Modelling the Impact of Drug Resistance on Treatment as Prevention as an HIV Control Strategy

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The International Relations Office at KTH the Royal Institute of Technology, Stockholm, Sweden, administers the MFS Program within engineering and applied natural sciences.

Katie Znijewski
Program Officer
MFS Program, KTH International Relations Office
Modellering av den inverkan läkemedelsresistans har på framgången för smittorisk-förebyggande behandling av HIV

Sammanfattning


Nyckelord

Kandidatexamensarbete, Tillämpad Matematik, Stokastisk Modellering, HIV, Smittorisk-förebyggande Behandling av HIV, Resistansprofilering
Modelling the Impact of Drug Resistance on Treatment as Prevention as an HIV Control Strategy

Abstract

Uganda is using a strategy called treatment as prevention where as many individuals as possible that are infected with HIV receive treatment. As a result, the number of newly infected individuals has decreased significantly. However, there is a discussion about a potential problem regarding transmitted drug resistance. This work aims to investigate if this in fact will be a problem in the future, and to estimate the costs for different scenarios. Through developing a population-based mathematical model that describes transmission dynamics of HIV in Uganda, stochastic simulations are made for different conditions. Through analysing our simulations, we can see that Uganda may have to change their approach to HIV treatment.

Keywords

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1. Introduction

1.1 Background

1.1.1 HIV

HIV stands for Human Immunodeficiency Virus. Through zoonotic transmission, it developed through a virus amongst chimpanzees in West Central Africa. The spread of HIV is known to have started in the beginning of the 20th century. The virus attacks the immune system of an infected individual and if antiretroviral treatment is not performed, the virus will in time develop to AIDS resulting in death by opportunistic infections due to a non-functioning immune system.\(^1\)

1.1.2 HIV Life Cycle

The HIV life cycle can be explained by the picture above which shows a CD4-cell in the human body.\(^2\) An HIV negative individual has about 1000 CD4-cells/μL blood. When an individual gets infected with HIV, the virus attaches to a CD4-cell and then enters the cell. Reverse transcription is performed so that the virus can be integrated into the DNA of the human. Later when the cell reproduces itself, the virus is replicated instead of the original CD4-cell. This leads to a decrease in the number of CD4-cells within the host. When the number of CD4-cells is below 300 cells/μL blood, the immune response is weakened and opportunistic infections start to develop. The state of AIDS-defining illness in an infected individual is when the number of CD4-cells go below 200 cells/μL blood.\(^3\)

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1.1.3 Transmission of HIV

HIV is primarily a sexually transmitted disease and the most common transmission for the disease is unprotected sex. In addition to this, both transmission through pregnancy and by parenteral administration of drugs are common too. The risk for getting infected is higher when being exposed to viral loads through bloodstreams, for instance through pregnancy, blood transfusion and needle stick injuries, in comparison to being exposed to viral loads through unprotected sex.

Clinical symptoms such as fever, lymph node enlargement, fatigue and rash are observed in the majority of infected individuals after 3-6 weeks after infection. But all of these symptoms are non-specific for HIV and are also observed as symptoms caused by other viral infections. Usually, an initial symptomatic phase of this kind caused by HIV is followed by an asymptomatic phase that can last for years. As a consequence, an infected individual can unknowingly live with HIV for a long time while also being able to transmit the virus to others.

1.1.4 Antiretroviral Treatment

Antiretroviral treatment is used to treat HIV in infected individuals. It is known that antiretroviral treatment will suppress HIV below detection in most individuals with the original wild-type virus, since this virus type is sensitive to the medication. This refers to a lifelong treatment using a cocktail of drugs to reduce levels of the HIV virus in an infected individual, meaning that the process of the spreading virus and a decrease in CD4-cells within a host is suppressed.

Reduced levels of the HIV virus in an individual will not only result in positive consequences regarding health, but it will also reduce the risk of HIV transmission to other individuals. For successful treatment, pills must be taken every day. If not, there is an increased risk that the infected individual can develop resistance to the medication. Different mixes of drugs can be used since it is possible to block different parts of the HIV life cycle to prevent the distribution of the virus within the host.

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4 Ibid
7 Parienti, JJ et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy, Department of Infectious Diseases and Virology, Côte de Nacre Hospital, 2004.
1.1.5 Treatment as Prevention

Treatment as prevention is a strategy that targets the use of antiretroviral treatment. The purpose of this strategy is to control the HIV epidemic by reducing the risks of HIV transmission by treating as many infected individuals as possible.8 According to Kayongo, performing treatment as prevention achieves a 96% reduction in the risk of HIV transmission.9 Earlier recommendations set by the World Health Organisation regarding antiretroviral treatment have been to target a limited number of individuals, where it has been a priority to offer treatment to individuals with a highly developed illness. But since 2015, the World Health Organisation has set new recommendations stating that every known infected individual should receive antiretroviral treatment.10 Since then, there has been a decrease in newly infected individuals globally.11 But due to higher levels of treatment, there can also be an increased risk of the development of transmitted drug resistance.

1.1.6 Transmitted Drug Resistance

Under drug pressure, the HIV virus in an infected individual can develop a resistance to the drugs that are used for treatment. If infected individuals have high levels of the drug resistant HIV virus, it is likely that in case of transmitting the virus to another individual, the transmitted virus will be of the drug resistant type. This is known as transmitted drug resistance. Due to this, newly infected individuals with no history of drug exposure can be resistant to the drugs used for treatment which can lead to treatment failure.12

1.1.7 Resistance Profiling

Resistance profiling refers to the act of inspecting what drugs a certain individual is susceptible to before performing antiretroviral treatment. Such an analysis will provide information that hopefully will lead to an appropriate prescribing of drugs suited to maximize the chances for successful treatment.13 If this is not done in a population where the resistant virus exists, an infected individual can be treated by drugs which the individual in fact is resistant to. This can lead to treatment failure and increased levels of resistance prior to future treatment. Due to lower levels of treatment in the past, the occurrence of the resistant HIV virus may not have been seen as a problem before.14 But through implementing the strategy of treatment as prevention, the resistant HIV virus may now be seen as a potential problem. Due to this, the use of resistance profiling can be of higher interest than before.

9 Kayongo Mutebi, A. A case for HIV treatment as prevention - TasP: Challenges and Prospects in Uganda.
1.1.8 The HIV Epidemic Globally

UNAIDS estimated that 36.9 million people in the world lived with HIV in 2017, Around 64% of these are expected to be in the Sub-Saharan Africa. The same year, the number of newly infected individuals was 1.8 million and the number of deaths caused by AIDS was 0.94 million.\footnote{UNAIDS, http://www.unaids.org/en/resources/fact-sheet (2019-05-05).} In some countries the epidemic has affected the life expectancy dramatically. For instance, in Swaziland, the HIV prevalence in the age group 15-49 was 27.4% in 2017.\footnote{UNAIDS, http://www.unaids.org/en/regionscountries/countries/swaziland (2019-05-06).} However, there has been a continuously decrease in newly infected individuals globally since 1999.\footnote{Seitz, Rainer. \textit{Human Immunodeficiency Virus (HIV)}. Paul-Ehrlich-Institut, 2016.}

1.1.9 The HIV Epidemic in Uganda

The HIV prevalence in Uganda has been estimated to be 5.9% in the age group 15-49 years old.\footnote{Ibid} Due to this high number, the HIV epidemic can be considered a serious problem affecting the public health in Uganda. According to the World Health Organisation, treatment as prevention needs to be considered a key element in HIV prevention and as a part of the solution to end the HIV epidemic. From 2010-2016, the coverage of infected individuals in Uganda receiving antiretroviral treatment has increased from 21% to 62%.

During this time period, both the number of newly infected individuals and the number of deaths caused by AIDS have decreased with 43%.\footnote{UNAIDS, http://www.unaids.org/en/regionscountries/countries/uganda (2019-05-06).} Nevertheless, many individuals in Uganda can fail the first-line treatment due to the existence of drug resistance and the lack of resistance profiling prior to treatment.\footnote{World Health Organisation. \textit{HIV Drug Resistance Report 2017}.}

1.1.10 Earlier Research

Lately, research within the field of mathematical modelling applied on virus dynamics has increased, partly because of the HIV epidemic. This is done to get a better understanding of the disease and of the drug therapy strategies that are used.\footnote{De Leenheer, Patrick and L.Smith, Hal. \textit{Virus Dynamics: A Global Analysis}. Society for Industrial and Applied Mathematics, 2003.} Through the variability of nature, it is suitable to use stochastic epidemic models to describe transmissions within a population. This can be done in two different stochastic settings, using continuous-time Markov chains or stochastic differential equations.\footnote{J.S. Allen, Linda. \textit{A primer on stochastic epidemic models: Formulation, numerical simulation, and analysis}. Texas Tech University, 2017.}
1.2 Problem Statement

Uganda practises treatment as prevention and thereby antiretroviral treatment for as many known infected individuals as possible. This has resulted in a significant reduction in the number of newly affected individuals in the country. However, in resource limited areas such as Uganda, resistance profiling is not performed due to the added costs. This leads to treatment failures for individuals that carry the resistant virus. As a result, this may also lead to an increase in transmitted drug resistance. How much this potential increase in transmitted drug resistance will affect the HIV epidemic in Uganda is still up for debate.

1.3 Aims and Objectives

The aim of the project is to get a clear picture of how big influence the transmitted drug resistance affects the strategy of treatment as prevention and the HIV epidemic in general. It is important for the decision makers in Uganda to know what levels of benefits resistance profiling could achieve and thereby being able to assess whether implementation of resistance profiling is cost-effective or not.

Aims of the project:
• Develop a population-based model for the transmission dynamics of HIV in Uganda
• Explore the impact of transmitted drug resistance on the overall success of treatment as prevention as a strategy to control the HIV epidemic in Uganda
• Provide evidence on the need for resistance profiling prior to treatment and make recommendations on future treatment strategies

1.4 Significance of the Research

Since HIV is one of the deadliest viruses seen in the human history it is necessary to do well informed decisions about the treatments of it. Actions with no or low benefits risk to take resources from more effective investments. In the battle of controlling or ending the HIV epidemic, well informed decisions about what strategies to apply will be essential.

The last years, the number of individuals infected with HIV receiving treatment in Uganda has increased dramatically as a consequence of the strategy of treatment as prevention. Since it can take a few years for the resistant HIV virus to significantly affect the HIV epidemic, it is highly relevant to investigate what impact transmitted drug resistance can have on treatment as prevention and on the HIV epidemic in general in Uganda.

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2. Mathematical Theory

2.1 Mathematical Modelling

2.1.1 Mathematical Modelling for an HIV Epidemic

A Mathematical model can be used to describe the HIV epidemic. The model should describe a population that is divided into different groups, where healthy individuals that are susceptible to the virus are distinguished from the infected individuals that can transmit the virus to others. Modelling the epidemic can be useful in many ways, such as getting an increased understanding for basic features that drives the epidemic and to analyse risk factors when establishing strategies for HIV prevention.\(^{24}\)

2.1.2 Stochastic Modelling

A stochastic model refers to a stochastic process that describe population dynamics with respect to the randomness of nature. Here components contained are seen as random variables. Such a model can be used to perform simulations of an HIV epidemic within a population, since the epidemic basically can be described by a stochastic process. This can be done since nature itself is stochastic due to the fact that many variables depend stochastic variations.

For instance, if we have a population containing three different groups of individuals where \(S\) represents healthy individuals susceptible to the virus, \(I\) represents individuals infected with the HIV virus and \(Z\) represents the cases of AIDS. Then we can define a three-dimensional stochastic process as \(X(t) = \{S(t), I(t), Z(t)\}\), where \(S(t), I(t)\) and \(Z(t)\) are random variables.\(^{25}\)

2.1.3 Markov Chain in Continuous Time

A stochastic process \(X(t)\) is called a Markov chain if

\[
P(X(t_{n+1}) = i_{n+1} | X(t_n) = i_n, X(t_{n-1}) = i_{n-1}, \ldots, X(t_0) = i_0) = P(X(t_{n+1}) = i_{n+1} | X(t_n) = i_n)
\]

Where \(P(X(t_{n+1}))\) describes the probability of jumping to the state \(i_{n+1}\). This implies that the next step to a new state in a Markov chain only depends on its last state. Furthermore, previous states before the last one will not affect where the process will end up next. In a continuous time setting, the jump to the next state can occur at any time \(t\).\(^{26}\)


\(^{25}\) Ibid

\(^{26}\) Enger, Jan and Grandell Jan. *Markovprocesser och köteori, Kompendium*. Matematiska institutionen KTH.
2.2 Basic Reproductive Number

2.2.1 Definition of the Basic Reproductive Number

The basic reproductive number, $R_0$, is the expected number of secondary cases produced by a single infection in a completely susceptible population. This number is virus specific and can be computed for disease transmission models described by ordinary differential equations.

If $R_0 < 1$, the disease-free equilibrium of a model is locally asymptotically stable and as a result the virus is expected to die out. But if $R_0 > 1$, the disease-free equilibrium is unstable and the virus is expected to spread. Consequently, $R_0$ can be seen as a threshold parameter for a disease transmission model. With other words, by examining $R_0$ it is possible to estimate how infectious a modeled epidemic is.\(^{27}\)

2.2.2 Calculation of the Basic Reproductive Number

$R_0$ depends on how we define infected and uninfected compartments in our model. To be able to calculate it, changes in the population caused by new infections needs to be distinguished. Let the vector $f$ consist of elements describing appearances of new infections in the different compartments. Then let the vector $v = v^+ - v^-$ consist of elements describing the transfers of individuals into and out of the different compartments, where $v^+$ consists of rates describing transfers into the compartments and $v^-$ consists of rates describing transfers out of the compartments.

Let $F$ be a matrix consisting of the partial derivatives for $f$ with respect to the different compartments. Let $V$ be a matrix consisting of the partial derivatives for $v$ with respect to the different compartments. The Next Generation Matrix is then given by the matrix $FV^{-1}$, where $R_0$ is defined as the highest positive eigenvalue of this matrix.\(^{28}\)


\(^{28}\) Ibid
2.3 Gillespie Algorithm

The Gillespie algorithm is used to simulate a stochastic process that is modelled as a continuous-time Markov chain. A model describing an HIV epidemic is only dependent of its last state. If all parameters in the model are also independent of time, it is per definition a Markov process. The algorithm produces realizations of different reactions according to the different flows. The process of simulation depends on the different reaction rates.

2.3.1 Reaction Rate

The reaction rate is defined as the probability that a specific reaction takes place in the next infinitesimal time interval. It can be seen as the reaction probability per a given time unit. The reaction rates are updated over time depending on changes in the different compartments of the stochastic process.

2.3.1 Implementing the Gillespie Algorithm

The Gillespie algorithm can be implemented with six different steps.

1. Initiate the model and the starting conditions. \( \{X_i(0)\} = x(0) \), where \( x(0) \) contains starting values for the different compartments in the model
2. Calculate the reaction rates \( R_j(X(t)) \) and the total reaction rate \( \theta(t) = \sum_j R_j(t) \)
3. Randomize the time to the next reaction \( \Delta \sim Exp(\theta(t)) \)
4. Randomize which reaction \( E_j \) that will occur (always exactly one). The probabilities are set by the reaction rates and the total reaction rate. \( P_j(t) \sim R_j/\Phi(t) \)
5. Change the number of the different components according to the reaction that occur in 4. Update the state by \( X(t + \Delta) = X(t) + \sum_j E_j v_{ij} \). Where \( v_{ij} \) is the change in \( x_i \) when the reaction \( E_j \) occurs.
6. Repeat from step 2 until some desired condition is met.

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32 Ibid
2.3.2 Implementing the Gillespie Algorithm with Tau leap

Tau leap is a method that speeds up the Gillespie algorithm. This can be done since Tau leap does not update the reaction rates every time a reaction occurs, instead these are updated after a fixed time interval. Since the reaction rates are not updated every time, Tau leap uses a Poisson distributed random variable for the number of reactions for every event in the time interval. The Gillespie algorithm with Tau leap is described below.  

1. Initiate the model and the starting conditions. \( \{X_i(0)\} = x(0) \), where \( x(0) \) contains starting values for the different compartments in the model.
2. Calculate the reaction rates \( R_j(X(t)) \).
3. Determine the timestep \( \tau \), it can be fixed or depend on some variables.
4. For each event \( E_j \), generate the number of reactions in to occur within the time step \( \tau \) with \( K_j \sim \text{Poisson}(R_j\tau) \).
5. Update the state by \( X(t + \tau) = X(t) + \sum_j K_j v_{ij} \), where \( v_{ij} \) is the change in \( x_i \) due to the reaction \( E_j \). Here it is also good to check if any value is unrealistic. For example, some variables can take negative values because of the Poisson distribution which is not bounded.
6. Repeat from step 2 until some desire condition is met.

2.4 Maximum Likelihood Method

The Maximum likelihood Method is used to estimate the most probable parameter value based on observed data. This is done by maximizing the likelihood function.  

Let \( X_1, \ldots, X_n \) be independent random variables depending on an unknown parameter \( \theta \). The Likelihood function in the continuous case will then be defined as

\[
L(\theta) = f_{X_1, \ldots, X_n}(x_1, x_2, \ldots, x_n; \theta)
\]

Where \( f_{X_1, \ldots, X_n}(x_1, x_2, \ldots, x_n) \) is the product of the probability density functions for the random variables \( X_1, \ldots, X_n \). To maximize the Likelihood function, its derivative is set to zero to find the parameter value of \( \theta \).

\[
\frac{dL}{d\theta} = 0
\]

The estimate of the mean of a normally distributed variable with the Maximum Likelihood Method, is always the same as taking the average of the observed data.

\[
\theta^* = \frac{1}{n} \sum_{i=1}^{n} x_i
\]

---

2.5 Central Limit Theorem

Central limit theorem establishes that when a large number of independent and equally distributed random variables \(X_1, X_2, \ldots, X_n\) with mean \(\mu\) and variance \(\sigma > 0\), the sum of these will be approximately normally distributed as \(N(\mu n, \sigma \sqrt{n})\). This holds even if the random variables themselves are not normally distributed.\(^{36}\)

2.6 Discounted Cash Flow Method

The Discounted Cash Flow Method can be used to compare future cash flows with respect to the time value of money. All future cash flows are then discounted using a discount rate.\(^{37}\) The formula used is

\[
DCF = \sum_{i} \frac{CF_i}{(1+r)^i}
\]

Where \(DCF\) denotes Discounted Cash Flow, \(CF_i\) denotes the cash flow for the year \(i\) and \(r\) denotes the discount rate.


3. Methodology

3.1 Model Constructing

For this case, the model was constructed so that transmitted drug resistance could be taken into account. To do this, it was necessary to create groups within the population where individuals infected with the sensitive and the resistant virus are differentiated from each other.

3.1.1 Population Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S$</td>
<td>Susceptible individuals</td>
</tr>
<tr>
<td>$I_s$</td>
<td>Individuals infected with the sensitive virus</td>
</tr>
<tr>
<td>$I_r$</td>
<td>Individuals infected with the resistant virus</td>
</tr>
<tr>
<td>$I_{st}$</td>
<td>Infected individuals receiving successful treatment</td>
</tr>
<tr>
<td>$I_{ft}$</td>
<td>Infected individuals receiving failing treatment</td>
</tr>
<tr>
<td>$N$</td>
<td>Total population, $N = S + I_s + I_r + I_{st} + I_{ft}$</td>
</tr>
</tbody>
</table>

Our model contains five different groups of individuals describing the whole population. $S$ represents the group of individuals that are susceptible to the virus, which is the same as being healthy and not infected of HIV. We then have two different groups of infected individuals, where $I_s$ represents individuals infected by the sensitive virus and $I_r$ represents individuals infected by the resistant virus. Finally, we have two different groups for infected individuals that receive treatment. Here $I_{st}$ represents individuals receiving successful treatment and $I_{rt}$ represents individuals receiving failing treatment. The total population $N$ is then given by the sum of all groups.
3.1.2 Graphic View of the Model

The graphic view gives a picture of how the model is constructed and how it describes the HIV epidemic within the population. Arrows are used to demonstrate all possible changes in the population, where individuals can be transferred from one group to another. For every possible transfer, flows are represented by expressions that depend on both the different groups of individuals and by stated parameters.

3.1.3 Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda$</td>
<td>Birth rate</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Death rate</td>
</tr>
<tr>
<td>$a, b$</td>
<td>Infection rates</td>
</tr>
<tr>
<td>$c$</td>
<td>Treatment rate</td>
</tr>
<tr>
<td>$k$</td>
<td>Fitness cost of resistance</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Resistance profiling rate</td>
</tr>
</tbody>
</table>

The birth and death rates define at what rates individuals are born and die respectively. Hence, these rates determine to what levels new individuals are recruited to the system and to what levels individuals are leaving the system. The infection rates define at what levels the virus is transmitted from a certain group. In this case, infection rate $b$ will have a much smaller value than infection rate $a$ since the risk of transmitting HIV after receiving successful treatment is assumed to be very low. The treatment rate defines at what level infected individuals are getting treatment.
Due to a fitness cost of resistance, parameter $k$ is stated since the resistant virus will be less fit than the sensitive virus.\textsuperscript{38} This means that the risk of HIV transmission from an individual infected with the resistant virus will be lower in comparison to the risk of HIV transmission from an individual infected with the sensitive virus. At last, the resistance profiling rate defines at which rate individuals infected with the resistant virus will receive successful treatment through resistant profiling.

For this case of study, this parameter will be of great interest. In a country without resource limited settings, one can argue that this parameter will have the value one due to resistance profiling prior to treatment. Meaning that everyone will get successful treatment, even individuals infected with the resistant virus. But in countries with resource limited settings, as Uganda, this parameter value is assumed to be zero due to no resistance profiling performed prior to treatment.

3.1.4 Model Assumptions

- The inflow equals the outflow ($\lambda = \mu$)
- Individuals cannot leave the states $I_{st}$ and $I_{ft}$ unless they die
- We do not include AIDS in the model
- All individuals in the model have the same possibility to die
- We assume that the flows are linearly proportional to the factors that affect the flows
- The HIV virus in an infected individual cannot change its kind, it is either sensitive or resistant

To get a manageable model we need to state assumptions regarding the system that describes the population. Our assumptions will make the model less fit to reality, but our intention is to make the errors caused by our assumptions as negligible as possible. We assume that the inflow and the outflow from the model is equal ($\lambda = \mu$). This will result in approximately the same number of individuals in the system over time. Also, we assume that individuals cannot leave the treatment states $I_{st}$ and $I_{ft}$ unless they die. An individual that fails treatment will remain in state $I_{ft}$ until leaving the system. In the same way an individual with successful treatment will remain in state $I_{st}$ until leaving the system.

Since we are modelling the HIV epidemic, we do not include AIDS in the model which is a deadly stage of HIV developed in an infected individual. Due to this, all individuals in our model have the same possibility to die and leave the system. We also make the assumption that all flows are proportional to individuals that affect the flow. This implies that all individuals have the same risk to infect each other, which would not be the case if parts of the population are living segregated from each other. Finally, we make the assumption that the HIV virus in an infected person cannot change from the resistant to the sensitive kind, and the other way around.

3.1.5 Differential Equations for the Deterministic Model

\[
\begin{align*}
\frac{dS}{dt} &= \mu N - \mu S - S(aI_s + bI_{st}) - kS(aI_r + aI_{ft}) \\
\frac{dI_s}{dt} &= -\mu I_s - cI_s + S(aI_s + bI_{st}) \\
\frac{dI_r}{dt} &= -\mu I_r - cI_r + kS(aI_r + aI_{ft}) \\
\frac{dI_{st}}{dt} &= -\mu I_{st} + cI_s + \rho cI_r \\
\frac{dI_{ft}}{dt} &= -\mu I_{ft} + (1 - \rho)cI_r
\end{align*}
\]

From our graphic view in 3.1.2, we can see the different flows into and out of the different compartments of the population. Based on these we can get system of differential equations that describe the model in a basic deterministic setting where the randomness of nature is ignored. The equations describe what happens to the number of individuals in every group. For instance, the group of susceptible individuals has an inflow from new births and an outflow from deaths and infections by both the sensitive and the resistant virus.

3.2 Basic Reproductive Number

\[
f = \begin{pmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \\ f_5 \end{pmatrix} = \begin{pmatrix} S(aI_s + bI_{st}) \\ kS(aI_r + aI_{ft}) \\ 0 \\ 0 \\ 0 \end{pmatrix}
\]

We define \( f \) as a vector describing the new infections in the different compartments, where \((f_1, f_2, f_3, f_4, f_5)\) refers to compartments \((I_s, I_r, I_{st}, I_{ft}, S)\).

\[
v = v^+ - v^- = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{pmatrix} = \begin{pmatrix} \mu I_s + cI_s \\ \mu I_r + cI_r \\ \mu I_{st} - cI_s - \rho cI_r \\ \mu I_{ft} - (1 - \rho)cI_r \\ \mu S - \lambda N + S(aI_s + bI_{st}) + kS(aI_r + aI_{ft}) \end{pmatrix}
\]

We define \( v \) as a vector describing the transfers of individuals in the different compartments, where \((v_1, v_2, v_3, v_4, v_5)\) refers to compartments \((I_s, I_r, I_{st}, I_{ft}, S)\).
Then we define \( F \) as a matrix consisting of all partial derivatives of the vector \( f \) with respect to the different compartments \((I_s, I_r, I_{st}, I_{ft}, S)\).

\[
F = \begin{pmatrix}
\frac{\partial f_s}{\partial I_s} & \frac{\partial f_s}{\partial I_r} & \frac{\partial f_s}{\partial I_{st}} & \frac{\partial f_s}{\partial I_{ft}} & \frac{\partial f_s}{\partial S} \\
\frac{\partial f_r}{\partial I_s} & \frac{\partial f_r}{\partial I_r} & \frac{\partial f_r}{\partial I_{st}} & \frac{\partial f_r}{\partial I_{ft}} & \frac{\partial f_r}{\partial S} \\
\frac{\partial f_{st}}{\partial I_s} & \frac{\partial f_{st}}{\partial I_r} & \frac{\partial f_{st}}{\partial I_{st}} & \frac{\partial f_{st}}{\partial I_{ft}} & \frac{\partial f_{st}}{\partial S} \\
\frac{\partial f_{ft}}{\partial I_s} & \frac{\partial f_{ft}}{\partial I_r} & \frac{\partial f_{ft}}{\partial I_{st}} & \frac{\partial f_{ft}}{\partial I_{ft}} & \frac{\partial f_{ft}}{\partial S}
\end{pmatrix} = \begin{pmatrix}
aS & 0 & bS & 0 & aI_s + bI_{st} \\
0 & akS & 0 & akS & k(aI_r + aI_{ft}) \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0
\end{pmatrix}
\]

Then we define \( V \) as a matrix consisting of all partial derivatives of the vector \( v \) with respect to the different compartments \((I_s, I_r, I_{st}, I_{ft}, S)\). \( R_0 \) is then calculated as the highest positive eigenvalue of the Next Generation Matrix \( FV^{-1} \), using different values of the parameter \( \rho \). Calculations are done in Matlab.

### 3.3 Stochastic Model Formulation

In order to perform stochastic simulations, we implement a stochastic version of the deterministic model using Gillespie algorithm with Tau leap. Our stochastic process is defined as \( X(t) = \{I_s(t), I_r(t), I_{st}(t), I_{ft}(t), S(t)\} \) where \( I_s(t), I_r(t), I_{st}(t), I_{ft}(t), S(t) \) are seen as random variables. This is implemented as a Markov chain, which means that the number of individuals in every group after next event only depends on the number of individuals in every group at the moment. This implies that all other parameters in the model are constants. For instance, the treatment rate or the infection rate are not dependent of time. The Markov chain is implemented in a continuous time setting, meaning that the next event can occur at any time \( t \), where is a positive real number.

To construct a stochastic model, we need to calculate the probability for each event to occur. The probability for a specific event to occur given that we know an event will take place, is calculated by dividing the flow for the specific event by the total flow. The total flow is given by the sum of all flows, which is the same as the total reaction rate. Changes in the population for the affected groups follows what specific event that occurs. The total reaction rate \( \theta \), is given by

\[
\theta = \lambda N + \mu S + \mu I_s + \mu I_r + \mu I_{st} + \mu I_{ft} + S(aI_s + bI_{st}) + kS(aI_r + aI_{ft}) + cI_s + pI_r + (1-\rho)cI_r
\]
Events with corresponding reaction rates and probabilities are given in the table below.

<table>
<thead>
<tr>
<th>Event</th>
<th>Change in population</th>
<th>Reaction rate</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>New birth ( S )</td>
<td>( S \to S + 1 )</td>
<td>( \lambda N )</td>
<td>( \lambda N/\theta )</td>
</tr>
<tr>
<td>Death ( S )</td>
<td>( S \to S - 1 )</td>
<td>( \mu S )</td>
<td>( \mu S/\theta )</td>
</tr>
<tr>
<td>Infection by sensitive virus</td>
<td>( S \to S - 1, I_s \to I_s + 1 )</td>
<td>( S(aI_s + bI_{st}) )</td>
<td>( S(aI_s + bI_{st})/\theta )</td>
</tr>
<tr>
<td>Infection by resistant virus</td>
<td>( S \to S - 1, I_r \to I_r + 1 )</td>
<td>( kS(aI_r + aI_{ft}) )</td>
<td>( kS(aI_r + aI_{ft})/\theta )</td>
</tr>
<tr>
<td>Death ( I_s )</td>
<td>( I_s \to I_s - 1 )</td>
<td>( \mu I_s )</td>
<td>( \mu I_s/\theta )</td>
</tr>
<tr>
<td>Death ( I_r )</td>
<td>( I_r \to I_r - 1 )</td>
<td>( \mu I_r )</td>
<td>( \mu I_r/\theta )</td>
</tr>
<tr>
<td>Successful treatment of ( I_s )</td>
<td>( I_s \to I_s - 1, I_{st} \to I_{st} + 1 )</td>
<td>( cI_s )</td>
<td>( cI_s/\theta )</td>
</tr>
<tr>
<td>Successful treatment of ( I_r )</td>
<td>( I_r \to I_r - 1, I_{st} \to I_{st} + 1 )</td>
<td>( pcI_r )</td>
<td>( pcI_r/\theta )</td>
</tr>
<tr>
<td>Failed treatment of ( I_r )</td>
<td>( I_r \to I_r - 1, I_{ft} \to I_{ft} + 1 )</td>
<td>( (1-\rho)cI_r )</td>
<td>( (1-\rho)cI_r/\theta )</td>
</tr>
<tr>
<td>Death ( I_{st} )</td>
<td>( I_{st} \to I_{st} - 1 )</td>
<td>( \mu I_{st} )</td>
<td>( \mu I_{st}/\theta )</td>
</tr>
<tr>
<td>Death ( I_{ft} )</td>
<td>( I_{ft} \to I_{ft} - 1 )</td>
<td>( \mu I_{ft} )</td>
<td>( \mu I_{ft}/\theta )</td>
</tr>
</tbody>
</table>

3.4 Applying a Ugandan Perspective

As the aim for this study is to analyse the HIV epidemic in Uganda, the model needs to be fitted to a Ugandan perspective. This requires estimations for both parameters and starting values for population groups with the country Uganda as an objective. Our parameters and starting values for population groups have been estimated in consultation with both the Uganda Virus Research Institute and with our supervisor at Makerere University.
3.4.1 Population Groups Estimations

<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>Population</td>
<td>42,900,000</td>
<td>Worldometer(^{39})</td>
</tr>
<tr>
<td>$I_{tot}$</td>
<td>Adults and children living with HIV</td>
<td>1,300,000</td>
<td>UNAIDS(^{40})</td>
</tr>
<tr>
<td>$I_{treat}$</td>
<td>Individuals living with HIV receiving treatment</td>
<td>970,000</td>
<td>UNAIDS(^{41})</td>
</tr>
<tr>
<td>$I_{st}$</td>
<td>Individuals living with HIV who has suppressed viral loads (Successful treatment)</td>
<td>760,000</td>
<td>UNAIDS(^{42})</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Proportion of infected individuals with the resistant HIV virus</td>
<td>15.4%</td>
<td>HIV Drug Resistance Report(^{43})</td>
</tr>
</tbody>
</table>

In order to perform simulations of our model, starting values for the different groups within the population are needed. These are based on the latest data available, which are from the year of 2017.

\[
S = N - I_{tot} = 42,900,000 - 1,300,000 = 41,600,000
\]

\[
I_s = (I_{tot} - I_{treat})(1 - \alpha) = (1,300,000 - 970,000)(1 - 0.154) \approx 279,000
\]

\[
I_r = (I_{tot} - I_{treat})\alpha = (1,300,000 - 970,000)0.154 \approx 51,000
\]

\[
I_{st} = 760,000
\]

\[
I_{ft} = I_{treat} - I_{st} = 970,000 - 760,000 = 210,000
\]

Calculations could then be made to estimate the starting values for the population groups.

3.4.2 Starting Values for the Population Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S$</td>
<td>Susceptible individuals</td>
<td>41,600,000</td>
</tr>
<tr>
<td>$I_s$</td>
<td>Individuals infected with the sensitive virus</td>
<td>279,000</td>
</tr>
<tr>
<td>$I_r$</td>
<td>Individuals infected with the resistant virus</td>
<td>51,000</td>
</tr>
<tr>
<td>$I_{st}$</td>
<td>Infected individuals receiving successful treatment</td>
<td>760,000</td>
</tr>
<tr>
<td>$I_{ft}$</td>
<td>Infected individuals receiving failing treatment</td>
<td>210,000</td>
</tr>
<tr>
<td>$N$</td>
<td>Total population, $N = S + I_s + I_r + I_{st} + I_{ft}$</td>
<td>42,900,000</td>
</tr>
</tbody>
</table>

\(^{41}\) Ibid
\(^{42}\) Ibid
3.4.3 Parameter Estimations

\( \lambda \) and \( \mu \)

In 2017, the birth rate in Uganda was estimated to be 4.3%.\(^{44}\) As mentioned earlier regarding model assumptions, we will then assume the same value for the death rate.

\( b \)

The adherence level for individuals infected with HIV in Uganda, regarding following the antiretroviral treatment correctly, is estimated to be 90.4%.\(^{45}\) Due to this, we make an estimation of \( b \) as 0.1\( a \).

\( c \)

United Nations has a target called 90-90-90 that means that 90% of all individuals who live with HIV should know their status. Out of this group 90% should be on antiretroviral therapy and 90% of those on treatment should have undetectable levels of the virus (successful treatment).\(^{46}\)

Hence, a target value of the treatment rate \( c \) can be estimated by the product 0.9*0.9=0.81 to cover the first two events (90-90), which both are components in our model. The rate of successful treatment should not be included here since we have divided the infected individuals into two groups. In our model, we assume 100% successful treatment for individuals infected with the sensitive virus and a much lower level of successful treatment for individuals infected with the resistant virus.

Worth mentioning is that in Uganda, 81% of all individuals living with HIV know their status and 88% out of this group are receiving treatment.\(^{47}\) In our simulations, we will set the treatment rate \( c \) to the target value set by United Nations.

\( k \)

The fitness cost of resistance in Uganda is estimated to be 0.81, which refers to the fact that resistant virus strains are less fit than sensitive virus strains.\(^{48}\)

\( \rho \)

Different values for the resistance profiling rate \( \rho \) will be tested in the the interval 0-1.


\(^{45}\) Elyanu et al. Adherence to antiretroviral therapy and retention in care for adolescents living with HIV from ten districts in Uganda.


By our model it follows that both flows representing new infections added together must equal the total number of new infections. Using this, $a$ can be calculated as:

$$S(aI_s + bIst) + kS(aI_r + aI_{ft}) = NewInfections \leftrightarrow$$

$$S(aI_s + 0.1aIst) + kS(aI_r + aI_{ft}) = NewInfections \leftrightarrow$$

$$a = \frac{NewInfections}{S(I_s + 0.1I_{st} + kI_r + kI_{ft})}$$

With the formula above, $a$ is then calculated for three consecutive years using the data in the table below.

<table>
<thead>
<tr>
<th>Group/Year</th>
<th>2017</th>
<th>2016</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>NewInfections</td>
<td>50,000</td>
<td>57,000</td>
<td>62,000</td>
</tr>
<tr>
<td>$I_{tot}$</td>
<td>1,300,000</td>
<td>1,300,000</td>
<td>1,300,000</td>
</tr>
<tr>
<td>$S$</td>
<td>41,600,000</td>
<td>40,200,000</td>
<td>38,800,000</td>
</tr>
<tr>
<td>$I_s$</td>
<td>279,000</td>
<td>401,000</td>
<td>492,000</td>
</tr>
<tr>
<td>$I_r$</td>
<td>51,000</td>
<td>73,000</td>
<td>89,000</td>
</tr>
<tr>
<td>$I_{st}$</td>
<td>760,000</td>
<td>644,000</td>
<td>561,000</td>
</tr>
<tr>
<td>$I_{ft}$</td>
<td>210,000</td>
<td>182,000</td>
<td>158,000</td>
</tr>
<tr>
<td>$k$</td>
<td>0.81</td>
<td>0.81</td>
<td>0.81</td>
</tr>
<tr>
<td>$a$</td>
<td>$2.12\times10^{-9}$</td>
<td>$2.11\times10^{-9}$</td>
<td>$2.14\times10^{-9}$</td>
</tr>
</tbody>
</table>

The Maximum Likelihood Method is used to determine the most probably value of $a$ using to the observed data. Since our stochastic process depends on a large number of independent random variables, the sum of them can be seen as approximately normally distributed according to the Central Limit Theorem. The infection rate $a$ can then be estimated as the average of our three observed values according to the Maximum Likelihood Method. This results in the parameter value $a = 2.12\times10^{-9}$. 

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3.4.4 Parameter Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda$</td>
<td>Birth rate</td>
<td>0.043</td>
<td>World Factbook$^{49}$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Death rate</td>
<td>0.043</td>
<td>Assumption</td>
</tr>
<tr>
<td>$a$</td>
<td>Infection rate</td>
<td>$2.12 \times 10^{-9}$</td>
<td>See calculations</td>
</tr>
<tr>
<td>$b$</td>
<td>Infection rate (by successfully treated)</td>
<td>$2.12 \times 10^{-10}$</td>
<td>Adherence level$^{50}$</td>
</tr>
<tr>
<td>$c$</td>
<td>Treatment rate</td>
<td>0.81</td>
<td>UNAIDS$^{51}$</td>
</tr>
<tr>
<td>$k$</td>
<td>Fitness cost of resistance</td>
<td>0.81</td>
<td>Kitayimbwa$^{52}$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Resistance profiling rate</td>
<td>$0 - 1$</td>
<td>-</td>
</tr>
</tbody>
</table>

3.5 Cost Analysis

All calculated costs are based on our stochastic simulations in Matlab.

3.5.1 Cost for Resistance Profiling

The price for resistance profiling is 150 dollar per individual, which is a one-time payment done prior to treatment. To calculate the total price for resistance profiling, we have added a cost to the individuals that transfer from the states $I_s$ and $I_r$ to $I_{st}$ and $I_{ft}$. After this, we have taken the cost of 150 dollars multiplied with the rate of resistant profiling used in the different simulations. For instance, if we set the resistance profiling rate as 0.35, we add 52.5 dollar ($0.35 \times 150$ dollar) for every person that receives treatment.

To be able to discount the cash flows we were forced to do a simplification. When we discount the cash flows for resistance profiling, we assume that all payments are done in the end of each year.

---


$^{50}$ US National Institutes of Health https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4647509/?fbclid=IwARthiEcOgWytQbD4NnyPDgr_Cx7kv3gwvex5ucjixpMG3ioh212wQiTQ (2019-04-13).


$^{53}$ Uganda Virus Research Institute, Telephone interview 2019-04-23.
3.5.2 Cost for Treatment

The price for treatment is 220 dollar per individual and year.\textsuperscript{54} To make it possible to calculate the total cost for treatment, we use the number of infected individuals on treatment in end of every year. We can then multiply this number by 220 to get the total cost for treatment each year. All cash flows are then discounted, which makes it possible to compare different options with respect to the time value of money.

3.5.3 Discount Rate

The discount rate is central in evaluating cash flows using the Discounted Cash Flow Method. We have used the rate of 15-years government bonds for Uganda as the discount rate. Since HIV is a long-term problem, we used the bond rate with respect to the longest period of time possible. This 15-years government bond has the rate 15.9\%.\textsuperscript{55}

4. Results

4.1 Basic Reproductive Number

<table>
<thead>
<tr>
<th>$\rho$</th>
<th>0.35</th>
<th>0.45</th>
<th>0.55</th>
<th>0.52</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_0$</td>
<td>1.34</td>
<td>1.14</td>
<td>0.95</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The basic reproductive number $R_0$ for our model is calculated for different values of the resistant profiling rate $\rho$ in the interval 0.35-0.55. We can see $R_0$ depends on the rate of resistance profiling, meaning that the HIV epidemic in our model is more infectious for lower rates of resistant profiling and less infectious for higher rates of resistance profiling. Also, a critical value of $\rho$ was found where $R_0$ equals 1. We know that if $R_0$ is equal or less than 1, the epidemic is expected to die out over time.

4.2 Model Simulations

Our results are obtained through simulations in Matlab where we apply the Gillespie algorithm on our model. For different simulations, we vary both the parameter value of $\rho$ and the time span for the simulation. For each simulation, we make 50 replications. The different groups of individuals within the population are expressed through different graphs with specific colours.

4.2.1 Simulation 1 ($\rho=0$, simulation time 7 years)

This gives a general view over a model simulation.
Here is zoomed view to analyse the group of healthy individuals in the population. We can see that even if $\rho = 0$, a positive effect is achieved in the short run regarding the number of healthy individuals. Since we have approximately a constant number of individuals in the system, this means that the total number of infected individuals is decreasing. However, in this view we cannot see how the infected individuals are distributed in the other four groups for infected individuals.

Here is a zoomed view for the same simulation that shows the distribution of the four other groups for infected individuals. We can see that the number of infected individuals that fail treatment is increasing. In the long run, this group will then contribute to a new epidemic.
4.2.2 Simulation 2 ($\rho = 0$, simulation time 100 years)

If we run the simulation with $\rho = 0$ for 100 years instead, it is confirmed that the group of infected individuals that fails treatment is creating a new epidemic due to an increase in transmitted drug resistance. For our further analysis, it would therefore be interesting to see for what value for $\rho$ this epidemic can be controlled and prevented.

4.2.3 Simulation 3 ($\rho = 0.35$, simulation time 7 years)

Through varying the value of $\rho$ for different simulations, it was found that the group of infected individuals that fails treatment was still increasing when $\rho = 0.35$. 
### 4.2.4 Simulation 4 ($\rho = 0.35$, simulation time 100 years)

Running the same simulation for 100 years instead, we can see the same pattern. The group of infected individuals failing treatment is dangerously increasing.

### 4.2.5 Simulation 5 ($\rho = 0.45$, simulation time 7 years)

When $\rho = 0.45$, we can see it was obtained that the graph for the group of infected individuals failing treatment seem to be approximately flat over time, meaning that this group is not increasing.
4.2.6 Simulation 6 ($\rho = 0.45$, simulation time 100 years)

When then run the simulation for 100 years instead to see what happens with the group of infected individuals that fail treatment in the long term. We can see that the graph for the group of infected individuals failing treatment still seems to be approximately flat over time. Consequently, $\rho = 0.45$ seems to a breaking point and a good estimation for the lowest value possible for $\rho$ resulting in a controlled epidemic.

4.2.7 Simulation 7 ($\rho = 0.55$, simulation time 7 years)

When increasing resistance profiling to $\rho = 0.55$, it was obtained that the group of infected individuals failing treatment is decreasing.
4.2.8 Simulation 8 ($\rho = 0.55$, simulation time 100 years)

When we run the simulation for 100 years instead, we can see that $\rho = 0.55$ will lead to a lasting decrease in the group of infected individuals failing treatment. Through running different simulations, we can see that $\rho = 0.55$ seems to be the lowest value for $\rho$ where epidemic is both under control and there is a distinct decrease in transmitted drug resistance over time.
## 4.3 Costs

<table>
<thead>
<tr>
<th>Simulation time</th>
<th>Resistance Profiling ($\rho$)</th>
<th>Cost of Treatment ($)</th>
<th>Cost of Resistant Profiling ($)</th>
<th>Total Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>212,260,000</td>
<td>0</td>
<td>212,260,000</td>
<td></td>
</tr>
<tr>
<td>0.35</td>
<td>212,330,000</td>
<td>8,797,200</td>
<td>221,130,000</td>
<td></td>
</tr>
<tr>
<td>0.45</td>
<td>212,380,000</td>
<td>11,318,000</td>
<td>223,700,000</td>
<td></td>
</tr>
<tr>
<td>0.55</td>
<td>212,240,000</td>
<td>13,759,000</td>
<td>226,000,000</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>212,220,000</td>
<td>25,038,000</td>
<td>237,260,000</td>
<td></td>
</tr>
<tr>
<td>3 Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>571,800,000</td>
<td>0</td>
<td>571,800,000</td>
<td></td>
</tr>
<tr>
<td>0.35</td>
<td>571,640,000</td>
<td>14,912,000</td>
<td>586,550,000</td>
<td></td>
</tr>
<tr>
<td>0.45</td>
<td>571,340,000</td>
<td>19,126,000</td>
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We can see that in a short-term perspective (1 and 3 years), a higher resistance profiling does not lead to significant decrease in individuals on treatment. Due to this, the extra cost added for resistance profiling therefore lead to a higher total cost. For example, we can see that in the first year an increase in resistance profiling from 0% to 55% will lead to around 6.5% higher total costs.

If we instead see it from a long-term perspective, a higher rate of resistance profiling leads to a decrease in infected individuals. In the long run, this results in less individuals on treatment and decreased costs for treatment. In 10 years, we see that the costs for treatment are starting to decrease significantly with higher rates of resistance profiling. However, the higher rates and costs for resistance profiling still leads to a higher total cost.
But in 80 years, we can see a break in the pattern as a 55% resistance profiling rate is the most economic option. In comparison to a 0% resistance profiling rate, the reduction in costs for treatment is significant enough to result in a decrease of total costs as well. It can be seen that performing resistance profiling will increase the total costs in a short-term perspective, but in the long run it is a more economic option to at least perform some resistance profiling.
5. Discussions and Conclusions

5.1 Model

Due to all our assumptions made, it is possible to argue how well our model fits the reality of the Ugandan situation today. For example, we have chosen to not include AIDS as our main area of focus is HIV epidemic and transmitted drug resistance. Also, since no individual that ends up in the group for failed treatment can leave this state until death, it is possible to argue that the model is more appropriate in a short-term perspective. However, we have also performed long run simulations as it is interesting to see how the epidemic develops using our model. After all, our model may be seen as useful tool in forecasting what impact transmitted drug resistance can have on the overall success of treatment as prevention. In an HIV epidemic, neglecting the transmitted drug resistance by not performing resistance profiling could be a long-term risk.

5.2 Basic Reproductive Number

Looking at the basic reproductive number, the resistance profiling rate should be set to a rate so that $R_0$ takes a maximum value of 1. As long as $R_0$ is not higher than 1, the epidemic is expected to die out over time. For our model, $R_0$ takes the value 1 when the resistant profiling rate is set to 52%. As a consequence, the rate of resistance profiling should according to this be 52% or higher in order to end the epidemic over time.

5.3 Simulations

By examining our simulations, we can see that the number of infected individuals in Uganda is going down fast due to the strategy of treatment as prevention targeting antiretroviral treatment. High levels of treatment seem to have a very positive effect on preventing an increase in the HIV epidemic, at least in a short-term perspective. However, we do not know if the lack of resistance profiling will lead to an increasing occurrence of the resistant HIV virus, which in a worst-case scenario could lead to an even worse epidemic in the future.

Thus, it is interesting to look at critical value of the resistant profiling rate, where the group for infected individuals that fail treatment is no longer increasing. By our simulations, we can see that a resistant profiling rate around 45% seems to be enough for controlling the epidemic. At this point, there is no increase in the epidemic. But if we also look at a resistant profiling rate around 55%, this seems to be a sufficient rate at which there also is a decrease in the epidemic in a long-term perspective as well as in a short-term perspective.
This also seem to match the resistant profiling rate calculated using the basic reproductive number, where a resistant profiling rate of 52% seems to a turning point. Hence, this could be a necessary level of resistance profiling to prevent an increase in transmitted drug resistance over time and to end the epidemic. Otherwise, an increase in transmitted drug resistance seem to be an inevitable consequence.

5.4 Costs

In our cost analysis, it is important to remember that we have only taken into account the direct costs related to treatment and resistance profiling. The costs for a society with a population suffering from an HIV epidemic are arguably even higher due to the consequences of the disease, but these costs may be harder to calculate. For instance, an epidemic will most likely result in increased indirect healthcare costs as well as opportunity costs due to a decrease in the labour force. It is also important to remember that the value set for the discount highly influences the results.

5.5 Recommendations Regarding HIV Control Strategies

Our recommendation is that it is important for Uganda to have at least a 55% resistance profiling rate. In our stochastic simulations we can see that a 55% resistance profiling rate will lead to a decrease in all groups for infected individuals, including the most dangerous group that fails treatment and thereby can transmit the resistant HIV virus to others. Without a resistance profiling rate of at least 55%, the transmitted drug resistance can have a negative impact on the overall success of treatment as prevention.

In addition to this, calculations of the basic reproductive number $R_0$ show that Uganda need at least a 52% resistance profiling rate to prevent an increase in the epidemic. This is a good confirmation of our simulation results as the rates are almost the same. However, it is recommended to be on the safe side and have at least a 55% resistant profiling rate. The positive effects Uganda has received from treatment as prevention the last years is most likely temporary and will disappear over time if resistant profiling is not performed. It could also lead to an even worse epidemic in the future due to an increase in transmitted drug resistance.

In our cost analysis, we see that it takes a long time before resistance profiling becomes an economic option. Nevertheless, it should not be an option to ignore the transmission of drug resistance because of the short-term costs for resistance profiling. Doing so will most certain lead to higher costs for the society in a long-term perspective, in comparison to the direct costs for both treatment and resistance profiling. A likely reason to that Uganda is not using resistance profiling today is probably because of the added costs. In a short-term perspective this is a fully legit reason. Another reason can be that in the short-term perspective, there will not be a significant change in the number of infected individuals whether you use resistance profiling or not. Resistant profiling is simply not cost effective in the short run.
However, it is both necessary and cost effective in a long-term perspective to have at least some resistance profiling. It is also important to see the costs in relation to each other. Even if the costs for resistance profiling can be seen as high, they are very small in relation to the costs of treatment. Consequently, few added short-term costs for investing in resistance profiling is necessary to improve the public health in Uganda and to prevent a future HIV epidemic.
References

19. Parienti, JJ et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy, Department of Infectious Diseases and Virology, Côte de Nacre Hospital, 2004.


29. US National Institutes of Health
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4647509/?fbclid=IwAR1hiEcOgWy1QbD4NnyPDgr_RuGbCX7Kv3gwex5uCjiXpMG3joh212wfQtQ (2019-04-13).


32. World Health Organisation,

33. World Health Organisation,

