

SIMULATING THE PROVISION OF ANTIRETROVIRAL THERAPY IN ZAMBIA

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ABSTRACT

Zambia has over 1.9 million HIV-infected people and is one of the countries hardest hit by the HIV pandemic. Limited information exists on the long-term survival and economic costs of antiretroviral therapy (ART) in the country. The study we describe here has two aims: 1. Provide better estimates for the long-term survival of people on ART; 2. Forecast the number of people on ART and the cost of providing ART in Zambia over the next decade. Survival analysis techniques have been used to estimate distributions for the time spent on ART using electronic records from the Zambian national database. We use Discrete Event Simulation to model the number of people on ART in Zambia and provide projections for the cost of providing ART in the future. HIV-infected patients enter the model when they commence ART and exit the system due to death, becoming lost to follow up or stopping treatment.

1 INTRODUCTION

Like many countries in sub-Saharan Africa which are affected by the human immunodeficiency virus (HIV) epidemic, Zambia faces the growing challenge of providing clinical care and other services for people infected with the HIV virus. With a 13.3 percent HIV prevalence in the general population in 2014, more than 1.9 million out of the country's 13 million people at the last population count in 2010 live with the virus.

As the HIV infection matures into acquired immune deficiency syndrome (AIDS) in each of the infected individuals, treatment with antiretroviral therapy (ART) is the only known and acceptable mitigation which can be provided to enable these individuals to lead close to normal lives while remaining economically productive in society. The number of these HIV-infected citizens who need ART is large and has been growing year on year in Zambia over the last decade. Consequently, planning how to provide ART is a national challenge. A critical aspect of this challenge is estimating the disease burden (the number of HIV positive people who are eligible for ART) and its economic cost in the long term from the public sector

standpoint since over 90 percent of infected patients receive treatment from public health facilities that are government funded.

The aim of the study is to provide a planning tool and reference for health intervention planners and financiers on the long term ART outcomes and economic costs. The tool takes the form of a simulation model, which incorporates survival profiles for People Living with HIV (PLWHA) who are on ART, where the models have been fitted to real data from Zambia. We concentrate mainly on survival of people on the ART program (i.e. time between commencing ART and either stopping, becoming lost to follow up or death) rather than time between commencing ART and death. The simulation model can then be used to generate long term program level estimates (national and sub-national) of the economic cost of providing ART in Zambia.

We begin by describing the HIV epidemic in Zambia and relevant literature in the area, before detailing the extensive data analysis necessary to provide input distributions for the survival of HIV patients on ART. This is followed by a description of the simulation model and some results, before we draw some conclusions and describe possibilities for future work.

2 BACKGROUND

HIV is a virus that attacks the human immune system by impairing or destroying CD4 cells. Persons infected with HIV are said to have developed AIDS if their immune systems become compromised by the virus to the extent that the body's immune system fails to fight off diseases (e.g. see of Health & Human Services (2013)).

The first documented case of HIV in Zambia was in 1984 and rates have risen to the extent that the national HIV prevalence in 2014 was estimated to be 13.3 percent of adults aged 15 to 49 years. HIV incidence (new infections) in the population aged 15 - 49 has been reported to stabilize at about 1.6 percent although the absolute number of new infections increases year on year as a result of consistent population growth in the country. Geography, age and gender define some of the most important factors that characterise the heterogeneity of HIV prevalence in Zambia. Women in the sexually active population (15 - 49 years) generally show a higher HIV prevalence than do their male counterparts and HIV prevalence in urban areas is twice that in rural areas (19.7 percent versus 10.3 percent).

The epidemic is primarily driven by heterosexual contact which accounts for approximately 78 percent of new infections (Ministry of Health Zambia 2009). Vertical transmission from mother to child during pregnancy, at birth or during breastfeeding is the next most important transmission route of HIV in Zambia, accounting for 10 percent of new infections.

As a consequence, the Zambian government has scaled up HIV-related services over the past decade in order to reach as many people in the country as possible. This includes a significant increase in counselling and testing services; HIV testing of pregnant women; male circumcision; and the provision of ART. It is the provision of ART that interests us most in this work.

During what could be described as the pilot phase in 2002, there were only 143 patients on ART in Zambia at the country's 2 national referral hospitals (one located in the nation's capital and the second one located in a town in the Copperbelt province). ART was offered at these sites because at the time, these facilities were the only ones in the country at which both specialist personnel and equipment required to monitor the patients were available. A trend of the number of people in need of treatment and the corresponding number who were receiving the treatment is presented in Figure 1 below. The 142 people on ART in Zambia in 2002 were against an estimated disease burden of 236,000 patients representing an unmet need for ART services of over 99 percent. During the development and expansion phases of the national ART response (2004 - 2005), capacity building and increases in the number of health facilities providing ART was put in place. This ensured that health care workers were trained, laboratory equipment, logistics and information systems developed and put in place and more patients put on treatment from an array of additional entry points such as Prevention of Mother to Child Transmission, tuberculosis (TB) clinics, sexually transmitted infection (STI) clinics and provider-initiated testing for HIV. By the end of

2005, more than 51,700 people were on ART against a disease burden of over 256,000 (the unmet need had been reduced to 80 percent from over 99 percent in 2002). Further expansion of ART services aimed at reaching rural and other remote communities was embarked on between 2006 and 2010. In 2010, patients on ART in rural areas increased to 34 percent compared with only 11 percent in 2008. The gap between people needing ART services and those actually receiving ART was consistently reduced over the years with only a 22 percent unmet need in 2011 (414,517 on ART vs. 535,685 requiring ART).

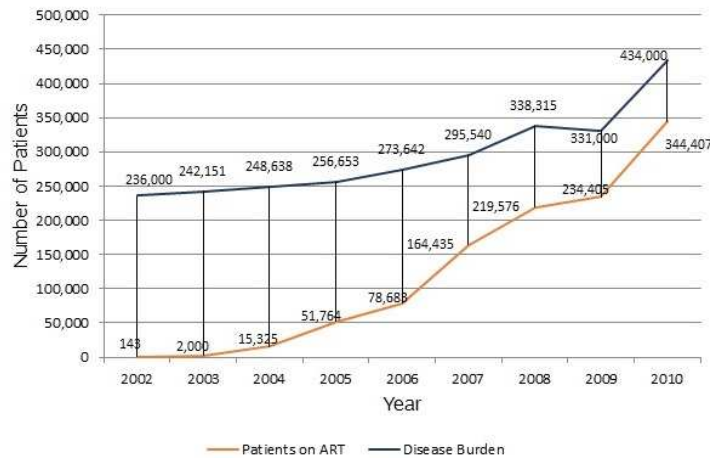


Figure 1: Antiretroviral therapy and disease burden in Zambia, where the disease burden is the number of people with HIV infections who are eligible for antiretroviral therapy.

3 LITERATURE REVIEW

The HIV epidemic has been studied and modeled by scientists from a wide range of disciplines. Early transmission models of HIV were generally deterministic compartmental models, e.g. Anderson et al. (1986), or system dynamics models, e.g. Roberts and Dangerfield (1990), but more recent work has used stochastic simulation models both Discrete Event Simulation (DES) and Agent-Based Modeling (ABM).

As with the model we describe here, studies using DES tend to focus more on the administration of treatment or prevention strategies for HIV than on transmission (although the work by Vieira et al. (2010) that uses small world networks to describe sexual networks is an exception). For example, DES is used to model strategies for the prevention of mother to child transmission in a developing country (Rauner et al. 2004, Vieira et al. 2003) using data from Tanzania and Botswana respectively, creating a population of individuals who have the attributes of the typical developing country population under study. Adams et al. (1998) used a DES model to compare possible HIV vaccines in a closed population of homosexual men in which complex transmission dynamics were modelled such as partnerships with differing rates of sexual activity, concurrent and monogamous partnerships or individuals with different partnership-seeking characteristics.

Agent based models of HIV tend to concentrate more on transmission dynamics, e.g. Beyrer et al. (2012), Richardson and Grund (2012), which can be used to assess interventions such as HIV prevention through behaviour change, e.g. Sullivan et al. (2012). In our case, transmission of infection does not form part of the study and we are concerned with progression through HIV stages and the time spent on ART.

The impact of HIV epidemics on opportunistic infections such as tuberculosis (TB) is very important. Due to lack of data from Zambia, we do not consider it here, but it has been explored in other work. For example, Mellor et al. (2011) developed a DES model of endemic TB, with HIV co-infection, incorporating household structure in the high HIV-prevalence Sub-Saharan Africa sub region. The model focused on the

transmission of TB against an assumed random transmission of HIV. Similar work has been carried out by Kasaie et al. (2013).

4 SURVIVAL ANALYSIS

A major input to the simulation model of ART provision is an estimate of the survival of PLWHA who are receiving ART. We are fortunate to have access to data from Zambia's national ART database, SmartCare, allowing us to estimate survival from a comprehensive set of data for our population of interest. This analysis is based on 487,492 patients eligible for analysis out of over 600,000 enrolled patients on the ART program in Zambia.

As with all large databases, the SmartCare database suffers from missing data in the form of empty fields for some attributes for some patients. The hot deck method of imputation was used to impute values for missing data (Twisk and de Vente 2002). In the hot deck method, a so-called donor patient is selected who comes from the same class as the patient who is missing a record for one of their attributes. The missing value is replaced by the donor patient's value for that attribute. This method avoids having to make assumptions about the distribution of data within the records.

We begin by identifying the drivers of survival from the Zambian national ART database. The analysis is necessarily limited to variables which are included in the database: gender; age; CD4 count at enrolment; urban/rural location. In the wider literature, CD4 and viral load stand out as being some of the most important (Egger et al. 2002). The CD4 counts have been used in the developing world mainly on account of the lower cost of the tests (Phillips et al. 2008) compared to viral load. Other studies have used CD4 cell counts, viral load, the development of opportunistic infections (OIs) and adverse drug reactions to estimate the clinical benefits and cost-effectiveness of ART (Freedberg et al. 2001).

4.1 Determining the Attributes that Affect Survival

Based on the heterogeneity of the HIV pandemic in Zambia discussed in earlier chapters, the survival of people on ART was examined for different sub-populations based on different CD4 count cut-offs, gender and residence. Survival functions for each category were compared using a log-rank test to make a decision on whether the differences in survival between sub-populations are statistically significant or not. This determines the risk groups used in the simulation model. As stated above, we consider the event of interest to be exiting ART rather than death in these analyses, where the exit may be due to stopping treatment, becoming lost to follow up or dying.

The Kaplan-Meier estimator is used to estimate the survival function $S(t)$ (Kaplan and Meier 1958) such that

$$\hat{S}(t) = \prod_t \frac{n_t - d_t}{n_t},$$

and $\hat{S}(0) = 1$. From the data we find that the mean time between starting ART and death is 80.3 months (95 percent confidence interval (CI): 80.2, 80.4) and between starting ART and exiting ART is 48.4 months (95 percent CI: 48.3, 48.5).

In order to test whether two sub-populations follow the same survival distribution, we carry out a hypothesis test, using the log-rank non-parametric test described by e.g. Hosmer et al. (2007). Results are summarised in Table 1.

Based on these results, the following attributes are used to determine risk groups in the simulation model: gender, baseline CD4 count split into above 350 and below 350; and age group. The location of the health facility was excluded due to discrepancies between the value recorded in the SmartCare database and the values recorded by the country's Central Statistical Office. During the change in ART drug regimens the database does not provide an accurate record of the drug regimens that the patients were using and consequently this attribute was also dropped from the analysis.

Table 1: Results of the log-rank non-parametric test indicating which attributes influence time spent on ART in Zambia.

Attribute	Significance of Log-Rank Test	Mean Survival Times (months)
Gender	0.000	Females: 50.0 (95% CI: 49.9, 50.2); Males: 45.9 (95% CI: 45.7, 46.0)
Baseline CD4 cut off at 200	0.075	CD4 < 200: 48.5 (95% CI: 48.4, 48.6); CD4 > 200: 48.1 (95% CI: 47.9, 48.3)
Baseline CD4 cut off at 350	0.003	CD4 < 350: 48.5 (95% CI: 48.3, 48.6); CD4 > 350: 47.9 (95% CI: 47.6, 48.2)
Location of health facility	0.000	Rural: 48.1 (95% CI: 47.7, 48.4); Urban: 48.5 (95% CI: 48.3, 48.6)
Age	0.000	Paediatric (< 15 years): 51.2 (95% CI: 50.8, 51.7); Adult (15 years +): 48.2 (95% CI: 48.1, 48.3)
ART regimen	0.000	Old: 52.5 (95% CI: 52.1, 52.4); New: 43.7 (95% CI: 43.5, 43.9)

4.2 Estimating the Survival Function

Having chosen the attributes to include in the analysis, we estimate survival functions for each of the sub-populations, making use of Royston-Parmar distributions to extrapolate beyond the end of the survey period (Royston and Lambert 2011). In effect, we are using a restricted cubic spline function to describe the distribution of the log of the survival times.

5 SIMULATION MODEL

The purpose of the simulation model is to forecast the number of people on ART and the cost of providing ART in Zambia over the next decade and this has informed the model structure. A transition diagram for the simulation model is given in Figure 2. Patients enter the ART system via one entry point, representing attendance at one of Zambia's ART clinics. The arrival distribution is set based on recorded arrivals into the ART system in the SmartCare database. Following enrolment, patients are assumed to commence treatment using a first/second line ART regimen. Only 0.02 percent of these patients will move to third line treatment (at the censorship point for this work, only 77 patients in Zambia were receiving third line treatment) and the majority of patients will exit the model through one of three routes: death (26 percent), stopping treatment (9 percent), lost to follow up (65 percent). Only one state is used for first and second line treatment because of changes in drug regimens during the period we have data for. Many of the drugs that were previously used as second line drugs are now administered as first line drugs and this makes it difficult to distinguish first and second line patients in the data.

The patients are split into eight risk groups based on the results of the survival analysis, with the two largest risk groups corresponding to adult females with CD4 < 350 (247,000) and adult males with CD4 < 350 (160,000). Each risk group uses a different distribution to determine the length of time they spend on first/second line ART, as discussed in the previous section.

5.1 Verification and Validation

We concentrate the validation on two outputs of interest: the duration of time spent on ART and the proportion of the simulation model population in each of the model states compared with the real data.

Considering initially the survival profiles, Figure 3 displays the empirical distribution functions (EDFs) for the time spent on ART for all patients in the simulation model and all patients in the SmartCare database.

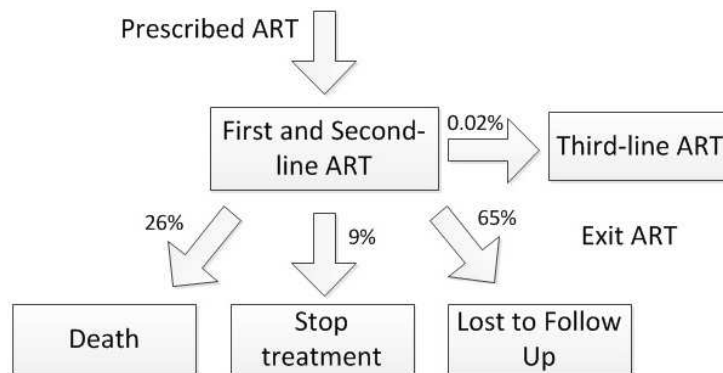


Figure 2: Transition diagram for the simulation model.

This shows a mismatch between the data and the simulation model, suggesting that the simulation model is outputting too many low values for survival times compared with the real data. We also use the Cramér-von-Mises goodness of fit test (Anderson 1962) to test whether the simulated times on ART can be assumed to come from the same distribution as those in the real data and this result confirms what can be seen visually in Figure 3, that the fit is poor. We suspect this is due to the small number of patients in the data who have been in the system for long periods, making it difficult to obtain adequate fits.

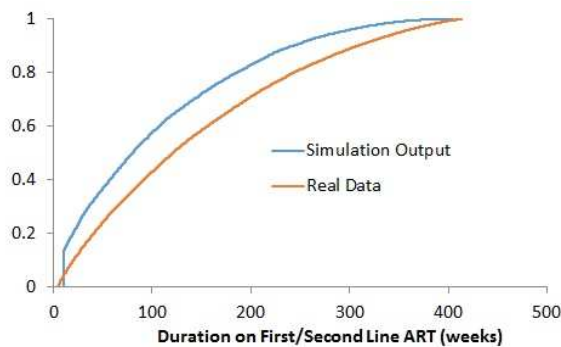


Figure 3: Comparison of the EDFs for the time spent on ART for all patients in the simulation model and for all patients in the SmartCare database.

The simulation model is started in 2005, corresponding to the introduction of the SmartCare system. It is then run to the present day and into the future. A first check is to verify that the numbers in each of the states at the end of the data collection period (31 March 2014) match those in the real data. Figure 4 shows the percentage of the population in each of the states: on ART, LTFU, Died or Stopped. The output is a close match to the numbers in the real data. The total number of patients in the SmartCare database is equal to 487,000 and in the simulation model 497,000 (95 percent confidence interval: 470,000; 523,590).

5.2 Calculating the Economic Cost of ART

Economic costs are derived from Tagar et al. (2014) who reported that the average annual cost of ART across Malawi, Rwanda, Ethiopia and Zambia was \$ 208 per patient year (ppy) in 2010 - 2011 (All costs are written in US Dollars). This multi-country costing of ART services is one of the most comprehensive and up-to-date works available at present and compares well with other, earlier research (Bratt et al. 2011). The specific annual cost ppy for Zambia calculated by Tager et. al. and his team of researchers was \$ 278 in 2010 US dollars. The estimated cost of ART service delivery was converted to 2014 US dollars to determine the cost of providing the service during that year which was the censorship point of the data

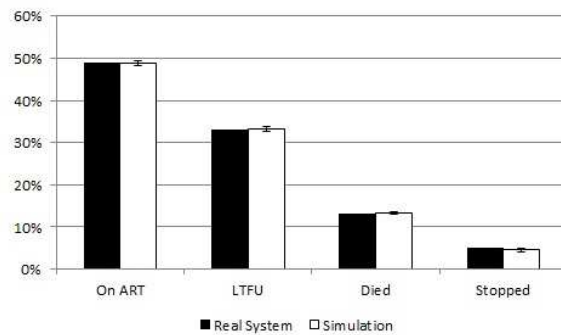


Figure 4: Percentage of the records in the SmartCare database in each of the possible categories compared with the output of the simulation model at the corresponding time point.

used to run the simulations. The conversion was achieved by first converting the cost of the services to the local currency, the Kwacha. This is because goods and services in the provision of ART services in the county are borne in this currency. This was followed by applying the annual inflation as computed using the Consumer Price index (CPI) obtained from the country’s Central Statistical Office (CSO) which is the only institution mandated by the Government of The Republic of Zambia to compile the CPI. The Zambian Kwacha (ZMW) value in 2014 was later converted back to US dollars at the average exchange rate between the two currencies for that year. At the end of 2014, the cost of providing ART services in Zambia was thus estimated to be \$ 284 ppy. This is the unit cost that was applied to the total person years at censorship point to compute the cost of ART service provision in Zambia during 2014. When projecting into the future, we used an average projected inflation rate to project the cost of ART and the official Zambian Ministry of Finance’s projected annual exchange rates to convert back to US dollars. The computed values of service provision are \$304 in 2019 and \$322 in 2024.

We use the simulation model to estimate the number of person years of treatment that are used in each model run. This is then multiplied by the unit cost of treatment to find the total cost of ART over the time period of interest.

6 RESULTS

We output results for the medium term (5 years) and the long term (10 years) and estimate the number of person years of treatment administered over these time periods and the economic cost of delivering ART.

The model predicts that the number of patients on ART will increase to 283,000 (95 percent CI: 258,000; 308,000) by the end of 5 years but will then fall slightly to 278,000 (95 percent CI: 265,000; 290,000) by the end of 10 years, as shown in Figure 5. This is a result of an increased number of patients being lost to follow up and dying rather than any change in the numbers starting treatment. Results for the medium term show that patients will spend an average of 3.04 years (95 percent CI: 2.25, 3.83) on ART before exiting treatment for whatever reason. In the long term, the estimate is 3.57 years (95 percent CI: 3.49, 3.64).

The unit annual cost of ART is estimated to be US\$ 284 calculated from Tagar et al. (2014) and allowing for inflation and differences in exchange rates between the study date of 2010 and the start date of our analysis in 2014. We estimate that the annual cost of providing treatment will increase from \$81 million (95 percent CI: \$72 million, \$85 million) over five years to \$90 million (95 percent CI: \$84 million, \$94 million) over ten years, due mainly to price inflation.

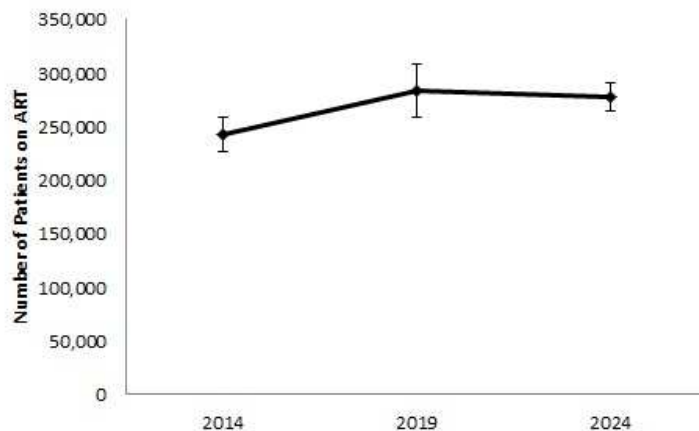


Figure 5: Simulation output showing the predicted number of patients on ART in Zambia with 95 percent confidence intervals.

7 CONCLUSION

This article describes a simulation model that has been developed to estimate the number of people on ART and the costs of ART in Zambia over the next five and ten years. Here, we make the assumption that conditions will remain the same during the next ten years but in future work we will consider different scenarios for the number of people enrolling onto treatment each year and different policies for deciding on who can access treatment. We intend to communicate the research findings to the Department of Policy and Planning at the Ministry of Health in Zambia by way of a presentation to the ministry's technical working group for monitoring and evaluation.

There are some discrepancies between the survival times generated by the simulation model and those in the real data set and this needs further consideration.

We show how survival analysis techniques can be used to determine parameters of interest for simulation models. The aim of survival analysis does not quite align with finding appropriate input distributions for simulation models and so some adaptations need to be made to the traditional tools for survival analysis in order to parameterise input distributions. Also of interest, is the hot deck method of imputation, which has the potential for being particularly useful in input analysis for simulation models in situations where data are messy and many values are missing or incorrect.

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