Mathematical modeling of treatment switch for people living with HIV

DEPARTMENT OF MATHEMATICS

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ADDIS ABABA UNIVERSITY

By

HELEN GIRMA

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A Thesis Submitted to the Department of Mathematics in Partial Fulfillment of the Requirements for the Degree of Master of Science in Mathematics

Advisor: Dr.Manalebish Debalike Asfaw

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COLLEGE OF NATURAL AND
COMPUTATIONAL SCIENCES

Approval of the Thesis for defense

I hereby certify that I have supervised, read and evaluated this Thesis entitled **"Mathematical modeling of treatment switch for people living with HIV"** prepared by Helen Girma under my guidance. I recommend that this thesis is submitted for oral defense.

Manalebis Debalike Asfaw (PhD)	_____	_____
Advisor Name	Signature	Date

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Approved by the Board of Examiners

	Name	**Signature**	**Date**
Internal Examiner I:	_____	_____	_____
Internal Examiner II:	_____	_____	_____

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List of Figures

List of Tables

Abstract

This thesis develops and analyzes a deterministic compartmental model to optimize treatment switching strategies for HIV/AIDS antiretroviral therapy (ART). Motivated by the critical need to mitigate drug resistance and prolong treatment efficacy, we extend the classical Susceptible-Infected-Treatment (SIT) framework to incorporate three distinct ART cocktail classes. The model explicitly allows strategic switching of patients between these classes to manage viral load and suppress resistance emergence. We formulate a system of nonlinear ordinary differential equations capturing population dynamics between susceptible (S), infected (I), and three treated compartments (T_1, T_2, T_3), with bidirectional switching rates between $T-$classes. The parameters include drug efficacy, switching rates, and resistance development thresholds. Analytical methods establish the basic reproduction number (R_0) and equilibrium stability, while sensitivity analysis identifies dominant control parameters. Numerical simulations evaluate optimal switching protocols under varying epidemiological scenarios. The results show that structured switching between cocktails significantly delays treatment failure and reduces cumulative resistance compared to static regimens. An adaptive "cycling" strategy, guided by viral load thresholds, is shown to be most effective in sustaining long-term treatment viability. The model provides quantitative evidence for personalized rotation-based ART policies, providing practitioners with a framework to maximize therapeutic outcomes while conserving limited drug options.

Keywords:- HIV/AIDS, ART drug resistance, mathematical model, treatment switching, compartmental model, reproduction number.

Contents

Chapter 1

Introduction

1.1. Background of the study

HIV continues to remain a major health issue worldwide, especially in poorer countries. Even with all the advances in treatment, millions still live with the virus. By 2023, an estimated 39 million people are living with HIV. Antiretroviral therapy has really helped people manage their infections and improve their quality of life.Managing HIV takes non stop dedication and effort since the virus will remain in the host, patients need to follow their treatment plans and go for regular checkups.One tricky part of managing chronic HIV is figuring out when to change treatment.

One of the most challenging parts of managing Chronic HIV is determining change of treatment. Switching medication and treatment is important when the current Plan is deemed to be not effective, in the event of drug resistance or if in case of severe side effects. In places with good resources, this decision is often based on regular testing for viral loads and resistance. But in low-resource areas, those tests might not be available, which makes it tougher to make informed decisions. The optimal timing for changing treatment is crucial, Delaying Switching treatments will result in drug resistance and side effects while premature change of treatment will result in less effective management of the disease.

Mathematical modeling is becoming a helpful way to figure out these treatment

choices. These models simulate how the virus, immune system, and medications interact, often using real patient data. Researchers and health professionals play around with different treatment strategies using computer algorithms to see the outcomes. For example, differential equation models help track how viral loads change with different treatments while considering drug resistance and how well patients stick to their plans. New techniques such as optimal control theory and Markov decision processes help in the decision for switching treatments. These methods look for a balance between avoiding drug resistance and achieving the best health outcomes. emerging technologies like machine learning and AI are being used to forecast treatment outcomes and guide decisions on switching therapies. Still, there are challenges like differences between patients, data quality issues, and limitations in healthcare systems. Mathematical modeling can help with analyzing, simulating, and predicting outcomes in clinical practice. Models can be adjusted for different resource situations and used to create treatment plans that work in real life. Policies can also be developed from these models to improve how resources are used, monitoring schedules, and overall treatment efficiency. integrating these models into HIV treatment policy could really help reach global health goals and improve care for those living with HIV. The Aim of this research is developing and analyzing a mathematical model describing HIV infection Progression, Antiretroviral therapy impacts over time specifically in switching regimens and treatment for HIV patients. The model will consider factors like viral load, CD4+ T cell counts, drug resistance, and how well patients stick to their treatment plans. By looking at different treatment paths and running simulations, this study aims to help make HIV treatment planning and health policy more effective and evidence-based

1.2. Statement of problem

HIV is primarily transmitted through contact with infected blood or other bodily fluids [8]. The most common modes of transmission include unprotected sexual intercourse and the sharing of needles. Additional transmission routes include blood transfusions

and vertical transmission from an HIV-positive mother to her child during pregnancy, childbirth, or breastfeeding. Importantly, HIV is not spread through casual contact such as kissing, sharing meals, using the same toilet, or via saliva, sweat, tears, or insect bites.

Before progressing to acquired immunodeficiency syndrome (AIDS), individuals infected with HIV often experience a range of clinical stages. Shortly after infection, some may develop mild flu-like symptoms including fever, muscle aches, diarrhea, and lymphadenopathy (swollen lymph nodes), similar to those seen in infectious mononucleosis. In some cases, acute neurological symptoms such as headache, confusion, or seizures may also occur [8]. This initial phase is often overlooked, yet it is marked by a rapid increase in the concentration of free virus in the blood. As the immune system begins to respond, antibody production reduces the free virus count. The appearance of detectable antibodies typically occurs within 19 to 56 days post-infection, though it may take longer [8].

Following this acute phase, the viral load declines and remains at a relatively low, yet infectious, level for a variable number of years. During this latent period, the individual may not exhibit any symptoms. However, over time, the CD4+ T-helper cell count gradually declines, while viral load increases and antibody levels to the viral core protein diminish. When the T-helper cell count drops to approximately 50

Antiretroviral therapy (ART) is the primary treatment for retroviruses such as HIV. While it is not a cure, ART can significantly prolong life and maintain health when taken consistently and correctly over the patient's lifetime [16]. The history of HIV treatment can be divided into three main eras: monotherapy (beginning in 1987) which utilized a single nucleoside reverse transcriptase inhibitor (NRTI); dual therapy (beginning in 1992) involving the combination of two NRTIs; and triple therapy (initiated in 1996), which uses drugs from at least two different classes, including non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) [9].

Currently, the standard of care is triple therapy with agents from at least two drug classes. Modern antiretroviral drugs fall primarily into two categories: reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) [10, 16, 4]. RTIs inhibit the

conversion of viral RNA into DNA, thereby preventing its integration into the host genome and blocking the infection of new T-cells. RTIs are further classified into nucleoside (NRTIs) and non-nucleoside (NNRTIs) inhibitors. In contrast, protease inhibitors target a different stage of the viral lifecycle, preventing the cleavage of viral proteins necessary for assembling functional new virions, thereby reducing the production of infectious virus particles [9]. Together, these drugs maintain the viral load at minimal levels, halt disease progression, prevent further immune damage, and support immune recovery [4].

If the HIV strain (meaning a genetic variant or subtype of the virus) develops resistance, it is necessary to switch drug cocktails. If we make an early switch we will lose the months or years of potential further survival benefit from the effective drug and if we make a late switch, we will compromise the effectiveness of the new drug and also increasing the risk of death [4]. Since both have consequences, the objective of this study is to find if there is an optimal time to switch treatments. We want to achieve an exact or a range of time to switch that will maximize the advantage of late switch and minimize the disadvantage of early switch.

1.3. Objectives

The General objective of this study is

- To construct a mathematical model that describes the dynamics of HIV progression under antiretroviral therapy (ART), incorporating drug resistance and treatment switching.

and the specific objectives of the study are

- To integrate switching behavior k_{ij} between drug regimens into the model, accounting for clinical thresholds such as CD4 counts in the patients blood.
- To explore the impact of switching between different classes of ART drugs (e.g., NRTIs, NNRTIs, PIs, integrase inhibitors) on resistance dynamics and outcomes.

1.4. Thesis structure

The thesis is structured as follows in the first chapter background, statement of the problem and objective of the study was stated. Chapter two is devoted to reviewing literature related to the topic and also give mathematical backgrounds used in the thesis. In chapter three the methodology used, that is, construction of the system of ODEs and its analysis was discussed. In Chapter four numerical simulations and their discussion-swas resented. The last chapter gives a summerized conclusion of the thesis and gives possible recomendations.

Chapter 2

Literature Review

2.1. Literature review

Diekmann et al. (1990) gave a milestone in epidemiological modeling with the use of the basic reproduction number (R_0) as a sharp global threshold for transmission in a combination of diverse populations. In their influential book, they also mathematically defined R_0 as the spectral radius (first eigenvalue) of the next-generation matrix formed with two principal components: the new infection matrix F and the disease transition matrix V (e.g., recovery, death).

Subscribing to the definition $R_0 = \rho(FV^{-1})$, in which ρ represents the spectral radius, the authors provided a formulaic method for assessment of disease persistence ($R_0 > 1$) or elimination ($R_0 < 1$) in a heterogeneously divided, complex population (e.g., geographic sub-divisions or age strata). This strategy filled long-standing disconnects within homogeneous models by introducing contact-pattern and rate heterogeneity and making explicit how subgroup highly connected agents (e.g., school children), could cause super-amplification of R_0.

The model was simple, employing deterministic dynamics and fixed populations, with interventions such as vaccination ruled out and stochastically, or population dynamics allowed. Despite these assumptions, Diekmann et al.'s approach remained the template for the computation of R_0, the cornerstone of modern disease research from HIV to

COVID-19. Their approach set the stage for subsequent generalizations, such as adding control measures and remains a mainstay of theoretical epidemiology.

Van den Driessche and Watmough (2002) took epidemiological modeling further by interpreting the next-generation matrix (NGM) method in the context of calculating the basic reproduction number R_0 for compartmental disease models. It provided a foundation upon which interventions such as vaccines or treatments could be developed and tested. Critical to their design was splitting the population (e.g., Susceptible S, Infected I, Recovered R) and completely separating infected compartments (e.g. Exposed E) from uninfected compartments. The NGM approach is based on two matrices: F (new infection) and V (compartment moves and transitions). F has transmission terms such as βSI, while V has recovery (γI) and death (μI)terms. The basic reproduction number is the spectral radius (largest eigenvalue) of FV^{-1}, i.e., $R_0 = \rho(FV^{-1})$. For the simple SIR model with vaccination, this gives:

$$R_0 = \frac{\beta S_0}{\gamma + \mu},$$

where S_0 is the initial number of susceptibles. The authors concluded that $R_0 > 1$ ensures disease persistence, while $R_0 < 1$ leads to eradication. They discovered, however, the possibility of sub-threshold endemic equilibria (i.e., backward bifurcations due to reinfection), where disease can persist even if $R_0 < 1$, which complicates the control measures.

Their deterministic model utilized time-constant parameters and assumed homogeneous mixing, excluding stochastic processes, demographic heterogeneity, and network-mediated interactions. Despite these simplifications, their work was the foundation of much contemporary outbreak modeling (e.g., COVID-19, Ebola) and supports most contemporary policy design frameworks. Van den Driessche and Watmough's paper [15] is a theoretical epidemiology keystone and necessary pivot linking the Diekmann et al. (1990) [3] R_0 theory and applied public health guidance.

Wu et al. (2007) [18] developed a deterministic compartmental model to analyze the

development of resistance of HIV under antiviral treatment, emphasizing interactions between viral mutation, treatment compliance, and fitness costs. Their mathematical model divided the system into target cells (T), virus-secreting infected cells of wild-type (I_w) or resistant (I_r) phenotype, and free virus particles (V_w, V_r). The dynamics were governed by the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - d_T T - \beta T(V_w + V_r), \\
\frac{dI_w}{dt} &= (1-m)\beta T V_w - \delta I_w - \eta_w I_w, \\
\frac{dI_r}{dt} &= m\beta T V_w + \beta T V_r - \delta I_r - \eta_r I_r, \\
\frac{dV_w}{dt} &= k_w I_w - c V_w, \\
\frac{dV_r}{dt} &= k_r I_r - c V_r.
\end{aligned}$$

Here, λ is the rate of target cell production, β the infection rate, m the mutation rate from wild-type to resistant virus, η_w and η_r the drug efficacy against wild-type and resistant strains, respectively, and k_w, k_r the viral production rates (with $k_r < k_w$ representing the fitness cost of resistance). The model revealed a critical paradox: increased drug adherence (higher η_w) suppressed wild-type virus but favored the emergence of resistant strains by allowing pre-existing mutants to dominate. A mutation threshold m_c was identified, above which resistance emerged even under perfect adherence. However, highly costly resistant strains (where $k_r \ll k_w$) remained suppressed unless drug pressure was intense.

The main limitations of this model were its deterministic nature (excluding stochastic extinction of mutants) and idealized drug kinetics (constant efficacy, no combination therapies). Nonetheless, the study demonstrated the inevitability of resistance in monotherapy and supported the use of combination antiretroviral therapy. Wu et. al.'s[18] work laid the foundation for later models that incorporated pharmacokinetics, immune dynamics, and stochastic processes, which remain central to understanding HIV adaptation under therapeutic pressure.

Asfaw's 2012 thesis [2], *"Modelling Treatment Switching: As drug resistance develops for HIV, patients may switch from one drug cocktail to another. Is there an optimal time to switch treatments? "*, addresses how and when to change antiretroviral therapies (ARTs) to maximize drug effectiveness and limit resistance. As in classical epidemiological models, the study applies the basic reproduction number (R_0) using next-generation matrix formulations [3] and compartmental ODE models[15]. Asfaw structures HIV transmission via R_0 thresholds across four population groups namely ; Susceptible (S), Primarily infected (P), Treatment-eligible (Y), On-treatment (T). The basic reproduction number is divided into stage-specific components: $R_0 = R_0^P + R_0^Y + R_0^T$, where R_0^P, R_0^Y, and R_0^T correspond to the respective stages. These interact through: Transmission rates: β, β^Y, β^T, Adherence parameters: V_i, w_i, Resistance rates: k_{ij}.

For instance, R_0 increases when treatment switching is delayed, as infection spreads and resistance levels (k_{ij}) drop.

The model uses a deterministic system of ordinary differential equations (ODEs) to describe transitions between stages. Treatment switching (e.g., from first-line T_1 to second-line T_2) is activated by resistance build-up. The assumptions include: Linear progression: $P \to Y \to T$, Homogeneous mixing of individuals, Constant transmission and mortality rates (e.g., β, μ), Fixed resistance rates k_{ij} (no cross-resistance), and Time-invariant education efficacy parameters: η, η_Y, η_T. In their result they show that: The disease-free equilibrium (DFE) is stable when $R_0 < 1$, This can be achieved by educating primarily infected individuals (P) to reduce β, If $R_0 > 1$, an endemic equilibrium arises, indicating persistent transmission.

The study has some limitations such as no stochastic effects (e.g., random outbreaks), No demographic variation (e.g., age, migration), No viral mutation or variable adherence, Parameters drawn from literature, not real data.

The model builds on classical frameworks such as Ross-Macdonald and Anderson & May models, extending them with HIV-specific mechanisms like treatment switching and resistance.

While [18] focused on real-time R_0 estimation for SARS, Asfaw emphasizes long-term ART planning and the role of education in mitigating transmission. However, the thesis does not incorporate recent developments such as time-varying R_t or machine learning-based parameter estimation, showing a preference for classical methods.

Policy implications:

- Switching ART after around 6 years is recommended to contain resistance,
- Education of primarily infected individuals is more effective than targeting treated patients,
- Expanding ART coverage and monitoring k_{ij} is vital for global HIV control.

In summary, [2] successfully bridges theory and practice in HIV modeling. While deterministic and simplified, the model emphasizes R_0-based thresholds for public health policy and leaves room for future extensions including stochasticity and adaptive treatment strategies.

2.2. Mathematical Preliminaries

This section provides basic mathematical notions applied in this thesis. It discusses the definition of ordinary differential equations (ODEs), equilibrium analysis, definition of the basic reproduction number, and methods of stability analysis and in particular the Routh–Hurwitz criterion. All of these are useful techniques for compartmental models analysis in epidemiology, e.g., HIV transmission dynamics with treatment switching.

2.2.1. Ordinary Differential Equations

An **ordinary differential equation (ODE)** of order n is an equation involving the derivatives of an unknown function $y(t)$, written as:

$$F\left(t, y, y', y'', \ldots, y^{(n)}\right) = 0. \tag{2.1}$$

Definition 1 *A **system of ODEs** is a set of equations involving multiple functions and their derivatives:*

$$\frac{d\mathbf{x}(t)}{dt} = \mathbf{F}(t, \mathbf{x}(t)), \tag{2.2}$$

where $\mathbf{x}(t) = [x_1(t), x_2(t), \ldots, x_n(t)]^T$ *and* $\mathbf{F} : \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}^n$.

If the right-hand side of a system of ODEs does not depend explicitly on time t, then the system is called **autonomous**:

$$\frac{d\mathbf{x}(t)}{dt} = \mathbf{F}(\mathbf{x}(t)). \tag{2.3}$$

ODEs and their systems form the mathematical foundation for dynamic models in biological and epidemiological studies [12].

2.2.2. Equilibrium Points and Local Stability

A point $\mathbf{x}^* \in \mathbb{R}^n$ is called an **equilibrium point** of the autonomous system $\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x})$ if

$$\mathbf{F}(\mathbf{x}^*) = \mathbf{0}. \tag{2.4}$$

Theorem 1 (Linear Stability via Jacobian) *Let* $\mathbf{x}^*$ *be an equilibrium point of the system* $\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x})$. *The local behavior near* $\mathbf{x}^*$ *is determined by the Jacobian matrix* $J = D\mathbf{F}(\mathbf{x}^*)$. *If all eigenvalues of* J *have negative real parts, then* $\mathbf{x}^*$ *is **locally asymptotically stable**.*

2.2.3. Routh–Hurwitz Stability Criterion

Theorem 2 (Routh–Hurwitz Stability Criterion [11]) *Consider a characteristic polynomial:*

$$P(\lambda) = a_n\lambda^n + a_{n-1}\lambda^{n-1} + \cdots + a_1\lambda + a_0. \tag{2.5}$$

All roots of $P(\lambda)$ have negative real parts (i.e., the system is stable) if and only if:

1. *All coefficients $a_i > 0$.*

2. *All elements of the first column of the Routh array are positive.*

2.2.4. Basic Reproduction Number R_0

The basic reproduction number (R_0), a dimensionless metric fundamental to epidemiology, originated in foundational studies dating to the 1880s [7]. Its formal application to disease dynamics began with Ross (1911) and MacDonald (1952) in malaria research [16]. Today, R_0 is very crucial for analyzing infectious disease spread. Epidemic severity correlates directly with R_0: values exceeding 1 indicate persistent transmission, with higher values implying greater challenges for containment [7]. By solving $R_0 = 1$, critical thresholds for vaccination coverage, treatment efficacy, or behavioral interventions required for eradication can be derived [16].

Biologically, R_0 represents "the expected number of secondary infections caused by a typical infectious individual in a fully susceptible population" [3]. An epidemic propagates when $R_0 > 1$ (each infection spawns > 1 new case) but declines when $R_0 < 1$ [3]. While multiple methods compute R_0, this work employs two:

1. **Next-generation method** for disease-free equilibrium,

2. **Constant-term method** for endemic equilibrium.

For the next-generation approach [3, 15], R_0 equals the spectral radius of FV^{-1}, where F is the Jacobian matrix of new infection rates, and V is the Jacobian of net transfer rates between compartments ($V = V^- - V^+$).

The constant-term method [7] simplifies stability analysis at endemic equilibrium (EE). After evaluating the system's Jacobian ($J_{\text{ac}}|_{\text{EE}}$) and solving the characteristic equation

$$\det(J_{\text{ac}}|_{\text{EE}} - \lambda I_n) = 0, \tag{2.6}$$

the resulting polynomial is

$$\lambda^n + p_{n-1}\lambda^{n-1} + \cdots + p_1\lambda + p_0 = 0.$$

When $n-1$ roots have negative real parts and coefficients $p_1, \ldots, p_{n-1} > 0$:

- $p_0 = 0$ implies marginal stability (zero dominant eigenvalue),
- $p_0 > 0$ guarantees asymptotic stability (all $\mathrm{Re}(\lambda) < 0$),
- $p_0 < 0$ indicates instability (positive real part in dominant λ).

Thus, EE stability hinges solely on p_0's sign.

Chapter 3

Methodology

3.1. Mathematical model of HIV

The Human Immunodeficiency Virus (HIV) and its advanced stage, Acquired Immunodeficiency Syndrome (AIDS), have remained a major global health concern since their emergence in the early 1980s. Despite significant advancements in prevention, treatment, and public health awareness, HIV/AIDS continues to impact millions of lives, particularly in low- and middle-income countries. Antiretroviral therapy (ART), introduced in the mid-1990s, has drastically improved the prognosis for people living with HIV by suppressing viral replication and enhancing immune function. However, challenges related to adherence to treatment, drug resistance, and equitable access persist.

Mathematical modeling plays an essential role in understanding the complex dynamics of HIV/AIDS transmission, progression, and treatment. These models provide insights into how the disease spreads through populations, evaluate the effectiveness of different intervention strategies, and support evidence-based policy decisions. By incorporating ART into these models, researchers can assess the impact of treatment coverage, timing, and adherence on both individual health outcomes and population-level disease dynamics.

3.2. The basic model

This mathematical model forecasts HIV disease transmission and treatment dynamics by incorporating hierarchical switching among antiretroviral therapies (ART) regimens. The whole population is divided into five compartments: susceptible individuals $S(t)$,infected individuals $I(t)$, and three treatment compartments $T_1(t)$, $T_2(t)$, and $T_3(t)$ for first-line, second-line, and third-line ART, respectively. Susceptibles S are entered into the system at rate Ω, and become infected through contact with either untreated infectives I or treated but still infectious T_j for $j = 1, 2, 3$. The infection rates from untreated and treated sources are β and $\beta_T > 0$, respectively. The compartment I consists of both untreated and treatment fail individuals. This is subject to a higher mortality rate μ due to suboptimal treatment. ART initiation follows a strict hierarchy, with initiation rates satisfying
$\theta_2 = \varepsilon_2\theta_1$ and $\theta_3 = \varepsilon_3\theta_1$, where $\varepsilon_2 \leq 0.1$ and $\varepsilon_3 \leq 0.01$
corresponding to realistic clinical constraints. Thus, most individuals initiate first-line treatment T_1, but some initiate directly in T_2 or T_3 due to drug intolerance, allergy, or previous drug resistance. Thus, the total initiation rate of treatment is given by

$$\theta_1 + \theta_2 + \theta_3 = \theta_1(1 + \varepsilon_2 + \varepsilon_3),$$

the reciprocal of the average treatment initiation time. This parameter is of specific interest to describe delays in care access. Transitions among treatment compartments occur hierarchically with patients moving from T_i to T_j $(i < j)$ at rate k_{ij} due to failure of treatment through drug resistance or drug toxicity. For example, k_{12} is moving from first-line to second-line. Mortality is also modeled with differentiation: untreated people in I have increased mortality rate μ compared to people on ART who have a reduced mortality rate μ_T, where μ_T accounts for the survival advantage from ART. Even with ART, there are some treatment compartment T_j individuals who remain infectious due to inadequate viral suppression, and this is accounted for by taking $\beta_T > 0$.

This is supplemented by treatment failure, accounted for by feedback terms in the form $w_j T_j$, moving individuals from the treatment class T_j back to the infected class I to account for non-compliance, drug resistance, or intolerance.

By incorporating these processes—regulated ART initiation, treatment failure, switching based on resistance, and mortality differences—the model estimates the effect of sequencing and clinical realities on long-term outcomes for HIV-infected individuals. The model offers guidance for optimizing the planning of ART policies by weighing the imperative of urgent earlier treatment initiation against the limits that result from limited availability of higher-line therapy. The differential equations corresponding to this model are given as

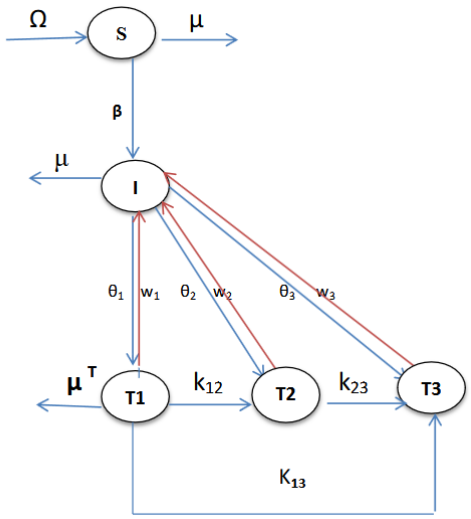

Figure 3.1: Flow diagram for the HIV treatment model

and the corresponding system of ODEs from the flowchart are give as in system 3.1

$$\frac{dS}{dt} = \Omega - \beta SI - \sum_{j=1}^{3} \beta_T S T_j - \mu S \tag{3.1}$$

$$\frac{dI}{dt} = \beta SI + \sum_{j=1}^{3} \beta_T S T_j + \sum_{j=1}^{3} w_j T_j - (\theta_1 + \theta_2 + \theta_3 + \mu_I) I \tag{3.2}$$

$$\frac{dT_1}{dt} = \theta_1 I - (w_1 + \mu_T + k_{12} + k_{13}) T_1 \tag{3.3}$$

$$\frac{dT_2}{dt} = \theta_2 I + k_{12} T_1 - (w_2 + \mu_T + k_{23}) T_2 \tag{3.4}$$

$$\frac{dT_3}{dt} = \theta_3 I + k_{13} T_1 + k_{23} T_2 - (w_3 + \mu_T) T_3 \tag{3.5}$$

β_T Transmission rate from treated individuals is smaller than β ,since people in I compartment has higher viral load) β greater than β_T

Population Boundedness

To establish the biological reasonableness and mathematical well-posedness of the model, we examine the dynamics of the total population. Let $N(t)$ represent the total population at time t, defined by

$$N(t) = S(t) + I(t) + T_1(t) + T_2(t) + T_3(t),$$

where $S(t)$ denotes the number of susceptible individuals, $I(t)$ the number of primary infected individuals, and $T_1(t)$, $T_2(t)$, and $T_3(t)$ represent the number of individuals on first-line, second-line, and third-line treatments, respectively.

By summing the right-hand sides of the differential equations for each compartment, we obtain the total population dynamic equation:

$$\frac{dN}{dt} = \Omega - \mu S - \mu_I I - \mu_T (T_1 + T_2 + T_3).$$

Given that individuals in the I compartment (infected and untreated) experience higher mortality (i.e., $\mu_I \gg \mu, \mu_T$), we consider the conservative upper-bound scenario by defining

$$\mu^* = \max\{\mu, \mu_I, \mu_T\}.$$

Substituting this into the total population equation gives the inequality:

$$\frac{dN}{dt} \leq \Omega - \mu^* N.$$

Solving this differential inequality reveals an upper bound on the total population. Assuming equilibrium, where $\frac{dN}{dt} = 0$, the critical value satisfies:

$$N \leq \frac{\Omega}{\mu^*}.$$

This shows that the total population is ultimately bounded by the ratio of the recruitment rate Ω to the maximum mortality rate μ^*. This boundedness ensures that all compartment populations remain finite and biologically meaningful for all future time. It also guarantees the solvability and robustness of the model in representing HIV dynamics and treatment-switching behaviors.

Equilibrium points

Equilibrium point is a solution obtained by putting the right hand side of equations((3.1)-(3.5)) equal to zero. The trivial solution is called disease-free.

The disease-free equilibrium (DFE) is when there is no disease; that is, $I = 0$ and $T_1 = T_2 = T_3 = 0$ then $N = S$. Hence we have $\Omega - \mu S = 0$ which implies $S = \Omega/\mu$. Thus the DFE is given by

$$(\overline{S}, \overline{I}, \overline{T}_1, \overline{T}_2, \overline{T}_3) = (\Omega/\mu, 0, 0, 0, 0). \tag{3.6}$$

In order to make the analysis, we subdivide the system into two subdivision. The first one is using only one treatment class-that is, without treatment switching-and the second one is allowing individuals to leave the treatment class and move to the other.

3.3. Treatment Without Switching

Focusing on the wild-type virus under the first treatment class (i.e., considering the compartments S', I', T_1'), we derive the equilibrium values, compute the basic reproduction number, and analyze the stability of the equilibrium points.

3.3.1. The First sub-model :

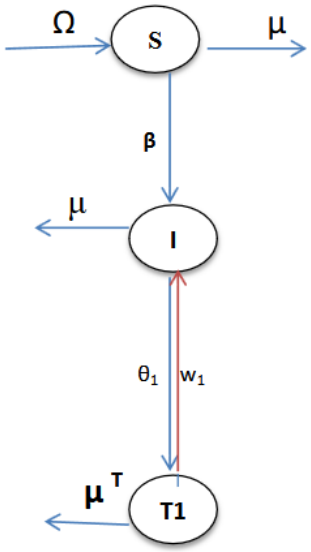

Figure 3.2: Flow diagram for the HIV treatment model

We consider a simplified scenario where HIV-infected individuals are either untreated or on first-line antiretroviral therapy (ART), with no switching to higher regimens. The population is divided into three compartments: susceptibles $S(t)$, infected individuals $I(t)$, and first-line treated individuals $T_1(t)$. The model equations are:

$$
\begin{aligned}
S' &= \Omega - \beta SI - \beta_T ST_1 - \mu S, \\
I' &= \beta SI + \beta_T ST_1 - (\theta_1 + \mu_I)I + w_1 T_1, \\
T_1' &= \theta_1 I - (\mu_T + w_1)T_1.
\end{aligned} \tag{3.7}
$$

These equations describe the dynamics of infection and treatment under a first-line-only ART policy, capturing recruitment, transmission, treatment initiation, and attrition due to mortality and treatment failure.

Disease-Free Equilibrium

We consider HIV dynamics under first-line treatment only and no switching in the first sub-model. To study the long-term behavior of the system, we start with the determination of the disease-free equilibrium (DFE), which represents the equilibrium where no infection exists in the population. At the DFE, both the infected and the treated populations are at zero level, i.e., $I = 0$ and $T_1 = 0$. With this condition, the only active equation is for the susceptible class.

Setting the steady-state equation to zero:

$$S' = \Omega - \mu S = 0,$$

we solve for S to get:

$$S^* = \frac{\Omega}{\mu}.$$

Hence, the disease-free equilibrium point is given by:

$$(S^*, I^*, T_1^*) = \left(\frac{\Omega}{\mu}, 0, 0\right). \tag{3.8}$$

This equilibrium describes the situation under which HIV is completely absent from the population and provides a reference point for analyzing the possibility of disease invasion and evaluating control strategies. To determine the threshold condition for disease invasion, we compute the basic reproduction number, denoted R_0, for the given

model. This value represents the average number of secondary infections caused by a single infected individual in a fully susceptible population. To compute this threshold we use the *Next Generation Matrix (NGM)* method.

The infected compartments are I and T_1. Let $x = (I, T_1)^T$ be the vector of infected variables. The infection and transition terms from the second and third equations of (3.7) are:

$$\mathcal{F}(x) = \begin{bmatrix} \beta SI + \beta_T S T_1 \\ 0 \end{bmatrix}, \quad \mathcal{V}(x) = \begin{bmatrix} (\theta_1 + \mu_I)I - w_1 T_1 \\ -\theta_1 I + (\mu_T + w_1)T_1 \end{bmatrix}.$$

Evaluating at the DFE, where $S = \dfrac{\Omega}{\mu}$, we compute the Jacobian matrices:

$$F = \begin{bmatrix} \beta\dfrac{\Omega}{\mu} & \beta_T\dfrac{\Omega}{\mu} \\ 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \theta_1 + \mu_I & -w_1 \\ -\theta_1 & \mu_T + w_1 \end{bmatrix}.$$

The determinant of V is:

$$\begin{aligned} \det(V) &= (\theta_1 + \mu_I)(\mu_T + w_1) - \theta_1 w_1. \\ \det(V) &= \theta_1\mu_T + \mu_I(\mu_T + w_1) \end{aligned}$$

The inverse of V is:

$$V^{-1} = \frac{1}{\det(V)} \begin{bmatrix} \mu_T + w_1 & w_1 \\ \theta_1 & \theta_1 + \mu_I \end{bmatrix}.$$

The next generation matrix is:

$$FV^{-1} = \frac{1}{\det(V)} \begin{bmatrix} \beta\dfrac{\Omega}{\mu} & \beta_T\dfrac{\Omega}{\mu} \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \mu_T + w_1 & w_1 \\ \theta_1 & \theta_1 + \mu_I \end{bmatrix}.$$

Multiplying the matrices gives:

$$FV^{-1} = \frac{1}{\det(V)} \cdot \begin{bmatrix} \frac{\Omega}{\mu}(\beta(\mu_T + w_1) + \beta_T\theta_1) & \frac{\Omega}{\mu}(\beta w_1 + \beta_T(\theta_1 + \mu_I)) \\ 0 & 0 \end{bmatrix}.$$

Since FV^{-1} is a rank-one matrix, the basic reproduction number R_0 is the spectral radius, which corresponds to the sum of the entries in the first row:

$$R_0 = \frac{1}{\det(V)} \cdot \frac{\Omega}{\mu} \left[\beta(\mu_T + w_1) + \beta_T\theta_1\right].$$

Simplifying the expression:

$$R_0^1 = \frac{\Omega\left(\beta(\mu_T + w_1) + \beta_T\theta_1\right)}{\mu[(\theta_1 + \mu_I)\mu_T + \mu_I w_1]}. \tag{3.9}$$

This expression defines the threshold value that determines whether the disease will spread in the population ($R_0 > 1$) or die out ($R_0 < 1$).

The stability of the disease-free equilibrium depends on the threshold R_0^1 . If $R_0^1 < 1$ then the DFE is stable, If $R_0^1 > 1$ then the DFE is unstable.

We derive the endemic equilibrium (S^*, I^*, T_1^*) of the system (3.7) by setting the derivatives in the model to zero.

At equilibrium, set all derivatives to zero:

$$0 = \Omega - \beta S^* I^* - \beta_T S^* T_1^* - \mu S^*, \tag{3.10}$$

$$0 = \beta S^* I^* + \beta_T S^* T_1^* - (\theta_1 + \mu) I^* + w_1 T_1^*, \tag{3.11}$$

$$0 = \theta_1 I^* - (\mu_T + w_1) T_1^*. \tag{3.12}$$

Here we are focusing for $I^* > 0$ First let us solve equation $T' = 0$ (3.12) for I^*.

$$T_1^* = \frac{\theta_1}{\mu_T + w_1} I^*$$

Then Substitute I^* into equation (3.10) we have,

$$\begin{aligned} 0 &= \Omega - \beta S^* I^* - \beta_T S^* T_1^* - \mu S^* \\ 0 &= \Omega - \beta S^* I^* - \beta_T S^* \frac{\theta_1}{\mu_T + w_1} I^* - \mu S^* \\ \Omega &= S^* I^* \left[\beta + \frac{\beta_T \theta_1}{\mu_T + w_1} \right] - \mu S^* \\ S^* &= \frac{\Omega(\mu_T + w_1)}{\mu(\mu_T + w_1) + I^*(\beta(\mu_T + w_1) + \beta_T \theta_1)} \end{aligned}$$

substituting in equation (3.11) and solve for I^*

we get

$$I^* = \frac{\Omega[\beta(\mu_T + w_1) + \theta_1 \beta_T] - \mu[(\theta_1 + \mu_I)(\mu_T + w_1) - w_1 \theta_1]}{\beta(\mu_T + w_1) + \theta_1 \beta_T)(\theta_1 + \mu_I - w_1 \theta_1)}$$

Therefore the endemic equilibrium point is given by

$$(S^*, I^*, T_1^*) = \left(\frac{\Omega(\mu_T + w_1)}{\mu(\mu_T + w_1) + I^*(\beta(\mu_T + w_1) + \theta_1 \beta_T)}, \quad I^*, \quad \frac{\theta_1}{\mu_T + w_1} \cdot I^* \right)$$

This endemic equilibrium exists and is biologically meaningful (i.e., all components positive) when the basic reproduction number $R_0 > 1$.indicating sustained transmission of infection in the population.

In this section, we investigate the local stability of the endemic equilibrium of the model using the Jacobian matrix and the constant-term method. The endemic equilibrium represents a steady-state solution where all three compartments (S^*, I^*, T_1^*) are non-zero, indicating persistent transmission of the infection within the population.

We denote the endemic equilibrium as (S^*, I^*, T_1^*), where $I^* > 0$ and $T_1^* > 0$. Our objective is to assess whether small perturbations around this equilibrium decay over time (i.e., stability), or grow (i.e., instability). To perform the stability analysis, we

compute the Jacobian matrix of the system evaluated at the endemic equilibrium:

$$J = \begin{bmatrix} \frac{\partial f_1}{\partial S} & \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial T_1} \\ \frac{\partial f_2}{\partial S} & \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial T_1} \\ \frac{\partial f_3}{\partial S} & \frac{\partial f_3}{\partial I} & \frac{\partial f_3}{\partial T_1} \end{bmatrix},$$

where f_1, f_2, and f_3 correspond to the right-hand sides of equations (1), (2), and (3), respectively.

Computing the partial derivatives, we obtain:

$$J = \begin{bmatrix} -\beta I^* - \beta_T T_1^* - \mu & -\beta S^* & -\beta_T S^* \\ \beta I^* + \beta_T T_1^* & \beta S^* - (\theta_1 + \mu) & \beta_T S^* + w_1 \\ 0 & \theta_1 & -(\mu_T + w_1) \end{bmatrix}$$

Evaluating at the endemic equilibrium and finding the eigenvalues by equating determinant of the characteristic equation to zero, we have

$$\det(J_{ac}|_{EE} - \lambda I_3) = 0$$

where λ is eigenvalue, a number, and $J_{ac}|_{EE}$ is a 3×3 matrix, we introduce I_3 which is a 3×3 identity matrix. Here the largest eigenvalue is the threshold. Using constant-term method (after checking the coefficients of λ are positive) we have found the value,

The characteristic polynomial of J is given by:

$$\det(J - \lambda I) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$$

Rather than computing all eigenvalues explicitly, we apply the *constant-term method* — a classical technique in dynamical systems. According to this method, the sign of the constant term a_3 (equal to $-\det(J)$) provides insight into stability:

- If $a_3 < 0$, then at least one eigenvalue has a positive real part $\Rightarrow$ **instability**.
- If $a_3 > 0$, and all other Routh–Hurwitz conditions are satisfied, then all eigenvalues

have negative real parts $\Rightarrow$ **local asymptotic stability**.

We compute the determinant of J at the endemic equilibrium:

$$\begin{aligned}\det(J) &= (-\beta I^* - \beta_T T_1^* - \mu)\left[(\beta S^* - \theta_1 - \mu)(-\mu_T - w_1) - (\beta_T S^* + w_1)\theta_1\right] \\ &= -(\beta I^* + \beta_T T_1^* + \mu) \cdot \left[(\beta S^* - \theta_1 - \mu)(\mu_T + w_1) + (\beta_T S^* + w_1)\theta_1\right]\end{aligned}$$

Therefore, the constant term in the characteristic polynomial is:

$$a_3 = -\det(J) = (\beta I^* + \beta_T T_1^* + \mu) \cdot \left[(\beta S^* - \theta_1 - \mu)(\mu_T + w_1) + (\beta_T S^* + w_1)\theta_1\right]$$

This expression is strictly positive under the following conditions:

- All model parameters are positive.
- $I^* > 0$, $T_1^* > 0$, and $S^* > 0$ (which holds when $R_0 > 1$).

Since the constant term a_3 is positive and all other coefficients of the characteristic polynomial are also positive under the same biological assumptions, it follows from the Routh–Hurwitz criteria that all eigenvalues of the Jacobian have negative real parts.

Therefore, the endemic equilibrium (S^*, I^*, T_1^*) is locally asymptotically stable whenever the basic reproduction number $R_{0ee} > 1$.

Substituting and simplifying:

$$\mathcal{R}_{0ee}^1 = \frac{\Omega}{\mu}\left(\beta\mu_I(\mu_T + w_1) + \beta_T w_1\right) \tag{3.13}$$

3.3.2. The second sub-model.

For the second class of treatment,

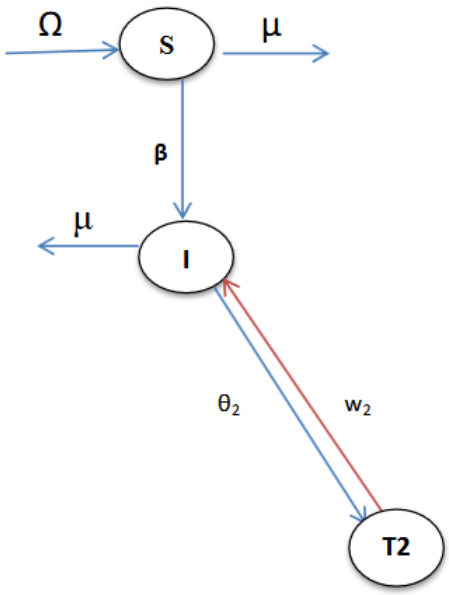

Figure 3.3: Flow diagram for the HIV treatment model

$$\begin{aligned}
\frac{dS}{dt} &= \Omega - \beta SI - \beta_T ST_2 - \mu S, \\
\frac{dI}{dt} &= \beta SI + \beta_T ST_2 + w_2 T_2 - (\theta_2 + \mu)I, \\
\frac{dT_2}{dt} &= \theta_2 I - (w_2 + \mu_T)T_2.
\end{aligned}$$

Here, the disease-free equilibrium is given by:

$$(S, I, T_2) = \left(\frac{\Omega}{\mu},\ 0,\ 0,\right)$$

Using the next-generation method, we have found that for class two, the basic reproduction number is

$$R_0^{(2)} = \frac{\dfrac{\Omega}{\mu}\left(\beta(\mu_T + w_2) + \beta_T\theta_2\right)}{(\theta_2 + \mu_I)(\mu_T + w_2) + \theta_2\mu_T} \tag{3.14}$$

We derive the endemic equilibrium (S^*, I^*, T_2^*) of the system by setting the derivatives in the model to zero. The system is:

$$\begin{aligned}
\frac{dS}{dt} &= \Omega - \beta SI - \beta_T ST_2 - \mu S, \\
\frac{dI}{dt} &= \beta SI + \beta_T ST_2 - (\theta_2 + \mu)I + w_2 T_2, \\
\frac{dT_2}{dt} &= \theta_2 I - (\mu_T + w_2)T_2.
\end{aligned}$$

At equilibrium, set all derivatives to zero:

$$0 = \Omega - \beta S^* I^* - \beta_T S^* T_2^* - \mu S^*, \tag{3.15}$$

$$0 = \beta S^* I^* + \beta_T S^* T_2^* - (\theta_2 + \mu)I^* + w_2 T_2^*, \tag{3.16}$$

$$0 = \theta_I^* - (\mu_T + w_2)T_2^*. \tag{3.17}$$

Solve equation (3.17) for T_2^*.

$$T_2^* = \frac{\theta_2}{\mu_T + w_2} I^*$$

Substitute T_2^* into equation (3.16).

$$0 = \beta S^* I^* + \beta_T S^* \left(\frac{\theta_2}{\mu_T + w_2} I^* \right) - (\theta_2 + \mu)I^* + w_2 \left(\frac{\theta_2}{\mu_T + w_2} I^* \right)$$

Factor out $I^* \neq 0$:

$$0 = I^* \left[\beta S^* + \frac{\theta_2 \beta_T}{\mu_T + w_2} S^* - (\theta_2 + \mu) + \frac{\theta_2 w_2}{\mu_T + w_2} \right]$$

Group terms:

$$\left(\beta + \frac{\theta_2 \beta_T}{\mu_T + w_2} \right) S^* = (\theta_2 + \mu) - \frac{\theta_2 w_2}{\mu_T + w_2}$$

Solve for S^*:

$$S^* = \frac{(\theta_2 + \mu)(\mu_T + w_2) - \theta_2 w_2}{\beta(\mu_T + w_2) + \theta_2 \beta_T} \tag{3.18}$$

Substitute T_1^* and S^* into equation (3.15) to find I^*.

$$0 = \Omega - \beta S^* I^* - \beta_T S^* \left(\frac{\theta_2}{\mu_T + w_2} I^* \right) - \mu S^*$$

Factor out I^*: in $0 = \Omega - S^* I^* \left(\beta + \dfrac{\beta_T \theta_2}{\mu_T + w_2} \right) - \mu S^*$

Solving for I^*: we have $I^* = \dfrac{\Omega - \mu S^*}{S^* \left(\beta + \dfrac{\beta_T \theta_2}{\mu_T + w_2} \right)}$

Recover T_2^* using equation (3) again. we have $T_2^* = \frac{\theta_2}{\mu_T + w_2} P^*$ Then the final Expression obtained is

$$(S^*, I^*, T_2^*) = \left(\frac{(\theta_2 + \mu)(\mu_T + w_2) - \theta_2 w_2}{\beta(\mu_T + w_2) + \theta_2 \beta_T}, \quad \frac{\Omega - \mu S^*}{S^* \left(\beta + \dfrac{\beta_T \theta_2}{\mu_T + w_2} \right)}, \quad \frac{\theta_2}{\mu_T + w_2} \cdot I^* \right) \tag{3.19}$$

The Jacobian for this second sub-model is

$$J = \begin{bmatrix} -\beta I^* - \beta_T T_2^* - \mu & -\beta S^* & -\beta_T S^* \\ \beta I^* + \beta_T T_2^* & \beta S^* - (\theta_2 + \mu) & \beta_T S^* + w_2 \\ 0 & \theta_2 & -(\mu_T + w_2) \end{bmatrix}$$

Evaluating at the endemic equilibrium and using the constant-term method, we find the threshold for the endemic equilibrium to be

$$\mathcal{R}_{0ee}^2 = \frac{\Omega}{\mu} \left(\beta \mu_I (\mu_T + w_2) + \beta_T w_2 \right) \tag{3.20}$$

3.3.3. The third sub-model.

Moreover, for the third class of treatment

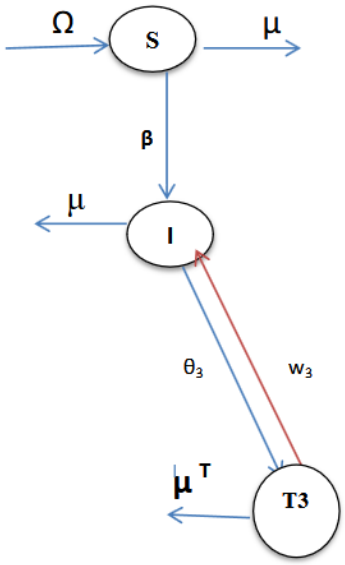

Figure 3.4: Model with treatment class three (T3)

$$S' = \Omega - \beta SI - \beta_T ST_3 - \mu S, \tag{3.21}$$

$$I' = \beta SI + \beta_T ST_3 - (\theta_3 + \mu)I + w_3 T_3, \tag{3.22}$$

$$T_3' = \theta_3 I - (\mu_T + w_3)T_3. \tag{3.23}$$

The disease-free equilibrium is the same as the other two cases, Thus

$$(S, I, T_3) = \left(\frac{\Omega}{\mu},\ 0,\ 0,\right)$$

and the threshold is

$$R_0^{(3)} = \frac{\dfrac{\Omega}{\mu}\left(\beta(\mu_T + w_3) + \beta_T\theta_3\right)}{(\theta_3 + \mu)(\mu_T + w_3) + \theta_3\mu_T} \tag{3.24}$$

The endemic equilibrium value :- Solve for S^*:

$$\begin{aligned} S^* &= \frac{(\theta_3+\mu)(\mu_T+w_3)-\theta_3 w_3}{\beta(\mu_T+w_3)+\theta_3\beta_T} \\ I^* &= \frac{\Omega-\mu S^*}{S^*\left(\beta+\dfrac{\beta_T\theta_3}{\mu_T+w_3}\right)} \\ T_3^* &= \frac{\theta_3}{\mu_T+w_3}I^* \\ (S^*,I^*,T_3^*) &= \left(\frac{(\theta_3+\mu)(\mu_T+w_2)-\theta_3 w_3}{\beta(\mu_T+w_3)+\theta_3\beta_T},\quad \frac{\Omega-\mu S^*}{S^*\left(\beta+\dfrac{\beta_T\theta_3}{\mu_T+w_3}\right)},\quad \frac{\theta_2}{\mu_T+w_3}\cdot I^*\right) \end{aligned}$$

The Jacobian for this third sub-model is

$$Jac=\begin{bmatrix} -\beta I^*-\beta_T T_3^*-\mu & -\beta S^* & -\beta_T S^* \\ \beta I^*+\beta_T T_3^* & \beta S^*-(\theta_3+\mu) & \beta_T S^*+w_3 \\ 0 & \theta_3 & -(\mu_T+w_3) \end{bmatrix}$$

Evaluating at the endemic equilibrium and using the constant-term method, we found the threshold

$$\mathcal{R}_{0ee}^3=\frac{\Omega}{\mu}\left(\beta\mu_I(\mu_T+w_3)+\beta_T w_3\right) \tag{3.25}$$

To give thresholds for the model without treatment switching, using the condition $\theta_1 >> \theta_2 >> \theta_3$, we can compare the three computed thresholds given by equations ((3.9)), ((3.14)), and ((3.24)) for the disease-free equilibrium, and take the maximum such that it can work for all sub-models:

$$\begin{aligned} R_0 &= \max\left\{R_0^{(1)},R_0^{(2)},R_0^{(3)}\right\} \\ R_0=R_0^1 &= \frac{\dfrac{\Omega}{\mu}\left(\beta(\mu_T+w_1)+\beta_T w_1\right)}{\mu(\mu_T+w_1)+\mu w_1} \end{aligned}$$

This expressions of the threshold can rewritten and be given biological meanings as the

sum of two R_0 as

$$R_0 = R_0^I + R_0^T$$

We can split the numerator and express this as the sum of two components:

Infection from untreated individuals (that is, from people in the infected compartment) :

$$R_0^I = \frac{\Omega}{\mu} \cdot \frac{\beta(\mu_T + w_1)}{\mu(\mu_T + w_1) + \mu w_1}$$

can be interpreted as: the probalikity of susceptibles $\frac{\Omega}{\mu}$ get infectiuos contact with an untreated individual causes disease during the time $\frac{1}{\mu + \frac{\theta_1 \mu_T}{\mu_T + \omega_1}}$ spent in the infection compartment I at infection rate β.

Infection from treated individuals:

$$R_0^T = \frac{\Omega}{\mu} \cdot \frac{\beta_T \theta_1}{\mu_I(\mu_T + w_1) + \theta_1 \mu_T}$$

where $R_0^T = \underbrace{\frac{\beta_T \Omega}{\mu}}_{\text{Infection potential}} \cdot \underbrace{\frac{w_1}{(\theta_1 + \mu)(\mu_T + w_1) - \theta_1 w_1}}_{\text{Average time in treatment class } (T)}$

Here, The first term, $\frac{\beta_T \Omega}{\mu}$, represents the number of new infections a treated individual can potentially cause per unit time, adjusted by recruitment and natural death. The second term, $\frac{w_1}{(\theta_1+\mu)(\mu_T+w_1)-\theta_1 w_1}$, gives the average time an individual spends in the treatment compartment, accounting for exit due to death, treatment success, or failure.

Hence, the disease-free equilibrium point given by equation ((3.8) equation number) is stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Similarly, we compare the endemic thresholds given by equations ((3.13)), ((3.20)), and ((3.25)) of the three systems of equations evaluated at the endemic equilibrium. By taking the maximum of these three thresholds, we ensure that the condition works for each sub-model, and we can conclude the threshold for the basic model as:

$$R_e = \max\left\{R_e^1, R_e^2, R_e^3\right\}.$$

This comparison is made using the same argument as in the case of disease-free equilibrium, under the assumption $\theta_1 << \theta_2 << \theta_3$.

$$\mathcal{R}_e = R_{e00}^1 = \frac{\Omega}{\mu}\left(\beta\mu_I(\mu_T + w_1) + \beta_T w_1\right) \tag{3.26}$$

Hence, the endemic equilibrium of the basic model without treatment switch is stable (i.e., the disease persists) if $R_e < 1$, and unstable if $R_e > 1$..

3.4. Treatment with switching

In our model, Let k be the rate of developing resistance to a treatment. Since R0 is based on newly infected individuals (the next-generation method), We will consider the case where leaving a system to another treatment class is allowed without considering entering the treatment class

3.4.1. The First sub model

The model focusing on the first treatment line T_1 with switching dynamics is:

$$\begin{aligned}
\frac{dS}{dt} &= \Omega - \beta SI - \beta_T ST_1 - \mu S,\\
\frac{dI}{dt} &= \beta SI + \beta_T ST_1 - (\theta_1 + \mu_I)I + w_1 T_1,\\
\frac{dT_1}{dt} &= \theta_1 I - (w_1 + \mu_T + k_{12} + k_{13})T_1
\end{aligned} \tag{3.27}$$

The disease-free equilibrium point for the system is given by:

$$(S^*, I^*, T_1^*) = \left(\frac{\Omega}{\mu},\ 0,\ 0\right)$$

To check the stability of this equilibrium point, we compute $\mathbb{R}_0$ using the next-generation

method, thus using the matrix f where the row represents new infections in each of the infection stages I, T_1 respectively.

$$\frac{d\mathbf{x}}{dt} = \mathcal{F}(\mathbf{x}) - \mathcal{V}(\mathbf{x}),$$

where

$$\mathcal{F}(\mathbf{x}) = \begin{bmatrix} \beta S^0 I + \beta_T S^0 T_1 \\ 0 \end{bmatrix}, \quad \mathcal{V}(\mathbf{x}) = \begin{bmatrix} (\theta_1 + \mu_I)I - w_1 T_1 \\ -\theta_1 I + (w_1 + \mu_T + k_{12} + k_{13})T_1 \end{bmatrix},$$

and $S^0 = \frac{\Omega}{\mu}$ is the susceptible population at disease-free equilibrium.

The Jacobians at the DFE are:

$$F = \begin{bmatrix} \beta S^0 & \beta_T S^0 \\ 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \theta_1 + \mu_I & -w_1 \\ -\theta_1 & w_1 + \mu_T + k_{12} + k_{13} \end{bmatrix}.$$

Let:

$$a = \theta_1 + \mu_I, \quad b = -w_1, \quad c = -\theta_1, \quad d = w_1 + \mu_T + k_{12} + k_{13}.$$

Then:

$$V^{-1} = \frac{1}{ad - bc} \begin{bmatrix} d & -b \\ -c & a \end{bmatrix}, \quad K = FV^{-1}.$$

The dominant eigenvalue of K gives R_0:

$$R_0 = \rho(K) = \frac{S^0 (\beta d + \beta_T \theta_1)}{ad - bc}.$$

Substituting $S^0 = \frac{\Omega}{\mu}$, we get:

$$R_0^1(k12, k13) = \frac{\frac{\Omega}{\mu} (\beta(w_1 + \mu_T + k_{12} + k_{13}) + \beta_T \theta_1)}{\theta_1(\mu_T + k_{12} + k_{13}) + \mu_I(w_1 + \mu_T + k_{12} + k_{13})}.$$

Let (S^*, I^*, T_1^*) denote the endemic equilibrium point of the system. At equilibrium, all time derivatives are zero, i.e.,

$$
\begin{aligned}
0 &= \Omega - \beta S^* I^* - \beta_T S^* T_1^* - \mu S^*, && (3.28)\\
0 &= \beta S^* I^* + \beta_T S^* T_1^* - (\theta_1 + \mu_I) I^* + w_1 T_1^*, && (3.29)\\
0 &= \theta_1 I^* - (w_1 + \mu_T + k_{12} + k_{13}) T_1^*. && (3.30)
\end{aligned}
$$

Solve Equation (3.30) for T_1^* Let

$$D := w_1 + \mu_T + k_{12} + k_{13}.$$

Then equation (3.30) becomes:

$$T_1^* = \frac{\theta_1}{D} I^*. \tag{3.31}$$

Substitute (3.31) into Equation (3.29)

$$
\begin{aligned}
0 &= \beta S^* I^* + \beta_T S^* \cdot \frac{\theta_1}{D} I^* - (\theta_1 + \mu_I) I^* + w_1 \cdot \frac{\theta_1}{D} I^* \\
&= I^* \left[\beta S^* + \frac{\beta_T \theta_1}{D} S^* - (\theta_1 + \mu_I) + \frac{w_1 \theta_1}{D} \right].
\end{aligned}
$$

Since $I^* \neq 0$, we obtain:

$$S^* \left(\beta + \frac{\beta_T \theta_1}{D} \right) = \theta_1 + \mu_I - \frac{w_1 \theta_1}{D}.$$

Hence,

$$S^* = \frac{\theta_1 + \mu_I - \dfrac{w_1 \theta_1}{D}}{\beta + \dfrac{\beta_T \theta_1}{D}}. \tag{3.32}$$

Substitute (3.32) to find I^*

substitute $T_1^* = \dfrac{\theta_1}{D} I^*$ and the expression for S^*:

$$\begin{aligned} 0 &= \Omega - \beta S^* I^* - \beta_T S^* \cdot \frac{\theta_1}{D} I^* - \mu S^* \\ &= \Omega - S^* I^* \left(\beta + \frac{\beta_T \theta_1}{D} \right) - \mu S^*. \end{aligned}$$

Solving for I^*:

$$S^* I^* \left(\beta + \frac{\beta_T \theta_1}{D} \right) = \Omega - \mu S^*,$$

$$I^* = \frac{\Omega - \mu S^*}{S^* \left(\beta + \dfrac{\beta_T \theta_1}{D} \right)}.$$

Compute T_1^* From equation (3.31) we have

$$T_1^* = \frac{\theta_1}{D} I^*.$$

Final Endemic Equilibrium:-

Let $D = w_1 + \mu_T + k_{12} + k_{13}$. Then:

$$\begin{aligned} S^* &= \frac{\theta_1 + \mu_I - \dfrac{w_1 \theta_1}{D}}{\beta + \dfrac{\beta_T \theta_1}{D}}, \\ I^* &= \frac{\Omega - \mu S^*}{S^* \left(\beta + \dfrac{\beta_T \theta_1}{D} \right)}, \\ T_1^* &= \frac{\theta_1}{D} I^*. \end{aligned}$$

The threshold for the endemic equilibrium is given by:

Using constant term method the threshold value for the endemic equilibrium point denoted by $R_e^{1(k12,k13)}$ is given by Simplifying:

$$\mathcal{R}_e^1(k12, k13) = \frac{\Omega}{\mu} \left(\beta \mu_I (\mu_T + w_1 + k_{12} + k_{13}) + \beta_T w_1 \right)$$

The threshold condition for the existence of an endemic equilibrium is:$\mathcal{R}_e > 1 \quad \Leftrightarrow$ Endemic equilibrium exists (i.e., $I^* > 0$, $T_1^* > 0$

3.4.2. Second sub model with switching

$$\begin{aligned}
\frac{dS}{dt} &= \Omega - \beta SI - \beta_{T_2} ST_2 - \mu S, \\
\frac{dI}{dt} &= \beta SI + \beta_{T_2} ST_2 - (\theta_2 + \mu_I) I, \\
\frac{dT_2}{dt} &= \theta_2 I - (w_2 + \mu_T + k_{23}) T_2.
\end{aligned}$$

The disease-free equilibrium point for the system is given by:

$$(S^*, I^*, T_1^*) = \left(\frac{\Omega}{\mu},\ 0,\ 0 \right)$$

To check the stability of this equilibrium point, we compute R0 using the next-generation method,

$$R_0^2(k23) = \frac{S^0(\beta D_2 + \beta_{T_2}\theta_2)}{(\theta_2 + \mu_I) D_2} = \frac{\dfrac{\Omega}{\mu}(\beta D_2 + \beta_{T_2}\theta_2)}{(\theta_2 + \mu_I) D_2}$$

At the endemic equilibrium, we set all derivatives to zero:

$$\frac{dS}{dt} = \frac{dI}{dt} = \frac{dT_2}{dt} = 0$$

Solve for T_2^*:-

From the third equation:

$$0 = \theta_2 I^* - D_2 T_2^* \quad \Rightarrow \quad T_2^* = \frac{\theta_2}{D_2} I^*$$

Solve for S^*:-

Substitute T_2^* into the second equation:

$$
\begin{aligned}
0 &= \beta S^* I^* + \beta_{T_2} S^* T_2^* - (\theta_2 + \mu_I) I^* \\
&= I^* \left(\beta S^* + \beta_{T_2} S^* \cdot \frac{\theta_2}{D_2} - (\theta_2 + \mu_I) \right)
\end{aligned}
$$

Solving for S^*, we get:

$$
S^* = \frac{\theta_2 + \mu_I}{\beta + \dfrac{\beta_{T_2} \theta_2}{D_2}}
$$

Solve for I^*:-

Substitute S^* into the first equation:

$$
0 = \Omega - \beta S^* I^* - \beta_{T_2} S^* T_2^* - \mu S^*
$$

Substitute $T_2^* = \dfrac{\theta_2}{D_2} I^*$:

$$
0 = \Omega - S^* I^* \left(\beta + \frac{\beta_{T_2} \theta_2}{D_2} \right) - \mu S^*
$$

Solving for I^*:

$$
I^* = \frac{\Omega - \mu S^*}{S^* \left(\beta + \dfrac{\beta_{T_2} \theta_2}{D_2} \right)}
$$

Solve for T_2^*

$$
T_2^* = \frac{\theta_2}{D_2} \cdot I^*
$$

Final Endemic Equilibrium:-

Let $C = \beta + \dfrac{\beta_{T_2} \theta_2}{D_2}$, then:

$$
\begin{aligned}
S^* &= \frac{\theta_2 + \mu_I}{C}, && (3.33) \\
I^* &= \frac{\Omega - \mu S^*}{S^* C}, && (3.34) \\
T_2^* &= \frac{\theta_2}{D_2} \cdot I^* && (3.35)
\end{aligned}
$$

The threshold for endemic equilibrium is The threshold for endemic equilibrium is

$$\mathcal{R}_e^{(2)}(k_{23}) = \frac{\Omega}{\mu}\left(\beta\mu_I(\mu_T + w_2 + k_{23}) + \beta_T w_2\right)$$

3.4.3. Third sub model with switching

$$\begin{aligned}
\frac{dS}{dt} &= \Omega - \beta SI - \beta_T ST_3 - \mu S, \\
\frac{dI}{dt} &= \beta SI + \beta_T ST_3 - (\theta_3 + \mu_I)I + w_3 T_3, \\
\frac{dT_3}{dt} &= \theta_3 I - (w_3 + \mu_T)T_3.
\end{aligned}$$

Hence the disease-free equilibrium is

$$\frac{dS}{dt} = \Omega - \mu S = 0 \quad \Rightarrow \quad S^0 = \frac{\Omega}{\mu}$$

Thus, the disease-free equilibrium is:

$$(S^0, I^0, T_3^0) = \left(\frac{\Omega}{\mu},\ 0,\ 0\right)$$

and the threshold is

$$R_0 = \frac{\dfrac{\Omega}{\mu}\left(\beta(w_3 + \mu_T) + \beta_T\theta_3\right)}{(\theta_3 + \mu_I)(w_3 + \mu_T) + \theta_3 w_3}$$

The endemic equilibrium value is

$$S^* = \frac{\theta_3 + \mu_I - \dfrac{w_3\theta_3}{w_3 + \mu_T}}{\beta + \dfrac{\beta_T\theta_3}{w_3 + \mu_T}},$$

$$I^* = \frac{\Omega - \mu S^*}{S^*\left(\beta + \dfrac{\beta_T\theta_3}{w_3 + \mu_T}\right)},$$

$$T_3^* = \frac{\theta_3}{w_3 + \mu_T} \cdot I^*$$

The threshold for the endemic equilibrium is

$$\mathcal{R}^3_{0ee} = \frac{\Omega}{\mu}\left(\beta\mu_I(\mu_T + w_3) + \beta_T w_3\right) \tag{3.36}$$

To determine the threshold condition for the full model described by equations(3.1), we compare the basic reproduction numbers of three sub-models. The basic reproduction number for the full system is then given by:

$$R_0(k) = \max\left\{R_0^{(1)}(k_{12}, k_{13}),\ R_0^{(2)}(k_{23}),\ R_0^{(3)}\right\}.$$

Since $\theta_1 >> \theta_2 >> \theta_3$, we can compare the contributions of the respective treatment pathways and use the largest sub-model reproduction number as the critical threshold for the overall system.

$$R_0(k) = R_0^1(k12, k13) = \frac{\frac{\Omega}{\mu}\left(\beta(w_1 + \mu_T + k_{12} + k_{13}) + \beta_T\theta_1\right)}{(\theta_1 + \mu_I)(w_1 + \mu_T + k_{12} + k_{13}) - w_1\theta_1}.$$

The threshold can be rewritten and given biological meaning as the sum of two components:

$$R_0(k) = R_0^I(k) + R_0^T(k)$$

where

$$R_0^I(k) = \frac{\frac{\Omega}{\mu}\beta(w_1 + \mu_T + k_{12} + k_{13})}{D}$$

represents infections from untreated individuals, and

$$R_0^T(k) = \frac{\frac{\Omega}{\mu}\beta_T\theta_1}{D}$$

represents infections from treated individuals, with

$$D = (\theta_1 + \mu_T)(w_1 + \mu_T + k_{12} + k_{13}) - w_1\theta_1.$$

Biological decomposition:

$$R_0^I(k) = \left(\frac{\beta\Omega}{\mu}\right) \times \left(\frac{w_1 + \mu_T + k_{12} + k_{13}}{D}\right)$$

$\frac{\beta\Omega}{\mu}$: Expected infections caused by one untreated individual per unit time in susceptible population $\frac{w_1 + \mu_T + k_{12} + k_{13}}{D}$: Effective time in untreated state, accounting for: Competing risks between treatment initiation (θ_1) and disease death (μ_T) Pathway transitions (k_{12}, k_{13}) Treatment progression (w_1)

$$R_0^T(k) = \left(\frac{\beta_T\Omega}{\mu}\right) \times \left(\frac{\theta_1}{w_1 + \mu_T + k_{12} + k_{13}}\right) \times \left(\frac{w_1 + \mu_T + k_{12} + k_{13}}{D}\right)$$

$\frac{\beta_T\Omega}{\mu}$: Expected infections caused by one treated individual per unit time

$\frac{\theta_1}{w_1 + \mu_T + k_{12} + k_{13}}$: Probability of entering treatment before exiting via:

- Disease death (μ_T)
- Alternative pathways (k_{12}, k_{13})
- Natural progression (w_1)

$\frac{w_1 + \mu_T + k_{12} + k_{13}}{D}$: Same duration factor as in $R_0^I(k)$

Hence, the disease-free equilibrium point given by equation ((3.8) equation number) is stable if $R_0 < 1$ and unstable if $R_0 > 1$.Similarly for the endemic threshold comparing equations

$$(R_e^{(1)}(k_{12}, k_{13})), (R_e^{(2)}(k_{23}))$$

and

$$(R_e^{(3)})$$

we have

$$R_e(k) = \max\left\{R_e^{(1)}(k_{12}, k_{13}),\ R_e^{(2)}(k_{23}),\ R_e^{(3)}\right\}$$

Because the rate of people who start treatment class one is higher than that of people who start treatment classes two T_2 and three T_3,

$$\mathcal{R}_e(k) = R_e(k12, k13) = \frac{(\beta D + \beta_T \theta_1)\left(\theta_1 + \mu_I - \dfrac{w_1\theta_1}{D}\right)}{[(\theta_1 + \mu_I)D - w_1\theta_1]\left(\beta + \dfrac{\beta_T\theta_1}{D}\right)}$$

Hence the endemic equilibrium of the whole basic model is stable or disease persists if $R_e(k) < 1$ and unstable if $R_e(k) > 1$.

In this chapter we find the threshold values for the disease-free equilibrium of a system that allows treatment switching R_0 and for the one that does not $R_0(k)$. In the next chapters, we give parameter values, find out factors that affect the thresholds most, and see how we can manage to keep the threshold values less than one to control and "eradicate" the disease.

3.5. Numerical analysis

This section focuses on the numerical simulation of the HIV transmission model developed in the previous sections. It focuses on how treatment works across three levels of antiretroviral therapy: first-line, second-line, and third-line treatments. The model goes into detail about starting treatment, what happens if it fails, and how patients switch between different treatments. Since we cannot find a simple analytical solution to the system of equations being used, we turn to numerical methods to study the model's behavior over time.

There are different Numerical methods to solve system of nonlinear equation such as the Euler method of order 2 Runge Kutta of order 4 and order 6 and so on.

We use **python** for our purpose because it is an open source software and user friendly, specifically the *ode45* function, which is based on the classical fourth-order Runge-Kutta method with adaptive step size control.

Chapter 4

Result and Discussion

Using the parameter values from table 4.2 and initial conditions from table 4.1 simulation that runs for 100 days was computed and tracks changes in the numbers of susceptible, infected, and treated individuals while varying certain key parameters. These parameters, such as infection rates, death rates, and treatment switching rates, are obtained from existing literature, including[2] and references therein. The aim of this analysis is to examine how changing treatment switching strategies affects HIV transmission and disease progression. We aim to highlight the differences in outcomes between delayed and early treatment switching, and how each line of treatment contributes to reducing the infected population over time. The results of the simulation are presented graphically and interpreted with respect to public health impact and treatment effectiveness.

Table 4.1: Initial conditions

$S(0)$	$I(0)$	$T_1(0)$	$T_2(0)$	$T_3(0)$
40	5	7	5	2

Table 4.2: Parameter values used in the simulation over 100 days

Parameter	**Value**	**Parameter**	**Value**
Ω	8.4	θ_1	0.02
β	0.005	θ_2	0.015
β_T	0.009	θ_3	0.01
μ	0.03	w_1	0.01
μ_I	0.2	w_2	0.015
μ_T	0.07	w_3	0.02
k_{12}	0.01	k_{13}	0.005
k_{23}	0.008		

Table 4.3: Basic reproduction number and infection outcome

Scenario	β	β_T	R_0 / Infection Outcome
Original	0.005	0.009	$R_0 = 1.9789 > 1 \Rightarrow$ Infection persists
After change	0.002	0	$R_0 < 1$ (assumed) $\Rightarrow$ Infection dies out

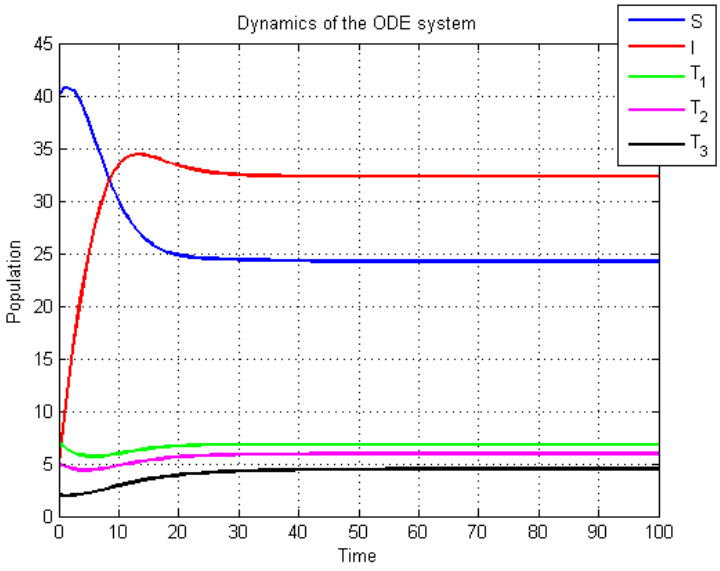

Figure 4.1: Dynamics of system variables with parameters chosen so that $R_0 > 1$.

Figure 4.1 illustrates the dynamics of the HIV treatment model over time when the basic reproduction number $R_0 > 1$, indicating that the disease can spread and persist within the population. The horizontal axis represents time, while the vertical axis shows the population size in each compartment. Initially, the susceptible population (S), shown in blue, is high but decreases rapidly as individuals become infected and enter treatment. The number of individuals on first-line treatment (T_1), represented by the red curve, rises quickly and stabilizes at a higher level, reflecting the immediate response to new infections. Second-line (T_2, green) and third-line (T_3, black) treatment populations start low and increase gradually, as some individuals fail previous treatment regimens and transition to more advanced therapy options. Over time, all compartments approach steady-state values, demonstrating the system's convergence to an endemic equilibrium. This outcome confirms that, under the condition $R_0 > 1$, the infection remains in the population and continuous treatment is necessary to manage its progression.

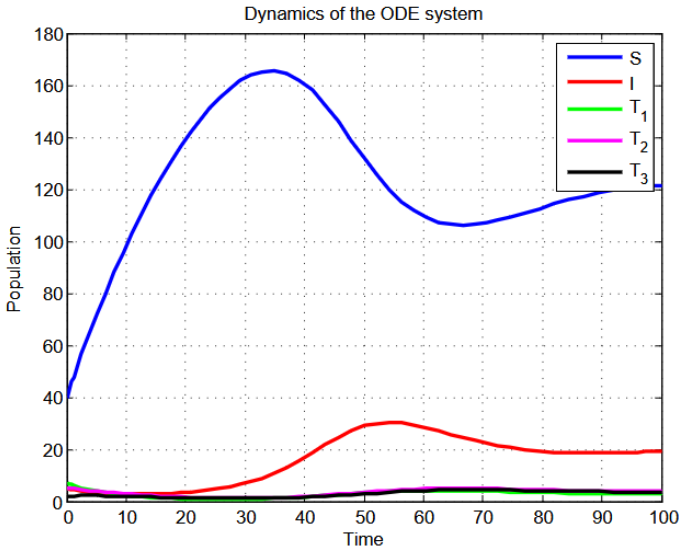

Figure 4.2: HIV dynamics over 100 days with $\mathcal{R}_0 = 0.8508 < 1$.

Figure 4.2 illustrates the dynamics of HIV infection over a period of 100 days, where the basic reproduction number is $\mathcal{R}_0 = 0.8508$, indicating the persistence of infection but at a much smaller rate . The number of susceptible individuals does not declines ,

driven by a low transmission rate ($\beta = 0.002$, $\beta_T = 0.0$). The infected population peaks early at approximately 34 individuals and stabilizes around 32–33, reflecting ongoing treatment failures characterized by rates $w_1 = 0.01$, $w_2 = 0.015$, and $w_3 = 0.02$. The treated compartments (T_1, T_2, and T_3) undergo redistribution through switching rates k_{12}, k_{13}, and k_{23}. This simulation underscores the importance of targeted interventions. Strategies such as reducing transmi1ssion (β), accelerating treatment initiation (θ_1), or optimizing treatment switching can help reduce $\mathcal{R}_0$ below 1, thereby eliminating the possibility of endemic persistence.

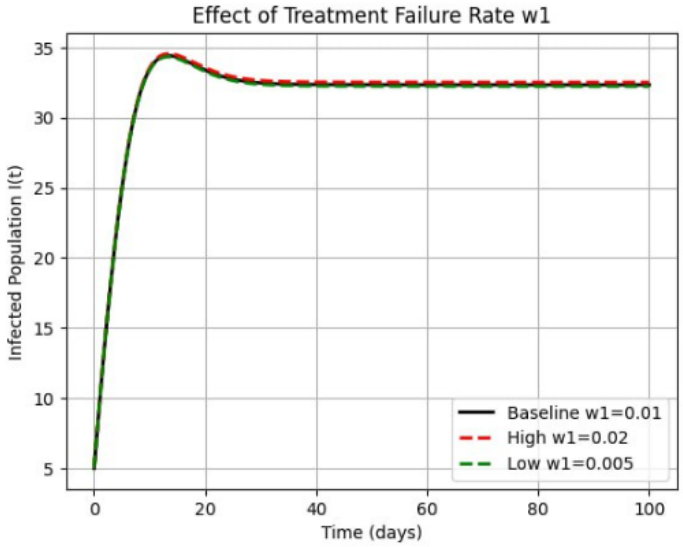

Figure 4.3: Effect of treatment failure rate w_1 on HIV dynamics.

Fig 4.3 shows how different treatment failure rates affect the number of infected people over 100 days. You can see that the number of infections jumps up quickly in all cases, hitting a high point around days 10 to 15 before leveling off. We looked at three failure rate scenarios: a baseline rate (0.01), a high rate (0.02), and a low rate (0.005). With a higher treatment failure rate, the steady number of infections is a bit higher, while a lower rate shows a slight drop. Even with these changes, the initial outbreak dynamics, like when the peak happens and how high it gets, stay pretty much the same. This shows that treatment failure doesn't greatly impact the peak or timing of the outbreak, but it does seem to influence the long-term number of infections. So, making treatments

more effective can really help lower ongoing infections and boost public health during the disease's endemic stage.

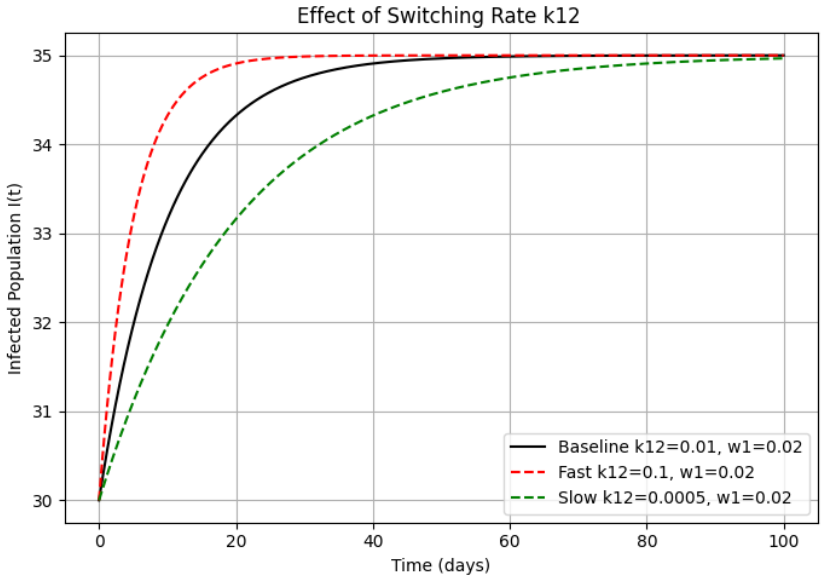

Figure 4.4: Effect of switching rate k_{12} on treated compartments.

Fig 4.4 illustrates the significant impact of varying the switching rate parameter k_{12} on the dynamics of a system over a 100-day period, while keeping another parameter w_1 constant at 0.02. The vertical axis represents some measured quantity (such as concentration or population size), starting around 35 and ending near 30. Three scenarios are compared: a baseline case ($k_{12} = 0.01$), a fast switching case ($k_{12} = 0.1$), and a slow switching case ($k_{12} = 0.0005$). Faster switching ($k_{12} = 0.1$) produces the highest initial level but also the steepest decline, resulting in the lowest final value by day 100. Conversely, slower switching ($k_{12} = 0.0005$) starts at a lower initial level but shows minimal decline over time, maintaining the highest final level. The baseline scenario ($k_{12} = 0.01$) exhibits intermediate behavior in both its starting point and decay rate. The key takeaway is that a higher k_{12} enables rapid achievement of a high state but leads to faster depletion and lower long-term levels, while a lower k_{12} causes slower buildup to a lower peak but sustains levels much more effectively over time. This demonstrates a fundamental trade-off between initial magnitude and long-term stability governed by

the switching rate.

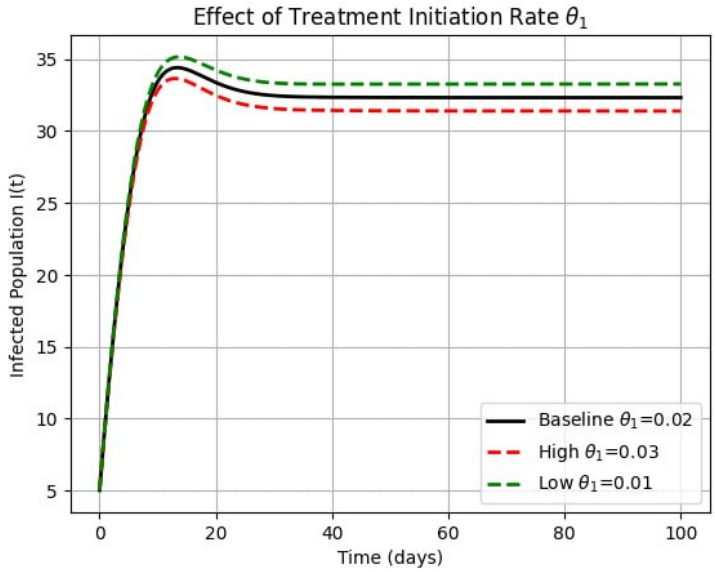

Figure 4.5: Effect of treatment initiation rate θ_1 on disease dynamics.

The Figure 4.5 shows how different treatment start rates (θ_1) affect the number of infected people $I(t)$ over 100 days. At the baseline rate ($\theta_1 = 0.02$), the number of infections rises quickly, peaks around day 15, and then levels off. When the treatment start rate is increased to $\theta_1 = 0.03$ (red dashed line), the peak infection level is lower, and fewer people remain infected in the long run. This indicates that initiating treatment sooner can effectively slow the spread of the illness.Conversely, a lower treatment start rate ($\theta_1 = 0.01$, green dashed line) leads to a higher peak and more individuals ending up chronically infected. This underscores the importance of timely treatment initiation.Overall, the model suggests that quicker and more accessible treatment significantly reduces infection rates in a community, highlighting that early treatment is key for public health.

Chapter 5

Conclusion and Recommendation

5.1. Conclusion

This thesis presents a deterministic mathematized model that well explores the complex dynamics of HIV transmission in the context of an antiretroviral therapy (ART) multi-stage environment. By extending the classical Susceptible-Infected-Treated (SIT) model into a five-compartment framework (S, I, T1, T2, T3), this research yields significant insights towards optimizing ART regimes against drug resistance. The key innovation of the model is its formal explicitation of hierarchical switching of treatment, and it presents a complex analysis of patient flow after failure or toxicity between first-, second-, and third-line treatments. Analytically, the study established the basic reproduction number (R_0) as the key epidemiological threshold. Disease-free and endemic equilibrium stability were discovered to be highly sensitive to the initial rate of treatment initiation (θ_1) and the standard transmission rate (β). Decomposition of R_0 revealed that ART reduces infectiousness by a significant portion but that treated individuals may continue to drive transmission, pointing to the necessity for high viral suppression levels.

Numerical simulations strongly corroborated these findings, demonstrating the tangible impact of policy choices. The results unambiguously identify an elevated treatment initiation rate (θ_1) as the most powerful instrument to manage epidemics. A rise in θ_1 not only reduces the long-term endemic equilibrium, but also reduces and retards the

first peak in infection, reducing the overall burden on healthcare systems. While treatment failure parameters (w_i) and switch parameters (k_{ij}) matter for long-term cohort management, these have secondary impact relative to direct impact of early first-line initiation.

Crystal-clear public health policy directives derive from these findings. The priority public health policy must first be to maximize early diagnosis and to allow barrier-free, fast access to first-line ART. This upstream activity proves much more effective at the population level than downstream effort at coping with complex switching schemes. While it is as important clinically to maximize second- and third-line regimens, their population-level effectiveness relies on a robust and available first-line program. This deterministic model provides a valid and fundamental description, with a valid foundation upon which later stochastic analysis can draw and superimpose on the realities of real-world variables including variable patient compliance, viral mutation, and cost-effectiveness in order to further optimize evidence-based HIV treatment policy.

5.2. Recommendation

Based on this thesis' mathematical modeling and numerical computation, it is suggested that the policies of antiretroviral therapy initiation and switching need to be optimized as an urgent priority in public health programs of HIV control. The results clearly suggest that increasing the rates of treatment initiation decreases peak infection levels and long-term infected individuals drastically, highlighting the urgent need for policies that facilitate early diagnosis and early access to treatment. Besides, the model advocates that frequent and timely cycling among combinations of drugs is vital to manage drug resistance and delay treatment failure. The application of adaptive, personalized "cycling" protocols to ART, using patient-specific markers such as viral load, is thus recommended for improved long-term efficacy of current drugs. Investment in more effective treatment regimens to curtail failure rates is also necessary because it has a direct bearing on the degree of ongoing infections at the endemic stage of infection. Imple-

mentation of such model-derived interventions into clinical practice and health policy facilitates the optimization of therapeutic impact, guards against limited drug options, and can make significant progress toward global HIV control.

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