blood spots (DBS) or point-of-care devices in remote areas, have to be addressed.

DBS testing is expected to be financially sustainable soon [62], and therefore it could be available in all rural areas. Alternatively samples transported by drones as attempted by UNICEF-innovation [63], or ideally, viral load point-of-care tests providing immediate results across the country should be arranged.

2.6 Food insecurity

“Food security exists when all people, at all times, have physical and economic access to sufficient safe and nutritious food that meets their dietary needs and

food preferences for an active and healthy life” [64].

Among the factors which generally influence retention of patients in ART programs, food insecurity has been already identified as relevant since it increases HIV related risk behaviors in Brazil [65], Uganda [66], Botswana and Swaziland [67]. The relationship between HIV and food has also been observed in Zimbabwe [68], in particular among pregnant women who should attend ANC or MTCT [69].

Food insecurity might lead to avoid maternal health services because of the perceived or real costs of ANC and related expenses [70] and expenses related to testing the HIV status [69], as these latter are still out-of-pocket to the patients. The under-use of services is also believed or be related to stress and depression given by the poor financial situation [71]. Moreover, food insecurity is generally associated to under-nutrition and breastfeeding less [72]. McCoy et al. conducted in 2012 a survey on a population of 8,790 Zimbabwean women from 5 provinces about food insecurity and attendance to ART programs [69]. The survey showed that women from food insecure household were more likely to be HIV-infected compared to women from food secure household. Moreover, women living in highly food insecure households were more prone to have an HIV-infected children compared to the other groups. In the sample in exam, the correlation between food security and attendance to ANC and ART programs was weak. It was noted that in facilities that charges a fee, fees often cover a series of ANC services and 6-week postnatal visit where exams are conducted, and this helps patient retention. Although the study showed a marginal effect sizes, the study highlighted that food insecurity is a challenge to patient retention, both in terms of pregnant women attending to ANC and to remaining into ART programs.

Finding solutions in this context represents a challenge, since food insecurity is just an aspect of poverty, and people with limited financial resources can engage in risk behaviors to obtain food or additional monetary resources. A possible solution can be given by food and nutrition programs which can be strengthened in Zimbabwe.

2.7 Funding Gap

The first challenge that the Government of Zimbabwe is encountering in the fight against HIV is the resources constrain, especially in human an financial

resources. The Joint United Nations Programme on HIV and AIDS (UNAIDS) in 2014 set the funding target of 9.7 billion USD for 2020 [73]. UNDP and the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria are running the Round 8 Grants for HIV/AIDS, TB, Health Systems Strengthening and the Single Stream of Funding for Malaria, where the Global Fund has committed a total of 293.6 millions USD. Despite this support, funding gaps occur constantly unexpected due to changes in the policies, and these are not so easily visible from the outside. However, it has been suggested that the national investment should be increased to fill eventual funding gaps. Attempts to change the situation have been the introduction of a health worker retention scheme, and the AIDS levy which saves the 3% of all taxable individual and corporate incomes to fund HIV programmes [14]. Further possibilities can be given by the expansion of the formal sector with the expected economic growth leading to higher tax revenues [74], or by the introduction of consumption taxes on alcohol and tobacco.

2.8 Conclusions

The aforementioned issues influence also data collection and therefore the trustworthiness of designed models. Other identified challenges include

- The cultural factors as strong masculinity believes [75].
- The supply chain management system which it is still relatively fragmented.
- The weak linkage between health centers and communities.

Zimbabwe has carried out incredible improvements in terms of forecast, procurement and reduction of stock-out of ART drugs as shown by a recent sample study [76]. However, as it has been mentioned in this chapter there is still room for improvement in terms of CD4+ cell counting and HIV testing especially for infants, both in terms of better testing infrastructures and sensitization in case of early symptoms.

Moreover, men still relatively see HIV/AIDS as a threat to their manhood, and exhibit fear of the disease also influencing the behavior of the spouses [75], and social marketing approaches should be considered.

3

Factors Influencing Data Collection

AIDS is not only a difficult challenge to our society for the disease burden, it is also difficult to measure it for fear of stigmatization, and due to some infrastructures for disease surveillance which might be inadequate [58].

HIV prevalence is the number of HIV cases still alive in a particular population at a given time, which is generally one year. HIV incidence is the number of new HIV cases occurring in a population during a certain time period (also generally one year). The HIV incidence rate is instead given by the ratio of HIV incidence and the total uninfected population, e.g. the new infected cases in Zimbabwe and the total population in the country. This also gives the the risk of becoming infected within an interval of time (e.g. one year). While HIV prevalence estimates the total disease burden, HIV incidence is an indicator whether the epidemics is decreasing or not.

Incidence is generally more cumbersome to be estimated than prevalence because it must be exhaustive and within a short interval of time as one year.

From the point of view of surveying and analyzing data, incidence and prevalence estimates obtained by using different approaches or intervals are often not directly comparable each other. This complicates further the assessment on time [77]. National statistics on HIV prevalence, also called sentinel surveillance data, are collected at public health facilities on the people attending them, for example pregnant women receiving care at public ANC clinics or people showing AIDS symptoms. Additionally, specialized surveys of selected high-risk subpopulations like sex workers and drug users are conducted.

3.1 Non-responder bias

With the aim of having updated and relevant indicators of progress, statistics are often conducted on representative samples, offering a probability-based gold-standard. Unfortunately, these data might not be always reliable, since people at higher risk of HIV infection may be the less likely to unveil their status and therefore to participate to survey. Homosexual men, sex-workers and drug addicted people might avoid to participate to surveys to avoid stigmatization. This is in high concern, since nonresponse bias is likely to influence surveys and gives a distorted picture which is brighter than the reality, because the non-responders are probably those at higher risk. A particular type of non-responders bias is the “*refusal bias*”, which occurs when a person with prior knowledge of his HIV status is less likely to participate in an HIV prevalence survey [78].

Some attempts to address the non-responders have been made. Brookmeyer defined the magnitude of the non-responders rate γ , which should be taken into account to evaluate how much this is invalidating or influencing the overall survey as [77]

$$\gamma = 1 + (1 - f)(R - 1), \quad (3.1)$$

where f is the percentage of those surveyed who agree to reveal their HIV test, and R is the ratio between the HIV prevalence in non-responders and responders.

For instance, in case the response rate is 90% (given as $f = 0.9$) and the ratio $R = 8$, the result of equation (3.1) is $\gamma = 1.7$, where the difference to 1 is giving us the magnitude of imprecision, which in this example is 0.7 and it means that the true prevalence is probably 70% higher. This example shows that without a quantitative measurement of γ it is difficult to know how much reliable the survey is, even when large sample sizes have been used.

Estimates of HIV status, in risk cohort like children of infected mothers, from ANC data in low-income countries can also be misleading. For example demographic and health surveys in Zimbabwe showed that only 85% of the pregnant women attend at least 1 ANC visit [79]. If those women miss their ANC visits or clinic delivery, they are also likely to be missed for potential HIV-testing.

Nevertheless, in a study [80], HIV prevalence rates from ANC surveillance surveys were compared to national surveys of 26 countries, observing that the HIV prevalence estimates from ANC clinics were overestimates by an average 20%. Subsequently, UNAIDS recommended that ANC prevalence rates are

decreased to their 80% value to be adjusted to the closest national value [81].

3.2 Respondent-driven sampling

A possible solution to address the non-responder bias, is the respondent-driven sampling (RDS) approach, since participants are contacted by other participants within their network. It is considered the evolution of snowball sampling [82] as this model was not considering statistics into account. RDS is a sampling method used when information from groups which are considered hard to reach is required, as this is the case of sex workers, drug addicts or men who have sex with men. RDS is a sampling method based upon numerous assumptions/constraints. Despite the aleatory elements of the approach, several requirements must be respected to obtain a representative sample [83].

First, the population being recruited must be socially networked; for instance, social network connections among sex-workers could be given by friends, colleagues, acquaintances, family or other members of their same group. Sampling starts with a planned selection of individuals from the target population, usually referred to as “seeds”. Then, starting with the seeds, each participant is allowed to recruit a specified number of subjects that will continue the sampling. This is known as a “recruitment quota”, which should be used to limit the seeds with large networks from over-recruiting in their network and therefore biasing the sample [84]. It is also important that the recruitment chains are long enough to be sure that participants involved have some degrees of separation from the seeds participants. Finally, RDS data must be analyzed to account for too much similarity within the resulting samples, difference in social network sizes and recruitment patterns. Otherwise further biases might be introduced.

3.3 Back-calculation methods

Apart the social issues related to surveys, other imprecision effects related to the virus incubation can occur. Back-calculation uses HIV/AIDS surveillance data to estimate HIV incidence [85]. The method uses the incubation period distribution to infer the numbers of persons infected in previous years that match the observed AIDS surveillance data. The idea is to consider the known cases of AIDS as just a part of the HIV infections since some cases are still

incubating.

At individual level, an AIDS diagnosis date is related to an infection date and incubation as

$$AIDS_{diagnosis-date} = HIV_{infection-date} + incubation. \quad (3.2)$$

By using AIDS diagnosis data together with information about the incubation period, it is possible to infer historical HIV infection dates and thus HIV incidence trends by inverting equation (3.2). A more precise way adjusts the estimate by deconvolving the observed diagnosis pattern with an estimated infection distribution [86, 87].

Generally, estimates are carried out at population level considering incidence and prevalence, namely a shift from AIDS incidence to HIV. The original version of back-calculation combined AIDS surveillance data with data on the incubation period in a statistical analysis, by using the relation

$$E(t) = \int_0^t I(s) * [1 - F(t - s)], \quad (3.3)$$

where $I(s)$ is the incidence at time s , $F(t)$ is the incubation distribution, and $*$ is the convolution operator. The incidence $I(s)$ can also be modeled as a Gamma distribution while the incubation is generally defined by a Weibull distribution [88].

To know the expected number of AIDS cases occurring in the interval $[t_{j-1}; t_j]$ the following integral can be used [89]:

$$E(t) = \int_{-\infty}^{t_j} I(s) * F(t_j - s|s) - F(t_{j-1} - s|s) ds, \quad (3.4)$$

where $I(s)$ is still the incidence at time s , and $F(t|s)$ is the probability of developing AIDS within t years of infection for those who were infected at time s , but here we use two time points which give the interval. In this way, the method of back-calculation allows to look backwards in time to estimate historical HIV incidence rates.

3.4 Serial prevalence surveys

To reach reliable incidence estimates, cross-sectional surveys are carried out, alternatively statistical estimation of changes in HIV prevalence can be computed. The latter approach is also called "serial prevalence" and it is more

financial and less time consuming than the first. It has been adopted by several organizations including UNAIDS.

In practice, serial prevalence is computed by inferring the HIV incidence M from changes in prevalence at 2 or more time points. For example, the change in two HIV prevalences N_1 and N_2 , computed respectively at the time-point t_1 and t_2 is given by

$$N_2 = N_1 + M - d + in - out, \quad (3.5)$$

where d , in and out are, respectively, the numbers of deaths, in-migrations and out-migrations of HIV-infected people within the temporal interval defined by the time-points t_1 and t_2 . Given all these values, it is possible to infer the HIV incidence from equation (3.5), by inverting it. The limitation of this approach is given by the need of precise values of the d , in , and out variables. It is common to use integer numbers and not percentages to facilitate the computations. Once these values are known, it is straightforward to invert the equation and compute the incidence M . It is important to keep in mind when this estimate is made, whether this was due to changes in prevalences or for the other factors as emigration or death.

3.5 Conclusions

Tracking relative changes of prevalence and incidence is important as the single estimates for these measures at one point in time. In fact this allows to understand the current and future trends or shed new lights on the effectiveness of used policies. Therefore, it is also important to understand the challenges and possible bias in estimating key features. Apart from mathematical models and equations which take into account uncertainty, some studies also mentioned the importance of using appropriate incentives for specific risk group to increase their participation to surveys [90]. The next chapter will propose a literature review on a stochastic models which use these data.

Further aspects that can reduce the defaulted monitored cases are related to the challenges mentioned in the previous chapter, as the difficult CD4+ testing in rural areas and food insecurity. Adoption of food supplementation as a strategy to reduce lost-to-follow-up would be useful, as shown in Zambia [91].

4

Epidemiological Impact Predicted by Mathematical Models

Improvement in health status, retention and factors associated to HIV-infected patients on ART can be modeled by mathematical models. These can give figures that can help understanding the current trend for disease prevention and monitoring, or to predict the effect of different interventions as shown in Figure 4.1.

A review of dynamical models for HIV-related policies can be found in [92]. Most models designed to examine ART impact assume homogeneous risk behavior. More realistic models include sexual behaviors as well [93]. Other use a realistic progression of HIV infection, and they can be classified into two types dynamical based on HIV incidence and prevalence [94], and linear models [95, 96].

Wood et al. [95] constructed a health economic model to predict the future effect of ART use in South Africa. The study used a cost effective analysis for MTCT interventions. Wilson and Blower [97] used a spatial mathematical model about ART allocation strategies in the province of KwaZulu-Natal, which is also in South Africa. Auvert et al. used a linear model to estimate the proportion of South African population requiring ART under the then WHO guidelines [98].

These models are mainly based on partial or ordinary differential equations producing continuous results. An alternative views is given by finite states model which models the dynamic behaviors by transition probabilities. Those are reviewed in details in the following sections.

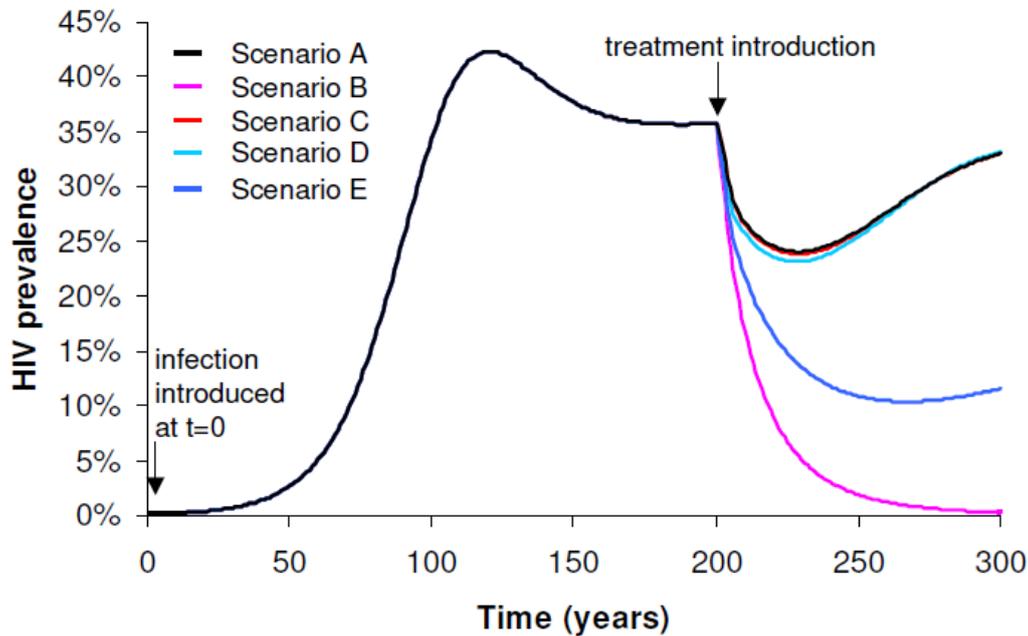


Figure 4.1: Model predictions of effect the ART under various assumptions, image taken from [92].

4.1 Markov Models in Economic Evaluation and Epidemiological Disease Progression

A Markov model is a stochastic model used to define systems which vary randomly in time, and in which it is assumed that the current state is dependent only on the previous without the need of reconstructing further the sequence of events that preceded it [99]. Markov models have been used in several fields, including medical and clinical evaluations. For example, among the many studies, Markov models have been used to determine efficacy of non-insulin-dependent diabetes [100], to predict disease progression for liver cancer [101], and Alzheimer's disease [102]. About our focus, Markov models can be used to predict future incidence or prevalence of HIV/AIDS, representing a further tool to estimate future public health needed resources. In this chapter used models for HIV-infection are reviewed, and a model for Zimbabwe is proposed in the following chapter taking into account the advantages of the reviewed models.

can be represented in a transition matrix T . This model follows the Markovian property:

$$p(x_n|x_1, \dots, x_{n-1}) = p(x_n|x_{n-1}), \quad (4.2)$$

where the distribution of predictions depends only on the value of immediate preceding observation and it is independent of all earlier observations. This approach allows to simulate the HIV epidemic as a Markov chain where the HIV-infected people progress to AIDS and death over time or remain in their current state. Lee et al. modeled the states as [106]:

- S_1 : The condition of healthy vulnerable people.
- S_2 : Being HIV-infected.
- S_3 : Being positive to AIDS diagnosis.
- S_4 : Being death.

The deaths from the AIDS/HIV virus can be converted in probabilities by computing the ratio of HIV-related deaths and population for the year in exam. This model is summarized in Figure 4.3, and the transition matrix for

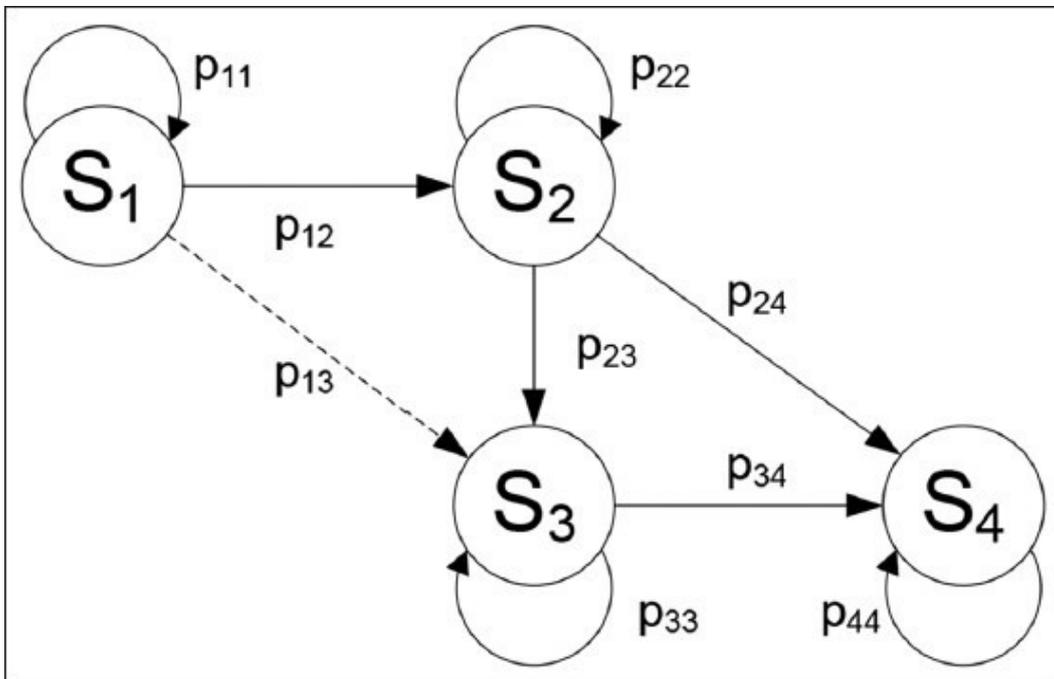


Figure 4.3: Transition diagram for the Markov-Chain Healthy(S_1) - HIV(S_2) - AIDS(S_3) - Death(S_4), image taken from [106].

this model is given as

$$T = \begin{bmatrix} 1 - p_{12} - p_{13} & p_{12} & p_{13} & 0 \\ 0 & 1 - p_{23} - p_{24} & p_{23} & p_{24} \\ 0 & 0 & p_{33} & p_{34} \\ 0 & 0 & 0 & 1 \end{bmatrix}. \quad (4.3)$$

In this work, the transition probabilities were estimated from statistics of the United States of America. For instance, the transition $p_{12} = 0.865$ was calculated by the inverse of the average of the HIV-incidence rate given in [106], and likewise p_{24} was computed from the same table. The transition p_{44} was assumed to be 1, since obviously it is not possible to change the state of death, once a subject is death. However, the transition probabilities p_{13} and p_{23} could not be directly obtained from the given data set since these values are hidden. Therefore, those were estimated by minimizing the mean squared error expressed in the following equation [106]:

$$J = \min_{p_{13}} \sum_{2011}^{2014} (||h_i - \hat{h}_i(p_{13}, p_{23})||^2 + ||g_i - \hat{g}_i(p_{13}, p_{23})||^2 + ||d_i - \hat{d}_i(p_{13}, p_{23})||^2), \quad (4.4)$$

where h_i and $\hat{h}_i(p_{13}, p_{23})$ are respectively the reported and estimated rate of people living with the HIV infection at the year i ; g_i and $\hat{g}_i(p_{13}, p_{23})$ are respectively the reported and estimated rate of persons living with AIDS diagnosis at the year of i ; and d_i and $\hat{d}_i(p_{13}, p_{23})$ are respectively the reported and estimated rate of deaths of people with either a diagnosis of HIV infection or AIDS diagnosis at the year i .

4.1.3 CD4+ Counting Transitions Model

Multi-state Markov models based on CD4+ cell count have been extensively used to evaluate the disease progression of HIV/AIDS patients. In fact, apart from the clinical progression from HIV to AIDS [103, 105], other studies developed Markov models based on the decline of CD4 cells in HIV infected individuals using 5 [107] and 8 states [108]. An example of the transition of states given by CD4+ counting (with the last representing death) is given in Figure 4.4:

In practice, a patient, after getting enrolled on a ART program, can go to a state S_i representing a health status depending on the CD4+ counting. In these works, the transition matrices are estimated from a intensities matrix Q .

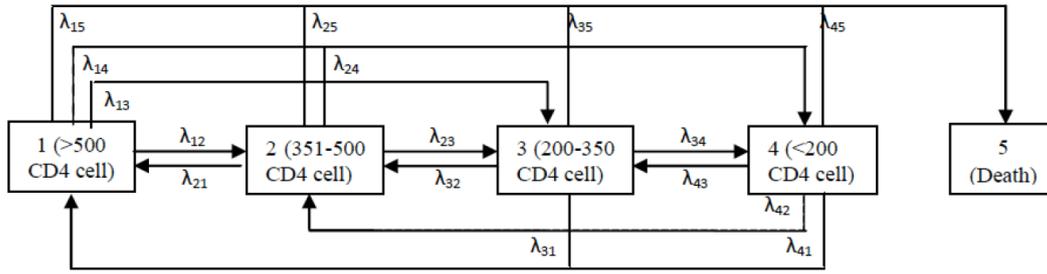


Figure 4.4: Graphical representation of the Multi-state Markov Model. The states of HIV/AIDS are defined by ranges of CD4+ cell counts. Here, λ_i represents the transition probabilities. Image taken from [107].

The intensity with which a patient moves to state S during at any time t , for any given interval $(t, t + \Delta)$ is defined as

$$q_{ij}(t) = \lim_{\Delta t \rightarrow 0} \frac{P_{ij}(t, t + \Delta t)}{\Delta t}. \quad (4.5)$$

All the $q_{ij}(t)$ can be collected into the intensity matrix Q . When intensities are considered time homogeneous, the time dependency can be removed, they can be found by using the maximum likelihood estimation procedures, and the transition matrix can be estimated as $T = \exp(Qt)$ [104].

4.1.4 Virus Load and Lost To Follow Up Model

In a study with South African data [109], the structure of the Markov model was based on detailed determinants of costs and effects. Compared to the aforementioned models, this was the most structured, including ART stage, differentiation between first and second line ART, virus load, and CD4+ counting as shown in Figure 4.5.

The parameters were derived from surveys of private-care programs and used to predict effects and costs. The simulations were run twice, once for 10 years and once until all people included in the simulation are considered dead. Moreover, a probabilistic sensitivity analysis was conducted to assess uncertainty by using Monte Carlo simulations.

More specifically, the model comprised two main parts defining the first and second line ART programs, as shown in Figure 4.5 a further part is given by the LTFU state. All patients were supposed to be enrolled in an ART program, and to remain in the program until events as death or LTFU occur. Health-care utilization and mortality has been shown to be significantly higher in the

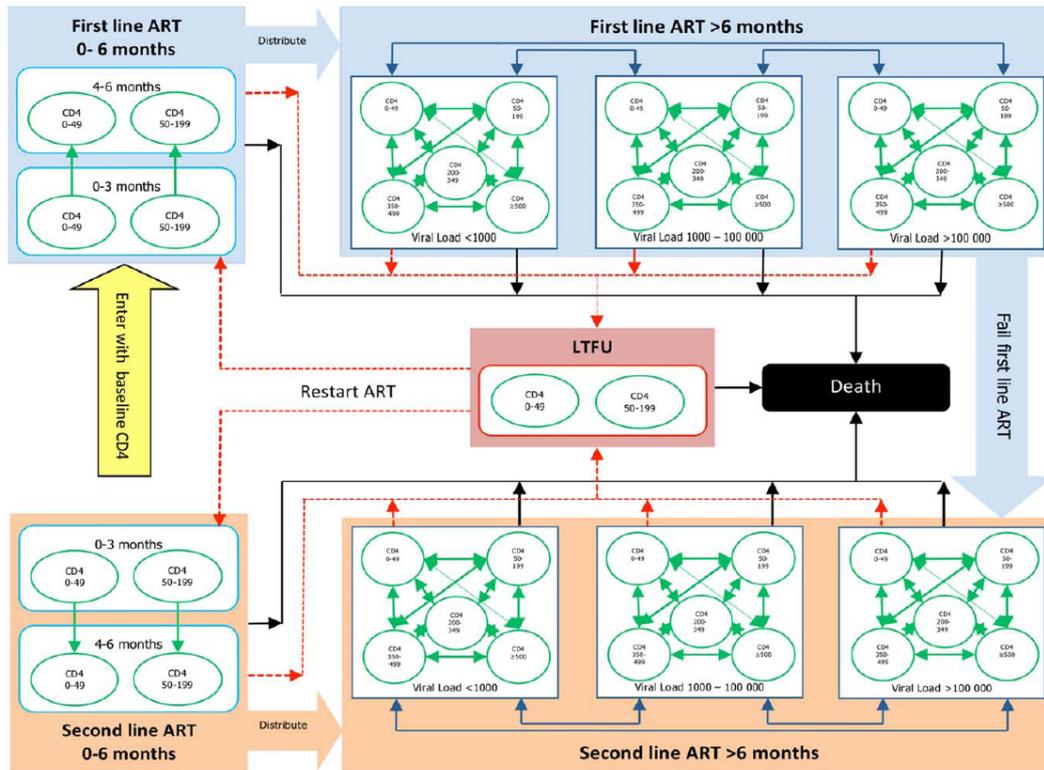


Figure 4.5: The ART-LTFU Markov model used in [109]. Image taken from [109].

first 6 months on ART [110]. Therefore, each ART part was further divided into two phases: an initial 0–6 months phase where people are starting or returning to ART programs, and a second phase after the initial 6 months. A patient was defined as LTFU when he/she was not participating to an ART program for more than 6 months. If a patient enters the LTFU state, he/she is supposed to stay in this state until he/she dies or moves back into the ART state. Parametric survival analysis was used to compute the transition probabilities and to define the outcomes sought by the model as number of HIV-related death, LTFU, values of CD4+ and virus load improvements. The model can also be seen as an extension of previous models based on CD4+ [107, 108], since it takes into account also this variable. In fact, each ART state comprises several sub-states based on ART CD4+ and virus load categories. At each simulation cycle, transitions were allowed either based on CD4+ counting or virus load category but not both.

4.2 Conclusions

Markov models have been exhaustively used in HIV/AIDS studies, generally estimating transition probabilities by using maximum likelihood or national statistics. They have been particularly useful in cost-effective analyses. In the next chapter, a Markov model is proposed for the Zimbabwe scenario considering prediction of the upcoming years and based on the available data. Here, the main goal is to predict the future ART needs when population growth will stabilize.

5

Proposed Model for Impact of ART Policies

The goal of the proposed model is to estimate the ART demand in Zimbabwe and related figures in future years. The model is assumed to be homogeneous or at least piece-wise homogeneous within 1-year interval. The piece-wise constant assumption provides a rather simplistic solution to the investigated challenges as therapy changes can occur frequently even within a 1-year frame but it is considered as a sufficient model to produce estimates of ART demand. Simulations can be run as in a first-order autoregressive model

$$f_{t+1} = g_t A f_t, \quad (5.1)$$

where g_t is a population growth factor, which for Zimbabwe has been estimated in 2015 as 2.1% [111], A is a regressors vector which can be estimated in a least-squared optimization process, and f_t and f_{t+1} are features at two consequent time points measured at homogeneous intervals as a year. Population growth factor should not be considered constant as it may vary as values of a sigmoid curve [112] as discussed later. In reality, several variables are involved and therefore the simulations have to consider several relationships which can be defined by a transition probabilities matrix of a Markov chain.

5.1 The proposed Markov chain

Before running simulations, a Markov chain depicted in Figure 5.1 is constructed considering the following states any person can go through:

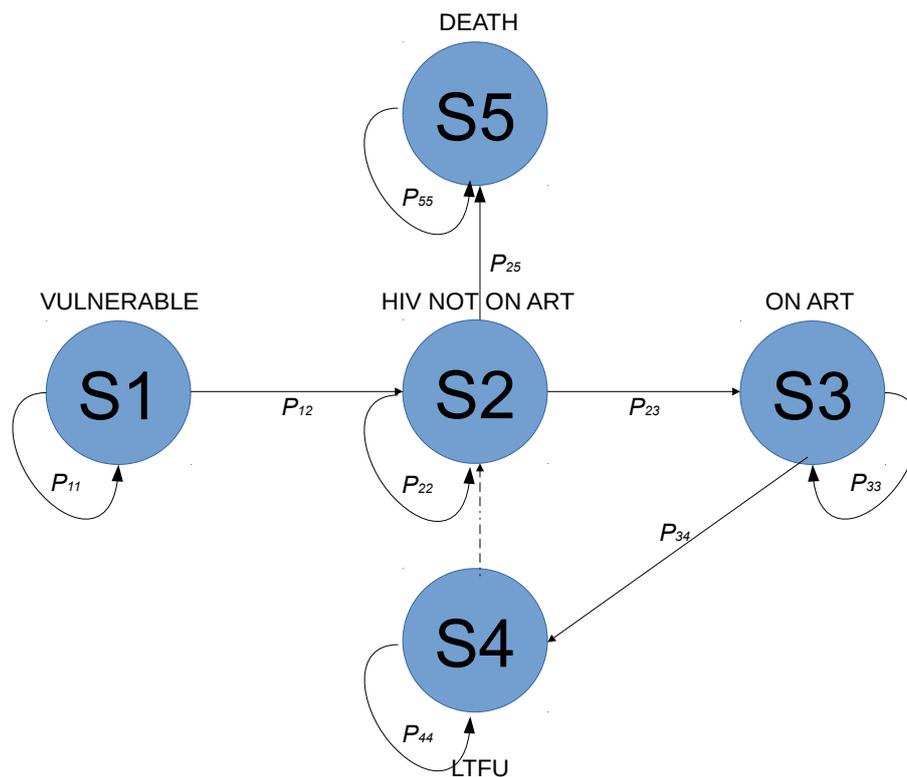


Figure 5.1: The proposed Markov model, where S1 is the state of being healthy but vulnerable, S2 of being HIV-infected but not on ART, S3 of someone who is on ART, S4 of someone LTFU, S5 of someone death.

- S1 is the state of being healthy but vulnerable to HIV-infection.
- S2 is the state of anybody leaving with HIV or AIDS (PLHA) and not being enrolled in any ART program. These represent the new infections.
- S3 is the state of someone enrolled in any ART program.
- S4 is the state of someone who was enrolled in an ART program and was lost-to-follow-up (LTFU) after 12 month.
- S5 is the state of someone who died of HIV/AIDS.

The model is constructed as a progression, from the least severe condition (healthy vulnerable) to the most severe (death). This is done because it is assumed that a person can never improve, in the best case he/she can stay in the current state. Moving from being healthy, to be HIV-infected, to have AIDS, to stay stable and to die. The transition probabilities can be summarized in

the following transition probabilities matrix:

$$T = \begin{bmatrix} 1 - p_{12} - p_{13} & p_{12} & 0 & 0 & 0 \\ 0 & 1 - p_{23} - p_{24} & p_{23} & 0 & p_{25} \\ 0 & 0 & p_{33} & 1 - p_{33} & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}. \quad (5.2)$$

The model does not take into account incubation and relative back-calculations mentioned in Chapter 3, since we are interested in modeling the ART demand based on eligible cases. Moreover, the model makes also the following assumptions:

1. If someone is properly enlisted in an ART program, he/she will not die by HIV/AIDS, TB-related deaths are not considered in the model.
2. If someone was on an ART program and then was LTFU, he/she is not considered to coming back into the program. His/her eventual death is considered jointly to the deaths of people who have never been treated.
3. Anybody who is on an ART program at some point has been HIV-infected and not being enrolled in any ART program.
4. The population growth factor is considered independent from transition probabilities and it is therefore left out and considered at the moment of the simulation (the estimate for the autoregressive model).
5. The model does not consider changes in the sexual behaviors or MTCT improvements, therefore no improvements in prophylaxis is considered, and the predictions are considered pessimistic from this point of view.
6. Incubation is not modeled, as this information is expected to be implicitly present in the increase of prevalence of the model.

Data from the UNAIDS/ZUNDAF evaluation (2012-2014) are used. Those are mostly percentages of population and instead of observation counts are already as statistics, without the need of a maximum likelihood estimation as done in [106]. Therefore the transition probability p_{12} is given by the mean HIV-incidence in the last observation years, and the transition probability p_{23} is representing the rate of new infected people starting the treatment. This latter value is given by the rate of average monthly enrolled people multiply

Table 5.1: Data used in the model

Features	2012	2013	2014
People living with HIV/AIDS	1,373,995	1,390,211	1,420,604
HIV-infection incidence ratio	1.25	0.98	1.1
People eligible of ART being on ART	85%	76.9%	63%
People still on ART after 12 months	85%	85.7%	89.5%
Ratio Deaths HIV-related and PLHA	0.0636	0.04422	0.0387

by 12 (108000) over mean incidence converted in people count (130000). Transition probability p_{33} is given by the mean percentage of people who are still on official ART programs after 12 months, and lastly the transition probability p_{25} is given by the rate of people dying from those who are PLHA. The used data taken from the UNAIDS/ZUNDAF reports are reported in Table 5.1.

The model can be used for simulations to predict future trends. This depends strongly on the current rate of population growth and HIV incidence. In practice, the rate of population growth is not linear nor exponential, but it has a behavior more similar to a *sigmoid curve*, where a country after a phase of exponential growth follows a transition phase and then a plateau phase where the population still grows to infinity but slowly and asymptotically. The sigmoid curve is also called *logistic function* or *S-shape curve*, and it can be defined as

$$f(x) = \frac{L}{1 + e^{-k(x-x_0)}}, \quad (5.3)$$

where e is the Euler number, x_0 is the sigmoid's midpoint, and k is the steepness value of the curve. To match the current short-term predictions [113] and data collected [111], we can assume $k = 1$ and the midpoint x_0 being in 5 years from now. With these assumption the prediction of population growth can be given as depicted in Figure 5.2 for 15 years after 2015.

5.1.1 Non-responder bias evaluation

In 2005 and 2006, the Zimbabwe Demographic and Health Survey was conducted to evaluate the impact of the refusal bias in the current HIV surveys [114]. The study concluded that the bias is negligible, and that the Zimbabwean institutions can continue using the current surveys. A 2008 study compared several national non-responses statistics including Zimbabwe [115]. According to this latter study, for Zimbabwe the respondent percentage f was

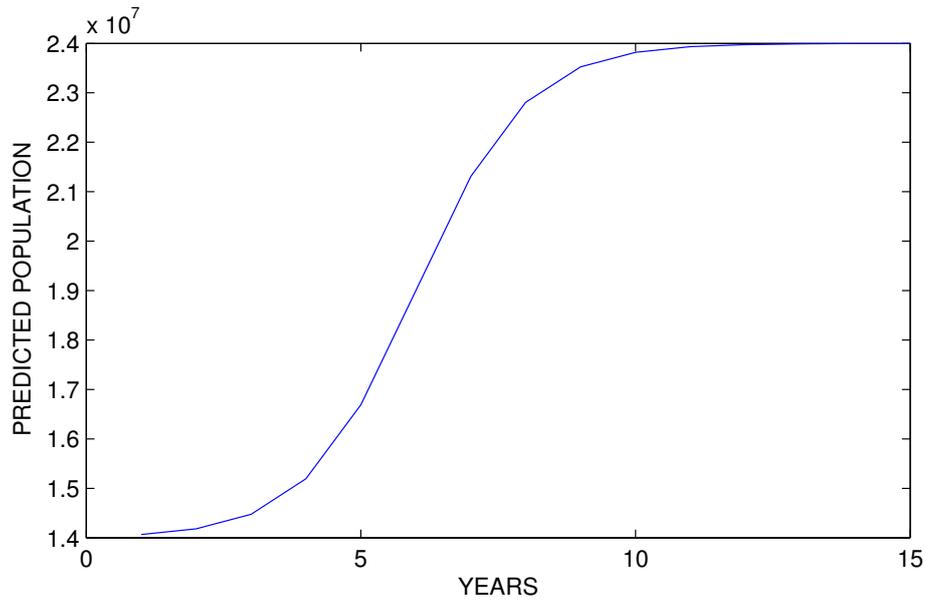


Figure 5.2: Predicted total population in Zimbabwe in 15 years after 2015.

0.87 and the prevalence ratio was $R = 0.99$ for women and $R = 1.07$ for men. Therefore using equation (3.1), the bias for the Zimbabwean women is $\gamma_w = 1 + (1 - f)(R - 1) = 1 + 0.13 \times 0.02 = 1.0026$, and for the men $\gamma_m = 1 + (1 - f)(R - 1) = 1 + 0.13 \times 0.07 = 1.0091$, which means that there might be an imprecision in the prevalence estimate for women and men respectively of the 0.26% and 0.91%. There were no more recent publicly available data. However, assuming that these values are approximatively unchanged, and considering their effect size, it is possible to neglect them.

5.1.2 Serial prevalence

If we want to double-check the incidence estimate computing it with the serial prevalence method described in Chapter 3, namely by using equation (3.5), it was noted that the method estimates values of prevalence similar to those reported in the ZUNDAF review though slightly underestimated. Immigration into the country is documented but negligible [116]. Emigration mostly towards the United Kingdom, South Africa and Botswana quantified in average as 11,620 emigrants [116]. In particular equation (3.5) is used by setting the prevalence N_1 and N_2 in turn for the years 2012, 2013 and 2014 from the ZUNDAF review data. In this way the incidence for 2013 is $M = N_2 - N_1 + d + out - in = 1,390,211 - 1,373,995 + 87335 + 0 - 11,620 = 91931$,

which quantified in incidence ratio dividing it by the uninfected population is 0.8 %. For the 2014 the incidence is estimated as $M = N_2 - N_1 + d + out - in = 1,420,604 - 1,390,211 + 61476 + 0 - 11,620 = 80249$, and the quantified incidence ratio 0.7%. Although the values are slightly underestimated the serial prevalence method showed that it can be considered approximately 1 as the averaged of the years reported in table 5.1. Due to this imprecision, instead of using the incidence values from the serial prevalence, the data acquired within the ZUNDAF review continue to be used in the simulation.

5.2 Results

The transition matrix T has been used by implementing a simulation run on the Matlab computing environment (Mathworks, MA, USA), with input the latest value of population and people leaving with HIV/AIDS and current deaths HIV-related as the starting point. The simulation has been run for 45 years from 2015 (namely up to 2060) based on the sigmoidal population growth as depicted in Figure 5.2, showing a behavior of increase of these variables which after some years stabilize as shown in Figure 5.3, 5.4 and 5.5 respectively. The simulation takes the pessimistic point of view that the HIV-incidence does not improve. Therefore, in reality the asymptotic behavior of equilibrium hopefully should be reached before than how reported here.

Given the assumption of no prophylaxis improvement explicitly, all variables reach an equilibrium at some point without reaching the target values as expected in the 90-90-90 targets [24]. Assuming that future trends will be more positive due to improvements in prophylaxis, a more advanced model can be used called switching Markov model [117], where the transition matrix is changed after behavioral changes occur (e.g. introduction of ROOT HIV-testing at national level), however predicting these changes is unreliable since it is difficult to predict whether effective behavioral changes will occur [92]. Nevertheless, in the following sections a comparison of the proposed model with the Spectrum software which consider prophylaxis improvement is reported.

5.2.1 Probabilistic sensitivity analysis

Being the simulation highly influenced by the population growth, sensitivity analysis varying this effect is expected to be carried out. In fact, it is worthwhile to be mentioned that other population growth prediction has been made

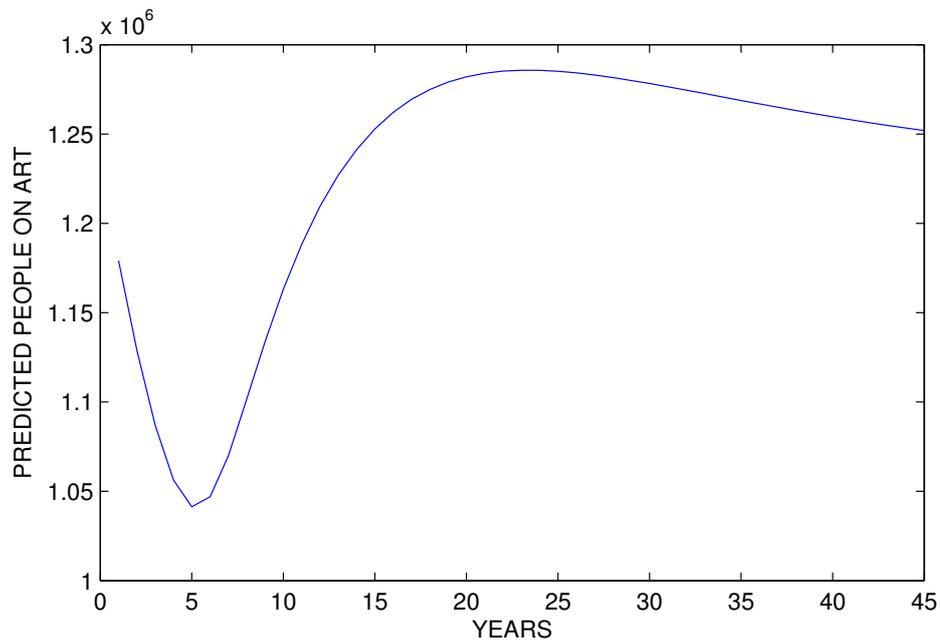


Figure 5.3: Predicted people on ART in 45 years after 2015 (up to 2060).

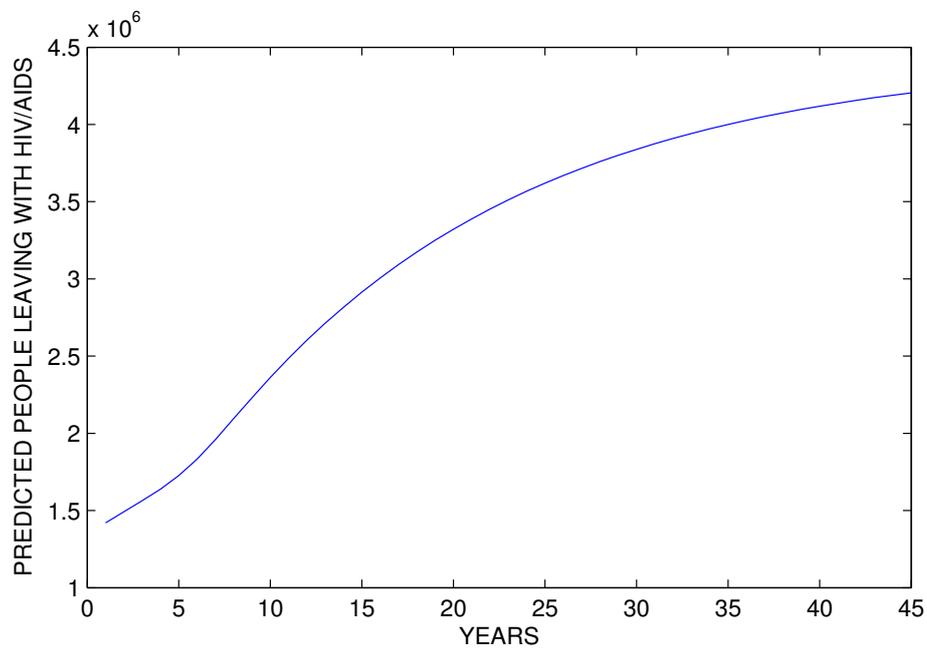


Figure 5.4: Predicted people leaving with HIV/AIDS in 45 years after 2015 (up to 2060) independently from being on ART or not.

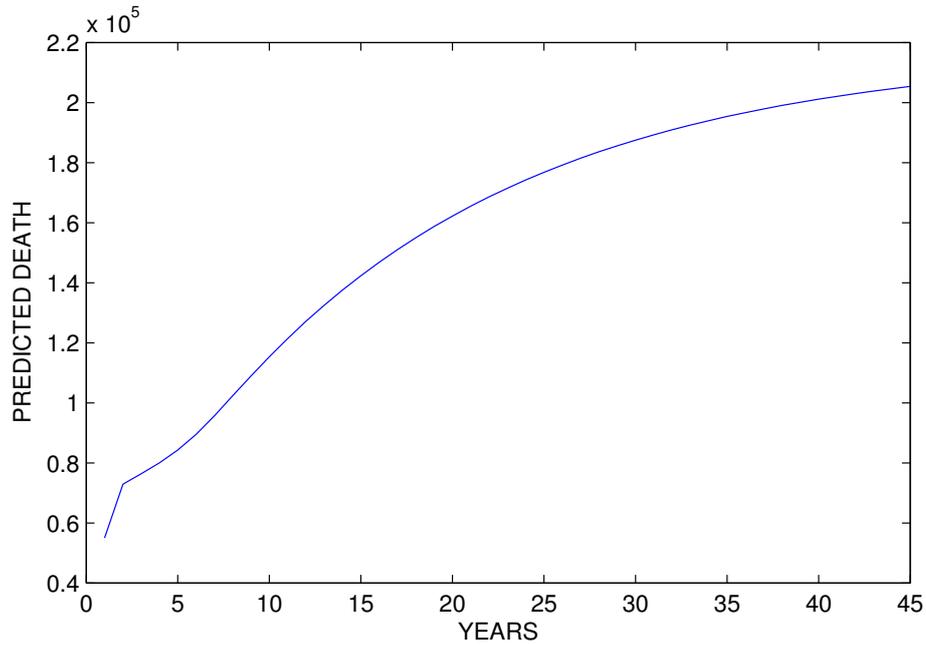


Figure 5.5: Predicted HIV-related deaths in 45 years after 2015 (up to 2060).

and they differ in the estimate [118]. More specifically, a probabilistic approach is considered, where for each year, samples obtained from a Normal distribution defining the population are extracted using the predicted value obtained from equation 5.1 as the mean of the distribution, and a standard deviation of 1,000,000 inhabitant. The means of the population growth are not updated along time using the Markov chain property but kept from the original equation 5.1. This stochastic perturbation does not seem to influence significantly the results. The resulting estimates considering this stochastic perturbation are shown in Figure 5.6, 5.7 and 5.8 respectively showing the predicted people on ART, people living with HIV/AIDS and predicted deaths.

5.3 Costs and QALYs estimation

This section attempts to estimate the main costs and effectiveness related to the ART prediction. Due to the lack of several data, this information is not to be considered a complete cost-benefit analysis or other forms of economic evaluation, but rather a simplification of those.

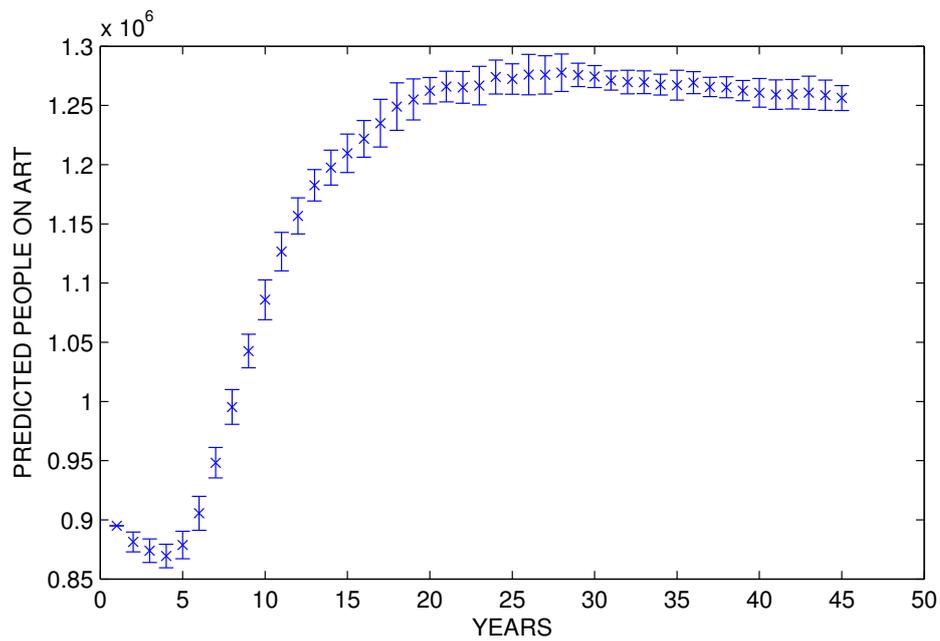


Figure 5.6: Stochastic predicted people on ART in 45 years after 2015 (up to 2060).

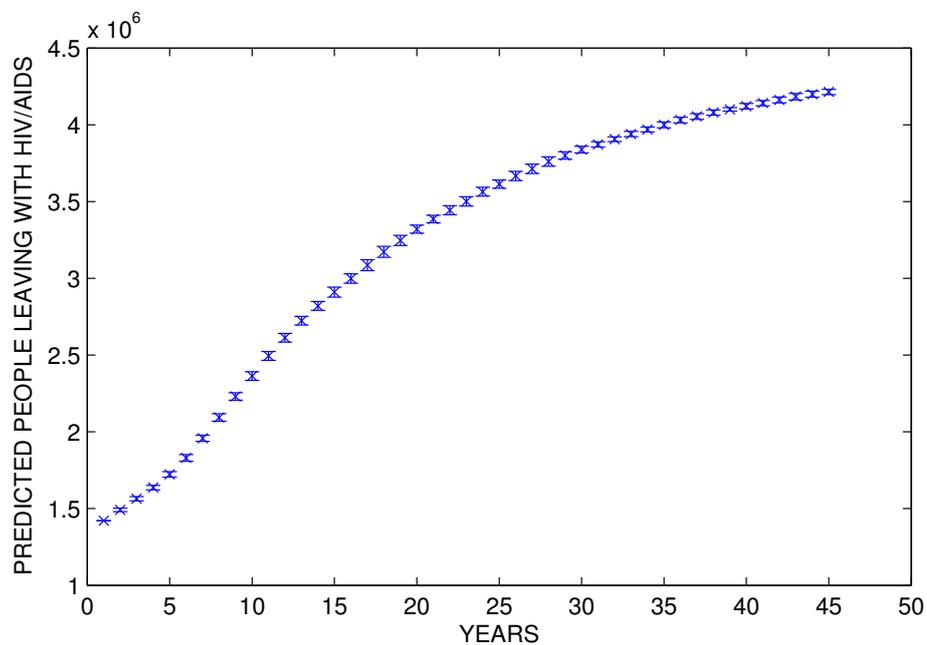


Figure 5.7: Stochastic predicted people leaving with HIV/AIDS in 45 years after 2015 (up to 2060) independently from being on ART or not.

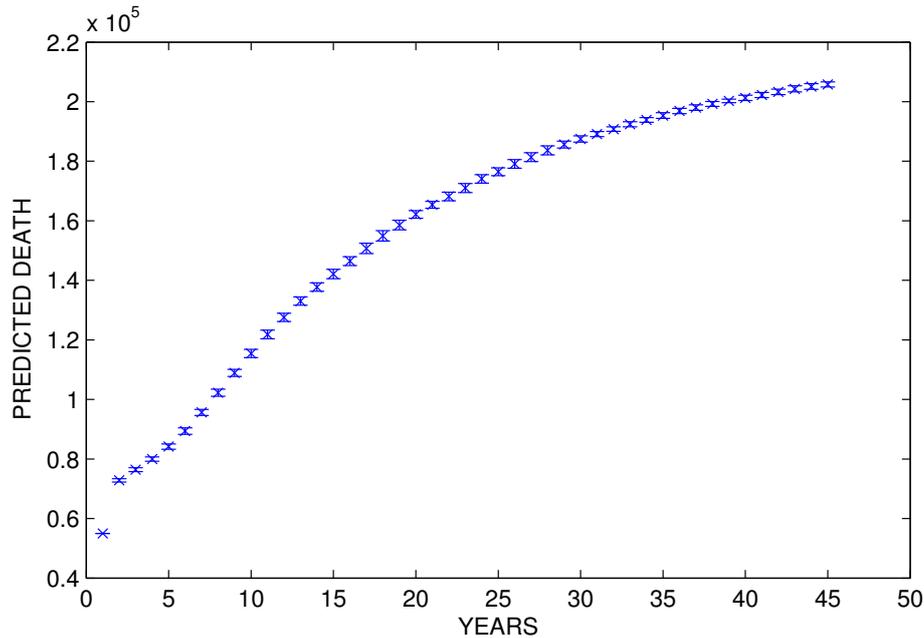


Figure 5.8: Stochastic predicted deaths HIV-related in 45 years after 2015 (up to 2060).

5.3.1 Costs

ART programs are generally costly. If an initial estimate of the costs varying on time has to be done according to the previous simulation, a first step is the estimate of the individual costs. Country-specific costs for hospital bed-days have been obtained by the WHO-related manuscript of Adam et al. [119]. ART medicines utilization is grouped into first line and second line therapy. The first line ART regimen comprises two nucleoside reverse transcriptase inhibitors (NRTI) and a non-nucleoside reverse transcriptase inhibitor (NNRTI). If a patient shows confirmed virologic failure, he/she is switched to a therapy still based on two NRTI (eventually different from those of the first line) and a protease inhibitor. Newer drugs for third line regimes are not considered in the scenario [120].

These drug combinations differ significantly in price. Therefore, costs are reported into first and second line [120] as an average of the three main therapies for each line considering the lower bound of generic drugs [120], these are considered as annual estimates. The use of second line ART can be assumed to 10% of the total need [121], though its effectiveness can be assumed to be the same as the first line for people without complications. Another possible

prediction related to the shift from first line to second line ART can be made. In fact, it has been argued that in sub-Saharan Africa there is an average annual shift in second line therapies quantified as 2.8% of the population in need [122].

CD4+ count costs were based on values taken from [123], and it can be assumed that a patient carries out tests at least each 6 months. Alternative costs should be estimated considering better settings than the current CD4+ testing, such as dried blood spots or point-of-care testing also in rural areas. Being the technologies related to these testing still ongoing improvements, costs are assumed for the already existing infrastructures at the urban centers.

Per diem hospital costs are estimated as in [119]. The other diagnostic investigation costs (as TB smears, X-rays...) are extracted by National Referral Laboratory reports [124] and reported as lump sum. All unit costs per single person are summarized as in Figure 5.9, where official daily Zimbabwean rates can be applied, though for the sake of simplicity costs are converted in USD.

Figure 5.9: Estimated unit costs for single person. ART abbreviations are: ZDV (Zidovudine), 3TC (Lamivudine), TDF (Tenofovir), NVP (Nevirapine), ABC (Abacavir), KAL (Kaletra), ATV (Atazanavir).

Item	Costs in USD	Discounted Costs in USD
First line ART therapy in annual costs ZDV+3TC+TDF/ ZDV+3TC+NVP / ZDV+3TC+ABC	148.5	104.1549122087
Second line ART therapy in annual costs ZDV+3TC+KAL/ ZDV+3TC+ATV	322	225.8443214221
CD4+ cell counts	15.79	11.0747883082
Haematology panel tests	6.46	4.530914026
Biochemistry panel tests	11.66	8.1780894031
Health Centre visit	3.26	2.2864984094
Per Diem hospital cost	25.57	17.9342835365
Other routine diagnostic tests (including. TB)	6.26	4.39063805

Summarizing, for each HIV-infection in case of no virologic failure during treatment, the total annual costs for each HIV-infection are 286.5 USD and 460 USD in case of need of second line ART. Two hypothesis are considered for estimating the total costs. One is the optimistic point of view where only 10% of the people on ART require second line drugs and another is the case with annual increase of 2.8% of the people in need of second line drug therapies. The ART costs are considered as an average of the three possible ART combi-

nation costs, which are similar within the two possible lines. The costs on time for the total population on ART considering two possible scenarios with first and second line ART are depicted on Figure 5.10 and 5.11. The prediction is limited to 15 years which seems a large interval enough to show an asymptotic equilibrium, and because it is expected that the ART prices will continue to drop and therefore a further horizon will be unreliable. The prediction on the assumption that there is an annual increase of people in Sub-Saharan Africa of 2.8% switching to second line ART drugs [122] appears more costly than the prediction assuming an average 10% of the people in need on second line for Zimbabwe [121].

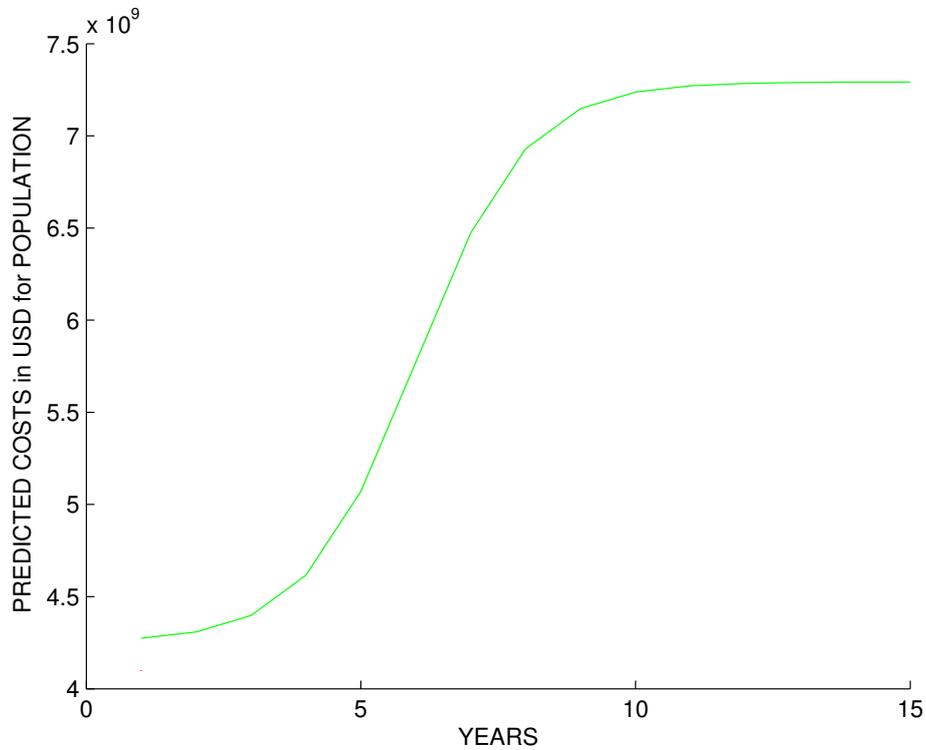


Figure 5.10: Predicted costs in USD for the population on ART growing on time. Green line is the optimistic case with only 10% on second line ART.

Apart from the mentioned costs, fixed costs were not included since considered as already implemented by the government for other purposes. Discounting can be computed considering the discount rate of $r = 3\%$ [125] by using Equation (5.4):

$$P = \frac{F}{(1+r)^t}, \quad (5.4)$$

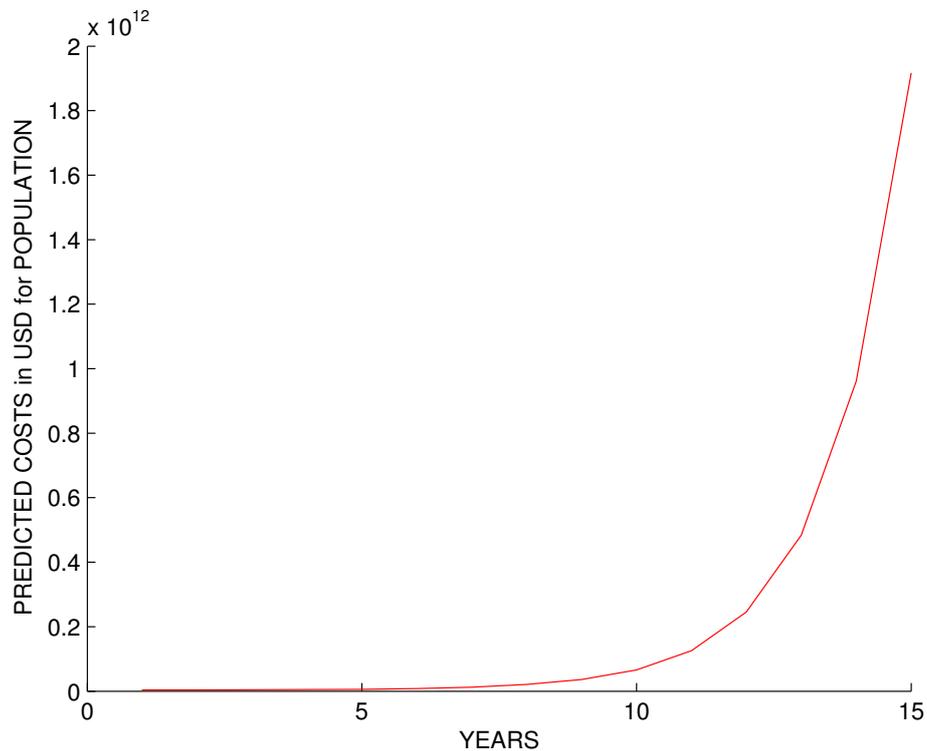


Figure 5.11: Predicted costs in USD for the population on ART growing on time. The red line represent the case of increasing 2.8% of the population on second line ART drugs each year. This is not linear since the increase of 2.8% year is also multiplied to the annual growth factor.

where P is the discounted price, F is the original full price, and t is the delay period. Those are also reported in the table in Figure 5.9.

However, given the global efforts on ART price reduction and patent expiring [120], it is expected that the price of these drugs will continue to decrease and also this is an over-estimate. It should be bear in mind that the future price can follow the trend foreseen by the Avenir-health team [126], depicted in Figure 5.12:

5.3.2 QALYs

To measure effectiveness, quality adjusted life years (QALYs) for the Zimbabwean population must be estimated. A first measure is the number of averted deaths, then the improved quality of life should be taken into account. The reduced quality of life is generally quantified in a value smaller than 1 [127].

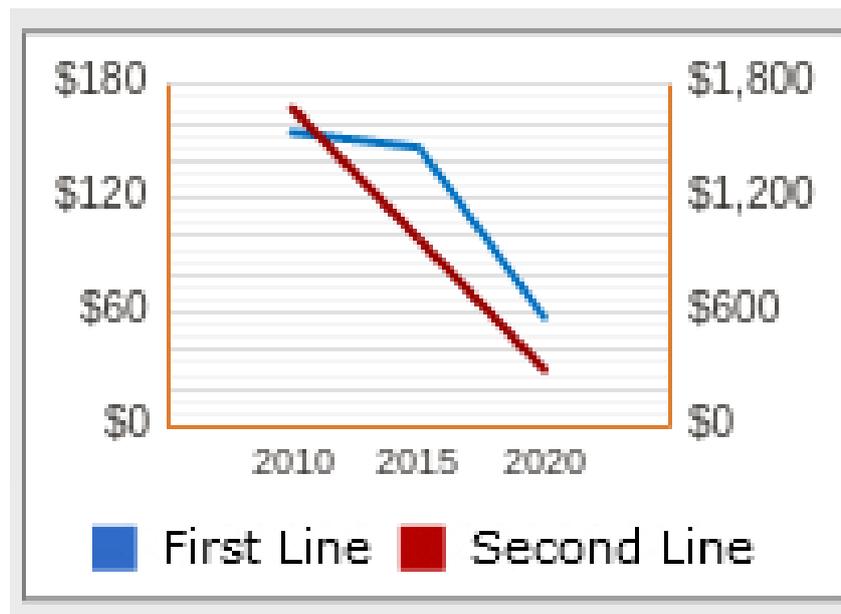


Figure 5.12: Predicted costs in USD for first and second ART drugs. Image taken from [126].

Pinkerton and Holtgrave [128] defined QALY rates according to the disease progression as reported in the following table:

Disease Stage	Description	QALY
Early HIV – undiagnosed	CD4+ count above $500/mm^3$, unaware of HIV serostatus	0.94
Early HIV – diagnosed	CD4+ count above $500/mm^3$, aware of HIV serostatus and no ART	0.87
Progressive HIV – undiagnosed	CD4+ count below $500/mm^3$, unaware of HIV serostatus	0.90
Progressive HIV – diagnosed	CD4+ count below $500/mm^3$ and on ART	0.76
AIDS	AIDS as defined by clinical condition	0.62

A simpler estimation which comes useful in our case, where detailed information is not available, is the value given in “The Global Burden of Disease” [129]. It is suggested to consider 0.5 life-years for each year of disability due to AIDS, eventually neglecting the years of asymptomatic HIV presence. The procedure is the following:

According to the simplistic burden estimate, we can use the methodology proposed in [130] to calculate the DALYs in the lifespan of an HIV-affected person. Assuming that the average HIV-infection occur at age $\mu = 22$ [125], and considering that without ART treatment the survival time is in average $de = 11$ years with $inc = 8$ years of incubation [6]. It is possible to compute the lost year subtracting this value to the years of life expectancy in the country ($le = 57$ years for both sexes [111]), and to consider the 3 years of disability as 0.5 each. Therefore for each HIV-infection properly managed there are 25.5

DALYs saved as summarized in the following equation:

$$DALYs = \mu + inc + 1.5 - le = 22 + 8 + 1.5 - 57 = (-)25.5. \quad (5.5)$$

The computation can also be discounted by using the same formula for costs in Equation (5.4).

5.4 Comparison with Avenir-health Spectrum

Spectrum is a software which provides a series of tools for policymakers with an analytical support. The Goals module helps during strategic planning at the national level by linking program goals and funding. In this study, the software has been used with the most recent data from the Avenir-health website [126] about Zimbabwe. The software has been used as a comparison to check if the results of the proposed model fits the predictions obtained with it or in what they differ. The Goals module produces relatively similar results to those given in the previous sections. However, it considers as well a series of interventions on prophylaxis which alter positively the results.

The Goal module of Spectrum comprises several stochastic models including a Markov model for the progression of HIV-Infected population with 6 stages based on CD4 groups. Additionally, the model is very advanced as it contains a transmission model for the infection that calculates the number of new HIV cases over time as a result of sexual activities, unsafe injecting drug behavior, and MTCT [133]. The new infections I are calculated by multiplying the vulnerable population X for the probability of becoming infected δ :

$$I_{s,k,t} = X_{s,k,t} \times \delta_{s,k,t}, \quad (5.6)$$

according to the model variables s for sex (male/female), k belonging to a risk group, and t time. The probability of transmission to an uninfected but vulnerable subject is related to the sexual behavior and defined as follow

$$\delta = 1 - [P_{s,kt} \times (1 - r \times R_t \times MC_{k,t} \times C_{k,t} \times V_{k,t} \times S_{k,t} \times Pr_{k,t})^a + (1 - P_{s,kt})]^n, \quad (5.7)$$

where $P_{s,kt}$ is the HIV prevalence, r is the base probability of HIV transmission per sexual act, R_t is the multiplier depending on the stage of the infection, $C_{k,t}$ is the effect of condom use, $MC_{k,t}$ is the effect of male circumcision, $S_{k,t}$ is the multiplier for effect of sexually transmitted infections, $Pr_{k,t}$ is the impact of PrEP policies, $V_{k,t}$ the impact of an eventual HIV vaccine, a the number of

acts per partner per year, and n is the number of partners per year. These variables in the models are estimated by other stochastic models or empirically by collected data [133, 134]. In the simulation the option of "automatically balance the male/female sex acts" has been used.

The software has been run by using the latest updated settings for Zimbabwe which are reported in the Appendix. It is worth to mention here that the software assumes a linear increase of population as depicted in Figure 5.13. The linear population growth assumption can be seen a simplification of the proposed Sigmoid population growth. The resulting population is slightly higher than the population after 45 years predicted with the Sigmoidal function. Considering the surface of Zimbabwe, this linear growth might be excessive in the long run. However, the software considering the prevention policies gives a more positive outlook than the proposed model as shown in the results.

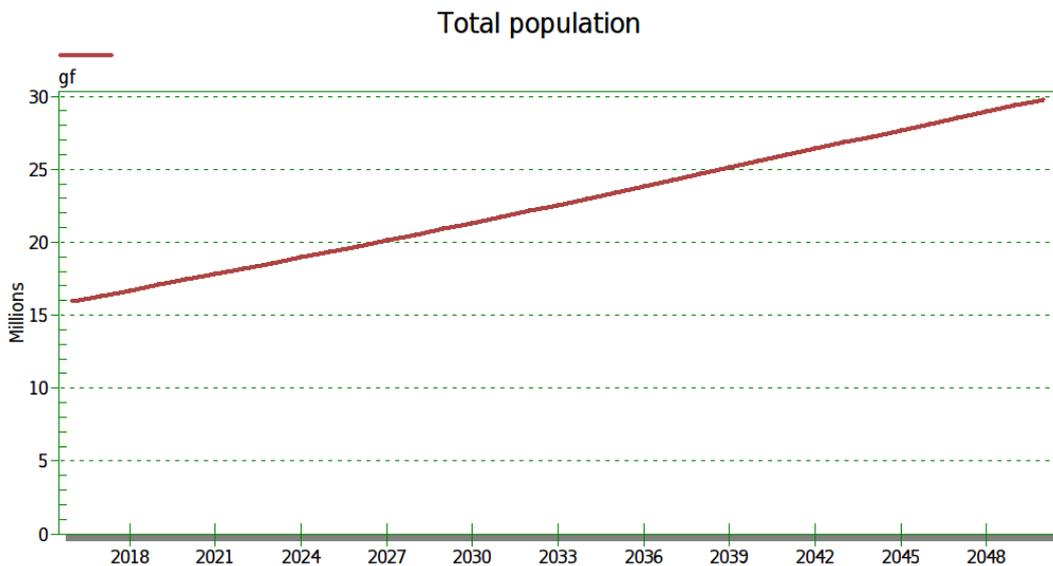


Figure 5.13: Population growth in Zimbabwe considered in the models

5.4.1 Results

Looking for similar outcomes to those produced by the proposed model, the Goals module gives the output for Zimbabwe as depicted in Figure 5.14 and 5.15 which depict respectively the number of people enrolled on ART programs, people living with HIV or AIDS and deaths related to HIV. Spectrum also allowed to estimate the total costs considering the ART programs in the

country and the prevention interventions. It is visible that with the decrease of the epidemics, the costs are also decreased though large amount of cash-flow and several years are required as shown in Figure 5.16.

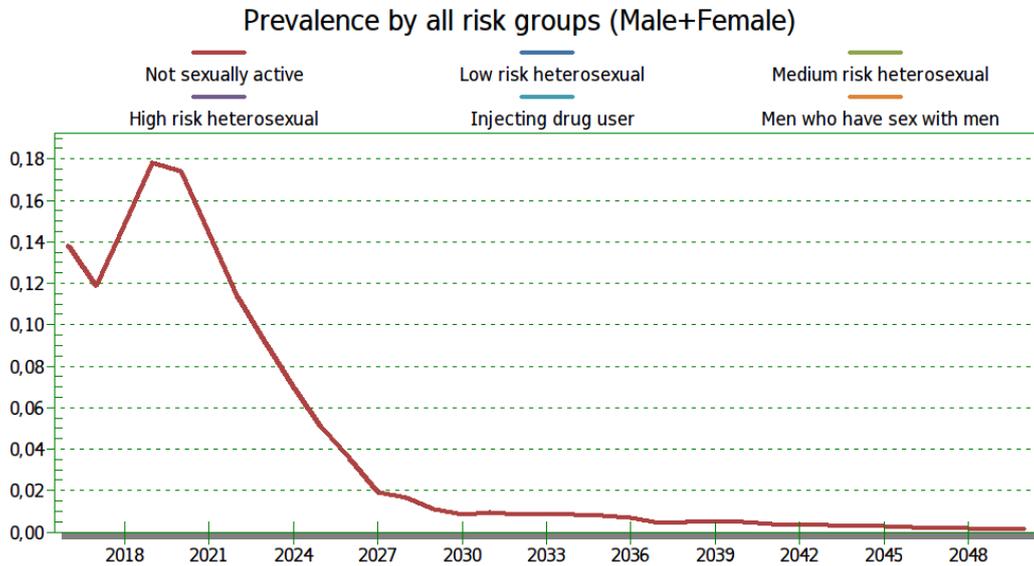


Figure 5.14: People living with HIV or AIDS, values shown as 10^7 (Spectrum projection).

5.5 User point of view

These estimates have been done under a series of assumptions and from the point of view of policy makers. From the point of view of the user, there is the interest in participating to ART programs, however it has been shown that many HIV-affected individuals do not achieve the adequate level of adherence needed for optimal treatment outcomes. Users have to be supported considering financial and infrastructure limitations. The food integration mentioned in Chapter 2 is only an example. Further possibilities are given by the adoption of ART adherence clubs [131] and mobile phone short message services (SMS) used as reminders for drug pick-up and clinic visit [132].

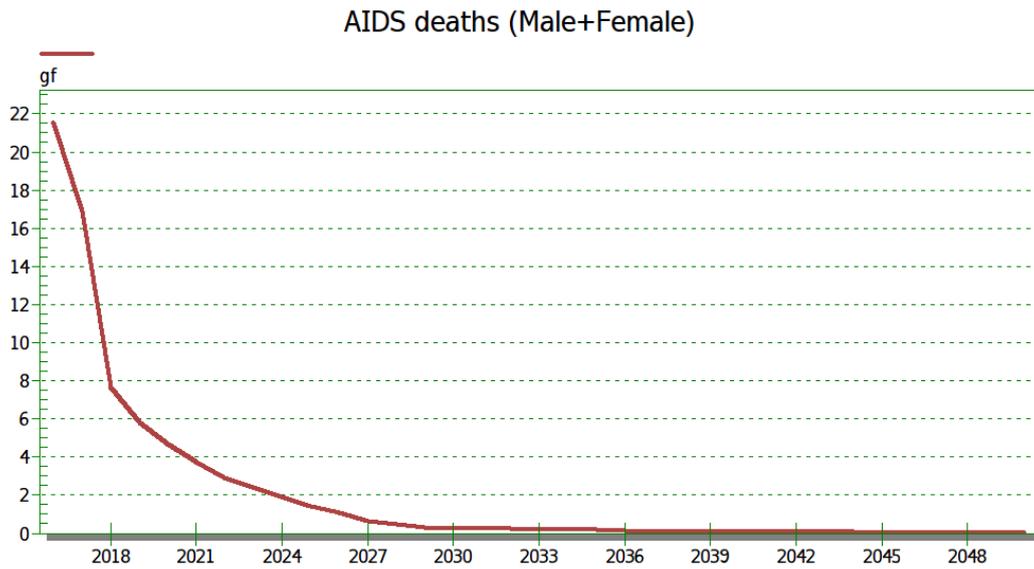


Figure 5.15: Deaths HIV-related, values reported in thousands (Spectrum projection).

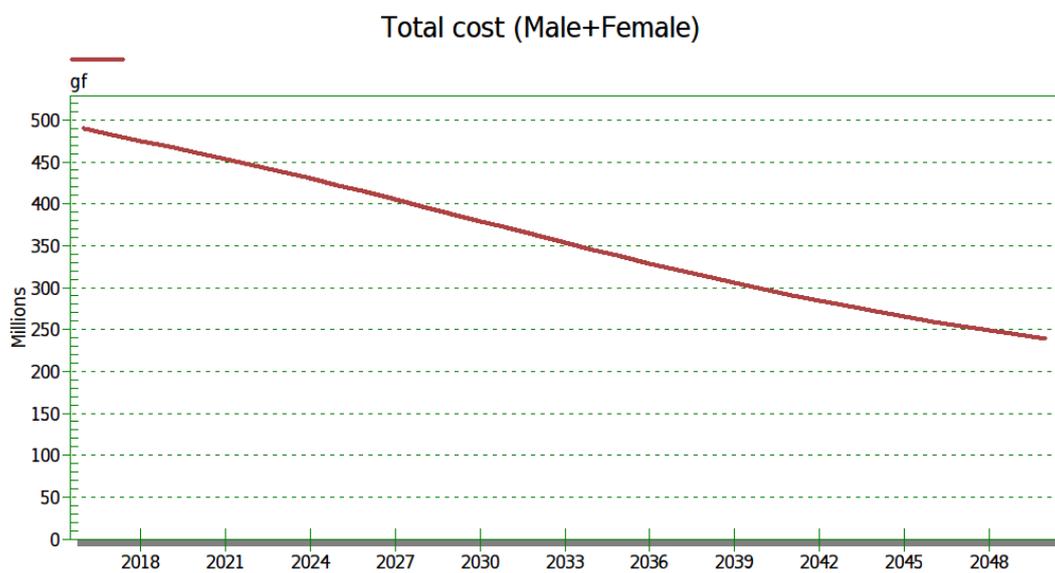


Figure 5.16: The total costs for Zimbabwe considering ART and prevention programs (Spectrum projection).

5.6 Drummond Checklist

The Drummond Checklist is a 10-item checklist used to assess the methodological quality of economic evaluation studies [25]. Generally, positive answers to all 10 questions/group of questions is an indicator of the validity of a study. However, very few studies commonly can answer positively in a satisfactory way to all 10 questions. The method is therefore a global assessment of the quality of evidence, but should not be used as a strict interpretation for accepting, rejecting or neglecting articles. It is a good practice to follow the the Drummond Checklist while revising the own work to identify eventual limitations. Alternatively, it is possible to use the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement which is a a 24-item checklist [135]. Although, this checklist is more used to assess the reporting quality. For instance, it is used to evaluate the quality of reporting of pharmaco-economic evaluations. Still the Drummond Checklist is the most commonly used.

In this section the ten questions of the Drummond checklist [25] are reported in italic with related answers to recap the relevant aspects of the study.

1. Was a well-defined question posed in answerable form?

The study had three questions. What are the current advancements in HIV-fight in Zimbabwe? What are the challenges in HIV-related data collection? Can we predict future ART need according to Markov models?

The first question is answered in form of reviews of recent pilots carried out in the country in Chapter 2. The second question is answered in Chapter 3 also in form of literature reviews. The last question is given as a developed Markov model and resulting simulation.

1.1. Did the study examine both costs and effects of the service(s) or programme(s)?

Unit costs per single person have been estimated according to available price-lists. Individual total annual costs are also given.

1.2. Did the study involve a comparison of alternatives?

The study focused on the possible best settings. Alternative solutions were mainly given by the use of different ART regimes, where the choice of first and second line ART drugs led to different calculations in cost terms.

However, alternative choices are not strictly compared.

1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

The point of view is assumed of policy makers from Ministry of Health, Ministry of Health and Child Care and partners as UNDP and GlobalFund staff.

2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?

2.1. Were there any important alternatives omitted?

The main limitation of the study is the absence of stratification of the patients by CD4+ count, which does not allow a proper estimation of costs. This was due to lack of information. The study has assumed an average disability based on HIV-AIDS.

2.2. Was (should) a do-nothing alternative be considered?

ART are vital for HIV-infected people. As mentioned in the first chapter, if no treatment is initiated, in healthy adult the survival time after infection is in average 11 years [6]. Therefore, the do-nothing alternative is not worthwhile to be considered as it will be unethical.

3. Was the effectiveness of the programme or services established?

3.1. Was this done through a randomized, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?

3.2. Was effectiveness established through an overview of clinical studies?

3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

The study is based on prediction for which there is no ground-truth to assess the effectiveness. This is one of the limitations of the study. However, it is quite common in study performing prediction of ART needs [92, 94–96, 136].

4. Were all the important and relevant costs and consequences for each alternative identified?

4.1. Was the range wide enough for the research question at hand?

4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)

The proposed model is designed for policy makers, without considering behavioral changes which can improve the scenario. Additional possible solutions seen from the point of view of patients, groups highly exposed to risk and relative communities are investigated in the review in Chapter 2.

4.3. Were the capital costs, as well as operating costs, included?

Capital costs are reported, but only operating costs strictly related to ART are reported, those already used by the system are not mentioned. Tests for detecting HIV and related costs are not considered since they are independent from the ART therapies, and it is expected that they will change in the upcoming years.

5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?

5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?

5.2. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

The costs estimated as single unit for patients were reported, though the ART use is reported as a total annual use. Prices of ART depends on whether the patients are on first line ART or second line ART. Being also for the two regimes several possibilities, their average cost is reported.

6. Were the cost and consequences valued credibly?

6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgments)

6.2. Were market values employed for changes involving resources gained or depleted?

6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?

6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?

Costs are reported by well-known sources, considering the lower bound of generic drugs.

7. Were costs and consequences adjusted for differential timing?

7.1. Were costs and consequences that occur in the future ‘discounted’ to their present values?

7.2. Was there any justification given for the discount rate used?

Values adjusted for differential timing are reported as well.

8. Was an incremental analysis of costs and consequences of alternatives performed?

8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

Incremental costs are reported in form of costs increasing by year.

9. Was allowance made for uncertainty in the estimates of costs and consequences?

9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?

9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)?

9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

Uncertainty has been introduced by varying the growth annual rate of the population which varies the values of people on ART and people leaving with HIV.

10. Did the presentation and discussion of study results include all issues of concern to users?

Concerns from the point of view of the users are mentioned in Chapter 2 and within this chapter.

10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?

Conclusions were made, though the study is focused on ART demand estima-

tions and not on cost-effectiveness ratios.

10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?

10.3. Did the study discuss the generalization of the results to other settings and patient/client groups?

The study is focused on Zimbabwe as a country without taking into consideration of generalization. However, it is believed that the proposed model can be applied to other countries with similar settings, by adapting the transition probabilities and the population growth model.

10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)?

10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the preferred programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

The planned ART programs and related improvements are technically feasible by the current country infrastructures. However, shortfall between financing and future needs often occurred and can occur in the future. The funding demands are considerable and domestic financing in the country will not be sufficient especially with the increasing enrollment of people in ART programs and population growth [74].

6

Discussions

Zimbabwe is one of the countries with highest HIV prevalence. Currently, 1.3-1.5 million people are living with HIV representing a 13-15% prevalence. New infections dropped by 34% between 2005 and 2013, probably due to behavioral changes communications and high treatment coverage. Difficulties in the health-care system are partially attributed to a deep economic crisis happened around 2009.

This thesis focused on identifying novel opportunities to update the current response of the Zimbabwean government and partners, and on a Markov model which can predict the future trends considering the population growth.

It can be seen that after some initial fluctuations with numeric increase of the values, all variables stabilize after 45 year/cycles. From the proposed ART patients analysis novel insights can be proposed. First of all with the predicted population growth in the country, the need of ART therapies will increase consequently. This scenario is therefore predicted to be costly in change of reduced HIV-related mortality and DALYs for the population, a scenario also predicted by other models [52]. This position is also based on the ethical responsibility to continue financing ART programs, and not to ignore HIV-infected people and leave them to death [137]. The graph in Figure 5.3 showed an initial down-turn which is probably already happening as an effect of slow population growth changes after the hyper-inflation in 2009.

The key point is also that if no improvement in prophylaxis is performed with behavioral changes in reproductive health and mother-to-child therapies, the improvements will be slow. One of the main conclusion in this study is that the government has done enormous efforts in decentralizing ART and it is on

the right path, but further efforts have to be made to promote testing and behavioral changes in people to get the infection close to zero and to reach the 90-90-90 goals [24]. Poor adherence is related to food insecurity (as a byproduct of poverty) [68] and social patterns [138]. Social constructions of masculinity are still present and represent an obstacle to men and their spouses [75]. Social marketing approaches should be used to develop interventions and to promote higher adherence. Theories as the Information-Motivation-Behavioral Skills model [139], the Health Belief Model [140] have already been used in interventions in other countries and should be considered. These interventions are targeted on individuals' beliefs and on the factors that interfere with their adherence. In practice this can be achieved by using ART adherence clubs [131] and SMS reminders for drug pick-up and clinic visit [132].

Not so many models to assess future ART demands have incorporated sexual behavior in predictions [93]. This is related to the fact that it is difficult to predict whether behavioral changes occur for real or not [92]. A model called STDSIM [141] has been used to simulate different scenarios related to HIV infections mostly related to dynamic network of sexual contacts. In particular certain models have been tested such as steady, causal and "commercial" relationships; sexual behavioral patterns, background prevention interventions. The scenarios highlighted relatively different outcomes, showing that depending on the model different predictions can be made. Those were however more pessimistic than previous predictions [141]. The results of the Markov model proposed in the previous chapter are even more pessimistic. This is probably due to the fact, that sexual behavioral changes have been left out from the model since, as mentioned several times, it is very hard to be modeled in a reliable way [92]. Therefore, it can be argued that the results given in the previous chapter are an upper bound and in reality things will improve in a faster way. Nevertheless, the results are in line with a recent study focusing on the long term financing needs of HIV in several sub-Saharan Africa [74]. This study used also the Goals module from Spectrum [126] to quantify the discrepancy between proper coverage and future funding. In fact, even if this model included prevention of MTCT, interventions related to medical male circumcision and sex-workers, the horizon for the end of the HIV epidemics is foreseen around 2050. Although, due to the prevention interventions the incidence is considerably reduced.

In the previous Chapter, Spectrum has been used focused on Zimbabwe re-

producing the results mentioned in [74], and highlighting similar results of the proposed model with the main difference that instead of decreasing asymptotically they lower to zero just after 6 years. This is imputable to the prevention interventions included in the Goal module of Spectrum.

Beyond the strong relationship to the population growth factor, the proposed model was based on some assumptions: TB-related deaths were not included into the model, giving possible over-optimistic effects of being enrolled in ART programs neglecting complications related to co-occurrence of TB. Conversely, the model did not consider changes in the sexual behaviors or MTCT improvements, neglecting possible improvements in prophylaxis which can lower incidence. Emigration and immigration factors are not considered in regards of population growth, and the population growth itself it is considered to behave as a sigmoid function with midpoint at 2020, assuming an equilibrium given by an asymptotic growth rate reached by 2025. The estimated non-responder bias has been estimated as negligible. Lastly, lack of public statistics relative to CD4+ count states did not allow to further extend the model in this direction, which also would have lead to more precise QALY and cost estimates.

Suitable ART program design and monitoring are given by differentiation of CD4+, from the point of view of cost-effectiveness of ART they can also be used to choice the whether it is necessary to give second line ART drugs to the patients. Resistance testing is a crucial decision factor for starting second line ART. It is believed that resistance testing at first line virologic failure is cost effective [142, 143] and it could be implemented in Zimbabwe. Strengthening laboratory services is a priority, toxicity testing should be more clinically guided and the access to quality-controlled diagnostic testing must be increased especially in rural areas. The reason of this delay is related to financial factors. The country has been successful to scale up and decentralize ART-related infrastructures also to peripheral health facilities [59], but the same has not occurred for CD4+ testing. Success is expected to be represented by more cost-effective approaches, which although being more costly they are expected to be more effective leading to better increase of QALYs.

In conclusion, despite the limitations, the proposed Markov model can help improving the accuracy of estimates of future costs and outcomes of long-term ART care. It was visible that with the current growth factor in the country and the current level of HIV-testing and enrolling into ART-program, the number of people involved into ART programs and their costs will continue

to grow. The findings suggests that increases in prophylaxis are required to avoid increasing costs and reducing the epidemics which otherwise will last approximatively for at least other 50 years.

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A

Appendix

A.1 Settings tables for Avenir-health Spectrum

The default parameters from the Avenir-health website for Zimbabwe used for the simulation reported in Chapter 5 are shown in this section. Epidemiological settings given in Figure A.1, data relative to coverage, risks and services in Figure A.3, A.2 and A.4 respectively. The model uses the most recent survey data from the country [126], and parameters model are set based on results of other stochastic models [133], or empirically by collected data [134]. The standard settings for Zimbabwe which have been used are based on epidemiological data on condoms use [144], male circumcision [145] and PrEP policies [146].

The average number of different sexual partners per year for each risk group is generally 1 for low risk groups and higher for the medium and high risk populations. These are summarized in Figure A.1 and A.2.

In the 'Coverage' and 'Service' tab of the software, the coverage of each intervention (e.g. community mobilization) in the country is specified, this represents the percentage of the eligible population reached by the intervention. These are also based on data evaluated by the Avenir-health team [144–146], and shown in Figure A.3 and A.4.

Epidemiology	
Transmission per act	
Transmission of HIV per act (female to male)	0.00110
Transmission multiplier for male to female	1.0000
Transmission multiplier for STI	6.00
Transmission multiplier for MSM contacts	2.60
Relative infectiousness by stage	
Primary Infection	8.00
Months in Primary Stage	3.00
Asymptomatic stage	1.00
Symptomatic stage (no ART)	4.00
Transmission reduction (0 - 100%)	
Condom efficacy	80.00
Reduction in male susceptibility when	60.00
Reduction in male infectiousness when circumcised	0.00
Initial pulse	
Size of initial pulse of infection (0 - 0.01)	0.0010

Figure A.1: Epidemiological settings for Zimbabwe used by the simulations with Spectrum.

	2015	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Female sex workers															
Sex workers reached by intervention per year	59.00	59.00	59.00	59.00	59.00	59.00	59.00	59.00	59.00	59.00	59.00	59.00	59.00	59.00	59.00
Male sex workers															
Sex workers reached by intervention per year	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Men who have sex with men															
MSMs reached by intervention per year	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MSMs receiving lubricants	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Injecting drug users															
IDUs receiving harm reduction intervention	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
IDUs receiving counseling and testing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
IDUs receiving community outreach and peer education	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
IDUs receiving needle and syringe exchange	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
IDUs receiving drug substitution	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Figure A.2: Risk settings for Zimbabwe used by the simulations with Spectrum.

	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Community mobilisation															
Reached by intervention per year	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
Missed in a day															
Reached by campaigns per year	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
Voluntary counseling and testing															
Adult population receiving VCT each year	27.00	27.00	27.00	27.00	27.00	27.00	27.00	27.00	27.00	27.00	27.00	27.00	27.00	27.00	27.00
Condom provision															
Condom coverage	46.00	46.00	46.00	46.00	46.00	46.00	46.00	46.00	46.00	46.00	46.00	46.00	46.00	46.00	46.00
Y 9/10th															
Primary students with teachers trained in AIDS	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Secondary students with teachers trained in AIDS	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00
Out-of-school youth reached	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Workplace programs															
Workforce receiving peer education	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Workforce receiving STI treatment	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Figure A.3: Coverage settings for Zimbabwe used by the simulations with Spectrum.

	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
STI management															
Males with STI receiving treatment	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00
Females with STI receiving treatment	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00
Blood safety															
Units of blood for transfusion tested	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Post-exposure prophylaxis															
Need that is met	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00	48.00
Safe medical injection															
Unsafe injections replaced with AD syringes	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Reduction in number of other injectors	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universal precautions															
Hospital beds covered	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Figure A.4: Service settings for Zimbabwe used by the simulations with Spectrum.

Declaration on Scientific Integrity

Erklärung zur wissenschaftlichen Redlichkeit

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Type of work — Typ der Arbeit

Master in Business Administration Thesis

Declaration — Erklärung

I hereby declare that this submission is my own work and that I have fully acknowledged the assistance received in completing this work and that it contains no material that has not been formally acknowledged. I have mentioned all source materials used and have cited these in accordance with recognised scientific rules.

Hiermit erkläre ich, dass mir bei der Abfassung dieser Arbeit nur die darin angegebene Hilfe zuteil wurde und dass ich sie nur mit den in der Arbeit

angegebenen Hilfsmitteln verfasst habe. Ich habe sämtliche verwendeten Quellen erwähnt und gemäss anerkannten wissenschaftlichen Regeln zitiert.

Basel, 22/04/2016

Signature — Unterschrift