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Modelling HIV Drug Resistance Dynamics with Pre- and Post-Treatment Resistance Profiling in Botswana

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Abstract

The present study introduces a mathematical model aimed at assessing the impact of HIV drug resistance (HIVDR) and resistance profiles on the transmission of HIV/AIDS in Botswana. We created two compartmental models: one for pre-resistance profiling and one for post-resistance profiling. The models include susceptible individuals, individuals infected with drug-sensitive or drug-resistant HIV, individuals receiving first-line ART, individuals receiving second-line or third-line ART, and individuals who have progressed to AIDS. We used Bayesian inference with Hamiltonian Monte Carlo sampling to estimate parameters from UNAIDS data from 2010 to 2023. Research reveals that resistance profiling lowers the reproduction number by making it easier to choose the right medication and reducing the transmission contribution of individuals receiving effective second-line or third-line ART. Using Lyapunov function theory, we found global asymptotic stability criteria for both disease-free and endemic equilibria. Numerical models demonstrate that elevating the resistance profiling proportion ρ transitions individuals from inefficient first-line to suitable regimens, markedly decreasing treatment failure rates and the progression of AIDS. The infectivity reduction parameter ξ in post-profiling reduces the force of infection. These results show that systematic resistance testing before starting ART, along with a quick switch to effective second-line and third-line regimens, is necessary to control HIVDR and reduce the spread of the disease in places like Botswana, where it is common.

Keywords— Modelling, HIV/AIDS, Drug Resistance, Profiling, Model analysis, Simulations

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1 Introduction

As of 2024, over 40.8 million individuals globally are living with HIV, rendering the global HIV/AIDS epidemic the most critical infectious disease challenge of the 21st century [1]. The emergence and transmission of drug-resistant HIV strains now put at risk decades of public health success, despite considerable gains in the extension of antiretroviral therapy (ART) coverage, transforming HIV from a uniformly deadly disease into a manageable chronic condition [2, 3]. The World Health Organisation has said that HIV drug resistance (HIVDR) is a major barrier to reaching the 95 – 95 – 95 goals. Recent surveillance data show that more than 10% of people in several high-burden countries are resistant to non-nucleoside reverse transcriptase inhibitors before they start therapy. This means that global treatment guidelines need to be changed right once [4].

The primary cause of HIV treatment resistance is the rapid replication of the virus, which introduces errors during reverse transcription, resulting in increased viral diversity even in the absence of medication pressure [5, 6]. When antiretroviral therapy begins, the viral variants that are sensitive to the drugs are controlled. However, pre-existing resistant mutations can persist and increase in number due to selective pressure [7, 8]. This process of evolution creates three types of drug resistance: acquired drug resistance (ADR), which happens to people on ART who have a virological failure; transmitted drug resistance (TDR), which is found in people who are ART-naive but already infected with resistant strains; and pretreatment drug resistance (PDR), which includes both transmitted resistance and previous exposure to antiretroviral drugs [9]. There are significant treatment disparities between the two groups. For example, patients with PDR who start treatments that do not work experience a longer period of uncontrolled viremia. This accelerates the disease's progression and helps resistant variants spread [10, 11].

Sub-Saharan Africa carries the disproportionate burden of global HIV infection, hosting more than two-thirds of all persons living with HIV, with Southern Africa having the highest regional prevalence rates internationally [1]. Botswana is a very interesting situation to look at in this way. About 20.8% of persons aged 15 to 64 in Botswana have HIV, which is one of the highest rates in the world. But the country has nevertheless done an amazing job of getting people the treatment they need and lowering the number of viruses [12, 13]. The Masa Program made Botswana the first government in Africa to offer free national ART in 2002. Botswana reached and exceeded the UNAIDS 95 – 95 – 95 goals by 2021. 95% of persons with HIV knew their status, 98% of diagnosed people got ART, and 98% of those on treatment had their viral load down [14]. The Treat All policy, which started in 2016 and delivered ART to everyone who was diagnosed with HIV straight away, no matter how many $CD4^+$ cells they had, made it even easier for patients to seek treatment and lessened the transmission of the virus [15].

Despite these achievements, the Botswana treatment program is grappling with the emergence of HIV drug resistance. Initially, the nation utilised efavirenz-based first-line treatment. Nevertheless, the escalating prevalence of NNRTI resistance across Southern Africa prompted a transition to

dolutegravir-based combinations between 2016 and 2018 [16]. Dolutegravir offers a greater genetic barrier against resistance and promotes faster viral suppression. Despite these advantages, cases of virological failure and integrase-associated resistance mutations have been documented, especially in patients demonstrating suboptimal adherence or delayed transitions between regimens [17, 18]. Recent studies show that transmitted drug resistance is becoming more common in people recently diagnosed with HIV who have not started treatment yet. Also, acquired drug resistance is seen in those already on antiretroviral therapy (ART). This resistance often involves reverse transcriptase inhibitors, which are key parts of first-line treatment plans [19, 20, 4].

Botswana has just started resistance profiling, which looks at persons who have never undergone treatment for drug-resistant mutations before they start taking antiretroviral drugs. People were worried about how many people were becoming resistant, so this program was devised. The method represents a significant shift from managing resistance reactively to managing it proactively. Most patients used to start with the traditional first-line treatment and only move to alternative treatments after they saw that the first one wasn't working. Resistance profiling enables the initiation of the most suitable treatment for patients from the outset, tailored to their resistance profile [21]. People can keep getting the normal first-line treatment if the infection is still responding to it. People who have drug-resistant strains, on the other hand, can skip their treatments.

Recent modelling advances have increasingly focused on treatment heterogeneity and regimen sequencing. Frameworks incorporating first-line, second-line, and third-line therapy compartments reveal that the pathway to epidemic control depends not merely on treatment coverage but on the quality, continuity, and appropriate sequencing of care [22, 23]. Conversely, the transition from standard treatment protocols to resistance-informed care has not been explicitly modelled in many instances, especially within high-prevalence environments that account for the majority of the global HIV burden. Existing frameworks typically conceptualise treatment failure and resistance emergence as discrete events, thereby neglecting the subtle transitions between treatment regimens that define contemporary HIV care, or they operate under the assumption of uniform treatment responses, failing to differentiate between monitored and unmonitored failure pathways [24, 25].

The present study addresses this critical gap by developing and analysing a pair of deterministic compartmental models that explicitly compare HIV transmission dynamics before and after the implementation of resistance profiling. Our framework introduces six epidemiological compartments: susceptible individuals; individuals infected with drug-sensitive HIV; individuals infected with drug-resistant HIV; individuals receiving first-line ART; individuals receiving second-line or third-line ART; and individuals who have progressed to AIDS. The pre-profiling model represents the usual care approach, where all patients starting ART for the first time receive first-line treatment, regardless of any resistance. If the treatment fails, the individual is transferred to second-line or third-line ART only after first-line treatment failure has been identified. In contrast, the post-profiling model includes immediate resistance testing when the patient is diagnosed. This allows for the direct use of the most suitable second-line or third-line therapies for patients with resistant virus.

This study is structured as follows: Section 2 presents the model formulation, while Section 3 focuses on the model analysis. Section 4 provides the corresponding simulation results. Finally, Section 5 concludes the study

2 Model Formulation

In this study, we propose two mathematical models for HIV/AIDS transmission dynamics with drug resistance before resistance profiling and after resistance profiling. For the before resistance profiling model, the total population ($N(t)$) is subdivided into six compartments: susceptible individuals ($S(t)$), individuals infected with drug-sensitive HIV ($I_s(t)$), individuals infected with drug-resistant HIV ($I_r(t)$), individuals receiving first-line ART ($T_1(t)$), individuals receiving second-line or third-line ART ($T_2(t)$), and individuals who have developed AIDS ($A(t)$). Thus, the total population is given as,

$$N(t) = S(t) + I_s(t) + I_r(t) + T_1(t) + T_2(t) + A(t). \quad (1)$$

We assume a natural death rate μ for all the classes and a death-induced rate δ for the AIDS class only, and a constant recruitment rate Π . We define our force of infection as,

$$\lambda(\rho) = \frac{\beta (I_s + \kappa_1 I_r + \kappa_2 T_1 + [(1 - \rho) + \rho\xi] \kappa_3 T_2)}{N},$$

and

$$\lambda(\rho) = \begin{cases} \lambda_{\text{pre}}, & \text{if } \rho = 0, \\ \lambda_{\text{post}}, & \text{if } 0 < \rho \leq 1, \end{cases}$$

where β is the effective contact rate and κ is the infectivity parameter between 0 and 2. The parameter ($\xi \in [0, 1]$) represents the reduction in infectivity among individuals receiving effective second-line or third-line ART. The compartment (T_2) has the same biological interpretation in both models. Before resistance profiling, individuals enter (T_2) after first-line treatment failure and subsequent regimen switching. After resistance profiling, individuals with identified drug-resistant HIV may be initiated directly on an appropriate second-line or third-line regimen. Consequently, resistance profiling changes the route and timing of entry into (T_2), rather than the definition of the compartment itself.

The factor ($[(1 - \rho) + \rho\xi]$) captures the reduction in the transmission contribution associated with resistance-informed treatment allocation. The factor ρ represents the proportion of resistant infections identified through profiling and directed immediately to T_2 . Therefore, $\rho = 0$, resistant individuals do not enter T_2 directly, when $\rho = 1$, all treated resistant individuals enter T_2 directly. As (ρ) increases, a greater proportion of resistant individuals are directed to appropriate advanced regimens, with their relative infectivity reduced by the factor (ξ). A fraction α of the new infections

are initially sensitive to ART, and the remaining $1 - \alpha$ are resistant. With probabilities p_s and p_r , the treatment is initiated on I_s and I_r at the rate σ_s and σ_r respectively. For the pre-resistance profiling, all the infected compartments go to the first treatment, while for the post-resistance profiling, the infected with sensitive virus go to the first treatment ($T_1(t)$) and the infected with resistant virus go straight to the second treatment ($T_2(t)$). We assume that second-line and third-line ART reduce, but do not necessarily eliminate, the infectivity of individuals in T_2 , as represented by ξ . This adherence leads to sustained viral suppression, which significantly decreases their contribution to the force of infection. Therefore, in the post-profiling force of infection λ_{post} , the transmission potential from T_2 is scaled by the parameter ξ , representing the reduced infectivity of this group due to effective treatment. The remaining progress to AIDS class at the rate γ_s and γ_r from I_s and I_r . Some infected individuals with sensitive virus may acquire resistance due to treatment at the rate, also those infected with resistant virus may not adhere to the first treatment and switch from unsuccessful first-line ART to second-/third-line ART at the rate ϵ . The system of ODE described above is given as;

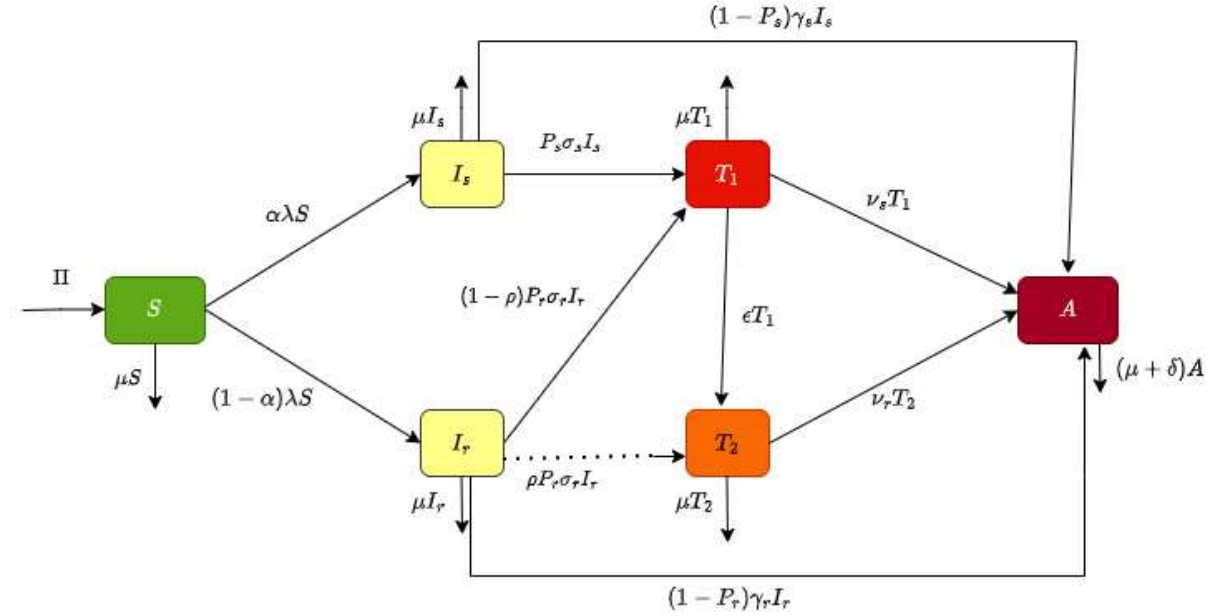


Figure 1: Drug resistance model diagram, the dotted line represents the post resistance profiling

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda(\rho)S - \mu S, \\
\frac{dI_s}{dt} &= \alpha\lambda(\rho)S - Q_1 I_s, \\
\frac{dI_r}{dt} &= (1 - \alpha)\lambda(\rho)S - Q_2 I_r, \\
\frac{dT_1}{dt} &= p_s \sigma_s I_s + (1 - \rho)p_r \sigma_r I_r - Q_3 T_1, \\
\frac{dT_2}{dt} &= \rho p_r \sigma_r I_r + \epsilon T_1 - Q_4 T_2, \\
\frac{dA}{dt} &= (1 - p_s)\gamma_s I_s + (1 - p_r)\gamma_r I_r + \nu_1 T_1 + \nu_r T_2 - Q_5 A.
\end{aligned}$$

where

$$\begin{cases}
Q_1 = (1 - p_s)\gamma_s + p_s \sigma_s + \mu, \\
Q_2 = (1 - p_r)\gamma_r + p_r \sigma_r + \mu, \\
Q_3 = \nu_s + \epsilon + \mu, \\
Q_4 = \nu_r + \mu, \\
Q_5 = \mu + \delta.
\end{cases}$$

When $\rho = 0$, the model reduces to the pre-resistance profiling system, while for $0 < \rho \leq 1$, it represents the post-resistance profiling system.

With initial conditions

$$S(0) > 0, I_s(0) \geq 0, I_r(0) \geq 0, T_1(0) \geq 0, T_2(0) \geq 0 \text{ and } A(0) \geq 0.$$

The feasible region of the model is given as

$$\Omega = \left\{ (S, I_s, I_r, T_1, T_2, A) \in \mathbb{R}_+^6 : 0 \leq N \leq \frac{\Pi}{\mu} \right\}. \quad (2)$$

State variable	Description
$S(t)$	Susceptible individuals
$I_s(t)$	Individuals infected with drug-sensitive HIV
$I_r(t)$	Individuals infected with drug-resistant HIV
$T_1(t)$	Individuals receiving first-line antiretroviral therapy
$T_2(t)$	Individuals receiving second-line or third-line antiretroviral therapy
$A(t)$	Individuals who have progressed to AIDS

Table 1: Description of the model state variables.

Parameter	Description	Unit
Π	Recruitment rate into the susceptible population.	individuals year ⁻¹
β	Effective HIV transmission rate.	year ⁻¹
α	Proportion of new infections caused by drug-sensitive HIV.	dimensionless
κ_1	Relative infectivity of individuals with drug-resistant HIV.	dimensionless
κ_2	Relative infectivity of individuals receiving first-line ART.	dimensionless
κ_3	Relative infectivity of individuals receiving second-line or third-line ART.	dimensionless
ρ	Proportion of resistant infections identified through profiling and assigned directly to second-line or third-line ART.	dimensionless
ξ	Relative infectivity reduction associated with effective second-line or third-line ART.	dimensionless
p_s	Proportion of individuals with drug-sensitive HIV who initiate ART.	dimensionless
p_r	Proportion of individuals with drug-resistant HIV who initiate ART.	dimensionless
σ_s	ART initiation rate for individuals with drug-sensitive HIV.	year ⁻¹
σ_r	ART initiation rate for individuals with drug-resistant HIV.	year ⁻¹
γ_s	AIDS progression rate among untreated individuals with drug-sensitive HIV.	year ⁻¹
γ_r	AIDS progression rate among untreated individuals with drug-resistant HIV.	year ⁻¹
ϵ	Switching rate from first-line to second-line or third-line ART following treatment failure.	year ⁻¹
ν_s	AIDS progression rate among individuals receiving first-line ART.	year ⁻¹
ν_r	AIDS progression rate among individuals receiving second-line or third-line ART.	year ⁻¹
μ	Natural mortality rate.	year ⁻¹
δ	AIDS-induced mortality rate.	year ⁻¹

Table 2: Description of the model parameters.

3 Model Analysis

In this section, we begin by analysing the system of differential equations representing the model for post-resistance profiling. This analysis provides critical insights into the progression of the epidemic in the presence of resistance profiling, when the profiling parameter ρ is equal to zero, which gives the analysis for before the resistance profiling model. We begin by considering the positivity and boundedness of solutions.

Lemma 1. *The solution for the model system with non-negative initial conditions $S(0) > 0$, $I_s(0) \geq 0$, $I_r(0) \geq 0$, $T_1(0) \geq 0$, $T_2(0) \geq 0$ and $A(0) \geq 0$ are non-negative for all $t \geq 0$.*

Proof. Using the initial condition, we prove that the solutions of the model system are positive. We assume a contradiction that there is a time t_1 such that $S(t_1) = 0$, $S'(t_1) < 0$, $S(t) > 0$, $I_s(t) > 0$, $I_r(t) > 0$, $T_1(t) > 0$, $T_2(t) > 0$ and $A(t) > 0$ for $0 < t < t_1$, but

$$S'(t_1) = \Pi > 0$$

which is a contradiction, meaning that S remains positive.

We also assume the contraction for the second equation of our model, that there exists a time t_1 such that $I_s(t_1) = 0$, $I'_s(t_1) < 0$, $S(t) > 0$, $I_r(t) > 0$, $T_1(t) > 0$, $T_2(t) > 0$ and $A(t) > 0$ for $0 < t < t_1$, but

$$I'_s(t_1) = \alpha\lambda(\rho)S > 0$$

which is a contradiction, meaning that I_s remains positive.

We follow the same procedure for the remaining state variables. Since all the state variables are positive, we can conclude that the solution for our model system is non-negative. $\square$

Lemma 2. *The feasible region $\Omega \subset \mathbb{R}_+^6$ is positively invariant with the non-negative initial conditions.*

Proof. The total population is given as,

$$\frac{dN}{dt} = \Pi - \mu N - \delta A \leq \Pi - \mu N$$

Therefore, the solution to the above equation is

$$N(t) = \left(\frac{\Pi}{\mu}\right) + \left(N_0 - \frac{\Pi}{\mu}\right) e^{-\mu t},$$

where $N_0 = N(0)$. We observe that if $N_0 < \frac{\Pi}{\mu}$, which it implies that $N(t) \rightarrow \frac{\Pi}{\mu}$ asymptotically as $t \rightarrow \infty$. If $N_0 > \frac{\Pi}{\mu}$, then $N(t) \rightarrow \frac{\Pi}{\mu}$. The region Ω is a positively attracting region. Hence, the model system is mathematically and biologically well-posed. $\square$

3.1 The basic reproduction number

The basic reproduction number, $\mathcal{R}_0$, is defined as the expected number of secondary infections generated by one infectious individual introduced into a wholly susceptible population. We derive $\mathcal{R}_0$ using the next-generation matrix method. The infected-state vector is defined as

$$\mathbf{x} = (I_s, I_r, T_1, T_2)^T.$$

The AIDS compartment, A , is excluded from the infected subsystem because individuals in this compartment are assumed not to contribute to the force of infection and do not return to the infectious compartments.

For convenience,

$$h(\rho, \xi) = (1 - \rho) + \rho\xi,$$

where $\rho \in [0, 1]$ represents the proportion of resistant infections identified through profiling and assigned directly to second-line or third-line ART, while $\xi \in [0, 1]$ represents the relative infectivity of individuals receiving effective second-line or third-line ART.

The vector of new infection terms is

$$\mathcal{F} = \begin{pmatrix} \alpha\lambda(\rho)S \\ (1 - \alpha)\lambda(\rho)S \\ 0 \\ 0 \end{pmatrix},$$

where

$$\lambda(\rho) = \frac{\beta [I_s + \kappa_1 I_r + \kappa_2 T_1 + h(\rho, \xi) \kappa_3 T_2]}{N}.$$

The vector of transition terms is

$$\mathcal{V} = \begin{pmatrix} Q_1 I_s \\ Q_2 I_r \\ Q_3 T_1 - p_s \sigma_s I_s - (1 - \rho) p_r \sigma_r I_r \\ Q_4 T_2 - \rho p_r \sigma_r I_r - \epsilon T_1 \end{pmatrix}.$$

The disease-free equilibrium is

$$E_0 = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0 \right).$$

Evaluating the Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ at E_0 gives

$$F = \frac{\partial \mathcal{F}}{\partial \mathbf{x}} \Big|_{E_0} = \begin{pmatrix} \alpha\beta & \alpha\beta\kappa_1 & \alpha\beta\kappa_2 & \alpha\beta h(\rho, \xi) \kappa_3 \\ (1 - \alpha)\beta & (1 - \alpha)\beta\kappa_1 & (1 - \alpha)\beta\kappa_2 & (1 - \alpha)\beta h(\rho, \xi) \kappa_3 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \frac{\partial \mathcal{V}}{\partial \mathbf{x}} \Big|_{E_0} = \begin{pmatrix} Q_1 & 0 & 0 & 0 \\ 0 & Q_2 & 0 & 0 \\ -p_s \sigma_s & -(1 - \rho) p_r \sigma_r & Q_3 & 0 \\ 0 & -\rho p_r \sigma_r & -\epsilon & Q_4 \end{pmatrix}.$$

The basic reproduction number is defined as

$$\mathcal{R}_0(\rho, \xi) = r \left(FV^{-1} \right),$$

where r denotes the spectral radius of the next-generation matrix.

The resulting reproduction number is

$$\begin{aligned} \mathcal{R}_0(\rho, \xi) = & \frac{\alpha\beta}{Q_1} + \frac{(1 - \alpha)\beta\kappa_1}{Q_2} + \frac{\alpha\beta\kappa_2 p_s \sigma_s}{Q_1 Q_3} + \frac{\alpha\beta h(\rho, \xi) \kappa_3 \epsilon p_s \sigma_s}{Q_1 Q_3 Q_4} \\ & + \frac{(1 - \alpha)\beta\kappa_2 (1 - \rho) p_r \sigma_r}{Q_2 Q_3} + \frac{(1 - \alpha)\beta h(\rho, \xi) \kappa_3 \rho p_r \sigma_r}{Q_2 Q_4} \\ & + \frac{(1 - \alpha)\beta h(\rho, \xi) \kappa_3 \epsilon (1 - \rho) p_r \sigma_r}{Q_2 Q_3 Q_4}. \end{aligned}$$

Pre-resistance profiling

In the absence of resistance profiling, $\rho = 0$, and therefore

$$h(0, \xi) = 1.$$

The reproduction number for the pre-profiling model is

$$\begin{aligned} \mathcal{R}_0^{\text{pre}} = \mathcal{R}_0(0, \xi) = & \frac{\alpha\beta}{Q_1} + \frac{(1-\alpha)\beta\kappa_1}{Q_2} + \frac{\alpha\beta\kappa_2 p_s \sigma_s}{Q_1 Q_3} + \frac{(1-\alpha)\beta\kappa_2 p_r \sigma_r}{Q_2 Q_3} + \frac{\alpha\beta\kappa_3 \epsilon p_s \sigma_s}{Q_1 Q_3 Q_4} \\ & + \frac{(1-\alpha)\beta\kappa_3 \epsilon p_r \sigma_r}{Q_2 Q_3 Q_4}. \end{aligned}$$

Complete resistance profiling

Under complete resistance profiling, $\rho = 1$, and therefore

$$h(1, \xi) = \xi.$$

All treated individuals infected with resistant HIV are assigned directly to second-line or third-line ART. Hence,

$$\mathcal{R}_0^{\text{post}} = \mathcal{R}_0(1, \xi) = \frac{\alpha\beta}{Q_1} + \frac{(1-\alpha)\beta\kappa_1}{Q_2} + \frac{\alpha\beta\kappa_2 p_s \sigma_s}{Q_1 Q_3} + \frac{\alpha\beta\xi\kappa_3 \epsilon p_s \sigma_s}{Q_1 Q_3 Q_4} + \frac{(1-\alpha)\beta\xi\kappa_3 p_r \sigma_r}{Q_2 Q_4}.$$

Thus, $\mathcal{R}_0^{\text{post}}$ represents the complete-profiling case, $\rho = 1$. For partial resistance profiling, where $0 < \rho < 1$, the general expression $\mathcal{R}_0(\rho, \xi)$ should be used.

The difference between complete profiling and no profiling is

$$\begin{aligned} \mathcal{R}_0^{\text{post}} - \mathcal{R}_0^{\text{pre}} = & (\xi - 1) \frac{\alpha\beta\kappa_3 \epsilon p_s \sigma_s}{Q_1 Q_3 Q_4} \\ & + \frac{(1-\alpha)\beta p_r \sigma_r}{Q_2} \left[\frac{\xi\kappa_3}{Q_4} - \frac{\kappa_2}{Q_3} - \frac{\kappa_3 \epsilon}{Q_3 Q_4} \right]. \end{aligned}$$

Since $0 \leq \xi \leq 1$, the first term is non-positive. A sufficient condition for

$$\mathcal{R}_0^{\text{post}} < \mathcal{R}_0^{\text{pre}}$$

is

$$\xi\kappa_3 Q_3 < \kappa_2 Q_4 + \kappa_3 \epsilon.$$

Under this condition, complete resistance profiling reduces the transmission potential by directing individuals infected with resistant HIV to effective second-line or third-line ART before they experience unsuccessful first-line treatment.

3.2 Existence of the endemic equilibrium

At the steady states, all time derivatives are set to zero

$$\Pi - \lambda(\rho)^* S^* - \mu S^* = 0, \quad (3)$$

$$\alpha \lambda(\rho)^* S^* - Q_1 I_s^* = 0, \quad (4)$$

$$(1 - \alpha) \lambda(\rho)^* S^* - Q_2 I_r^* = 0, \quad (5)$$

$$p_s \sigma_s I_s^* + (1 - \rho) p_r \sigma_r I_r^* - Q_3 T_1^* = 0, \quad (6)$$

$$\rho p_r \sigma_r I_r^* + \epsilon T_1^* - Q_4 T_2^* = 0, \quad (7)$$

$$(1 - p_s) \gamma_s I_s^* + (1 - p_r) \gamma_r I_r^* + \nu_1 T_1^* + \nu_r T_2^* - Q_5 A^* = 0. \quad (8)$$

From equation (4),

$$S^* = \frac{Q_1 I_s^*}{\alpha \lambda(\rho)}.$$

Using equation 5 and substituting S^* , we get

$$I_r^* = \frac{(1 - \alpha) Q_1}{\alpha Q_2} I_s^* = M_1 I_s^*.$$

From equation (6) and substituting I_r^* :

$$T_1^* = \frac{1}{Q_3} \left[\frac{p_s \sigma_s \alpha Q_2 + (1 - \rho) p_r \sigma_r (1 - \alpha) Q_1}{\alpha Q_2} \right] I_s^* = M_2 I_s^*.$$

From equation (7) and substituting I_r^* and T_1^* ,

$$T_2^* = \frac{1}{Q_4} \left[\frac{\rho p_r \sigma_r (1 - \alpha) Q_1}{\alpha Q_2} + \epsilon M_2 \right] I_s^* = M_3 I_s^*.$$

$\lambda(\rho)^*$ can now be expressed in terms of I_s^* to get

$$\lambda(\rho) = \frac{\psi I_s^*}{N}, \text{ where } \psi = \beta(1 + \kappa_1 M_1 + \kappa_2 M_2 + \kappa_3 M_3). \quad (9)$$

From equation (5)

$$(1 - \alpha) \lambda(\rho)^* S^* - Q_2 I_r^* = 0,$$

we substitute equation (2) and substituting I_r^* into above equation to get

$$I_s^* \left[\frac{S^*}{N} \left(\alpha \beta \left(1 + \frac{Q_1 \kappa_1 (1 - \alpha)}{Q_2 \alpha} + \kappa_2 M_1 + \kappa_3 M_2 \right) \right) - Q_1 \right] = 0,$$

$$I_s^* = 0 \quad \text{or} \quad \frac{S^*}{N} = \frac{Q_2 M_2}{\beta(1 - \alpha)(1 + \kappa_1 M_1 + \kappa_2 M_2 + \kappa_3 M_3)}. \quad (10)$$

If $I_s^* = 0$ then the $T_1^* = T_2^* = I_r^* = A^* = 0$ and Disease free equilibrium (DFE) is given as

$$\mathbf{E}_0 = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0 \right).$$

At the steady state, the total population is given as

$$N^* = S^* + I_s^* (1 + M_1 + M_2 + M_3 + M_4), \quad (11)$$

then substituting (11) into 10 we get,

$$\frac{S^*}{S^* + I_s^* (1 + M_1 + M_2 + M_3 + M_4)} = \frac{Q_2 M_2}{\beta(1 - \alpha)(1 + \kappa_1 M_1 + \kappa_2 M_2 + \kappa_3 M_3)}.$$

Then,

$$I_s^* = \frac{S^*}{1 + M_1 + M_2 + M_3 + M_4} (\mathcal{R}_0 - 1) \quad (12)$$

Substituting equation 12 and 9 into equation 3 we get,

$$S^* = \frac{\Pi(1 + M_1 + M_2 + M_3 + M_4)\mathcal{R}_0^{Post}}{\mu(1 + M_1 + M_2 + M_3 + M_4)\mathcal{R}_0^{Post} + \psi(\mathcal{R}_0^{Post} - 1)}. \quad (13)$$

Equation 12 corresponds to the endemic state, the endemic equilibrium is given by

$$E_1 = (S^*, I_s^*, I_r^*, T_1^*, T_2^*, A^*),$$

where,

$$\begin{cases} S^* = \frac{\Pi(1 + M_1 + M_2 + M_3 + M_4)\mathcal{R}_0^{Post}}{\mu(1 + M_1 + M_2 + M_3 + M_4)\mathcal{R}_0^{Post} + \psi(\mathcal{R}_0^{Post} - 1)}, \\ I_s^* = \frac{S^*}{1 + M_1 + M_2 + M_3 + M_4} (\mathcal{R}_0^{Post} - 1), \\ I_r^* = M_1 I_s^*, \\ T_1^* = M_2 I_s^*, \\ T_2^* = M_3 I_s^*, \\ A^* = M_4 I_s^*. \end{cases}$$

3.3 Global stability of the disease-free equilibrium

The global stability of the disease-free equilibrium is established using the Castillo–Chavez approach. The model is written in the form

$$\frac{dX}{dt} = F(X, Z), \quad \frac{dZ}{dt} = G(X, Z),$$

where $X = S$ represents the uninfected compartment and

$$Z = (I_s, I_r, T_1, T_2, A)^T$$

contains the infected compartments.

The disease-free equilibrium is

$$E_0 = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0 \right).$$

According to the Castillo–Chavez theorem, the disease-free equilibrium is globally asymptotically stable if the following conditions are satisfied:

$$(H_1) : \quad \frac{dX}{dt} = F(X, 0)$$

has a globally asymptotically stable equilibrium X_0 , and

$$(H_2) : \quad G(X, Z) = MZ - \widehat{G}(X, Z),$$

where

$$M = D_Z G(X_0, 0)$$

is a Metzler matrix and

$$\widehat{G}(X, Z) \geq 0$$

for all $(X, Z) \in \Omega$.

Lemma 3. *The disease-free equilibrium*

$$E_0 = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0 \right)$$

is globally asymptotically stable in Ω whenever

$$\mathcal{R}_0(\rho, \xi) < 1.$$

Proof. When $Z = 0$, the susceptible population satisfies

$$\frac{dS}{dt} = \Pi - \mu S.$$

The solution is

$$S(t) = \frac{\Pi}{\mu} + \left(S(0) - \frac{\Pi}{\mu} \right) e^{-\mu t}.$$

Therefore,

$$S(t) \longrightarrow \frac{\Pi}{\mu} \quad \text{as} \quad t \longrightarrow \infty.$$

Thus,

$$X_0 = \frac{\Pi}{\mu}$$

is globally asymptotically stable, and condition (H_1) is satisfied.

We define

$$L(Z) = I_s + \kappa_1 I_r + \kappa_2 T_1 + h(\rho, \xi) \kappa_3 T_2,$$

where

$$h(\rho, \xi) = (1 - \rho) + \rho \xi.$$

The infected subsystem is expressed as

$$G(X, Z) = \begin{pmatrix} \alpha\beta \frac{S}{N} L(Z) - Q_1 I_s \\ (1 - \alpha)\beta \frac{S}{N} L(Z) - Q_2 I_r \\ p_s \sigma_s I_s + (1 - \rho) p_r \sigma_r I_r - Q_3 T_1 \\ \rho p_r \sigma_r I_r + \epsilon T_1 - Q_4 T_2 \\ (1 - p_s) \gamma_s I_s + (1 - p_r) \gamma_r I_r + \nu_s T_1 + \nu_r T_2 - Q_5 A \end{pmatrix}.$$

At the disease-free equilibrium,

$$S_0 = N_0 = \frac{\Pi}{\mu},$$

and hence

$$\frac{S_0}{N_0} = 1.$$

The matrix

$$M = D_Z G(X_0, 0)$$

is therefore

$$M = \begin{pmatrix} \alpha\beta - Q_1 & \alpha\beta\kappa_1 & \alpha\beta\kappa_2 & \alpha\beta h(\rho, \xi) \kappa_3 & 0 \\ (1 - \alpha)\beta & (1 - \alpha)\beta\kappa_1 - Q_2 & (1 - \alpha)\beta\kappa_2 & (1 - \alpha)\beta h(\rho, \xi) \kappa_3 & 0 \\ p_s \sigma_s & (1 - \rho) p_r \sigma_r & -Q_3 & 0 & 0 \\ 0 & \rho p_r \sigma_r & \epsilon & -Q_4 & 0 \\ (1 - p_s) \gamma_s & (1 - p_r) \gamma_r & \nu_s & \nu_r & -Q_5 \end{pmatrix}.$$

Since all off-diagonal entries of M are non-negative, M is a Metzler matrix.

The nonlinear remainder is defined by

$$\hat{G}(X, Z) = MZ - G(X, Z).$$

Substituting MZ and $G(X, Z)$ gives

$$\hat{G}(X, Z) = \begin{pmatrix} \alpha\beta \left(1 - \frac{S}{N}\right) L(Z) \\ (1 - \alpha)\beta \left(1 - \frac{S}{N}\right) L(Z) \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Since

$$N = S + I_s + I_r + T_1 + T_2 + A,$$

it follows that

$$0 \leq \frac{S}{N} \leq 1$$

for all $(X, Z) \in \Omega$. Therefore,

$$1 - \frac{S}{N} \geq 0.$$

Furthermore,

$$L(Z) \geq 0,$$

because all state variables and infectivity parameters are non-negative. Consequently,

$$\hat{G}(X, Z) \geq 0$$

for all $(X, Z) \in \Omega$. Hence, condition (H_2) is satisfied.

The infected-subsystem Jacobian M is stable whenever

$$\mathcal{R}_0(\rho, \xi) < 1,$$

where

$$\mathcal{R}_0(\rho, \xi) = r \left(FV^{-1} \right).$$

Therefore, by the Castillo–Chavez global stability theorem, the disease-free equilibrium E_0 is globally asymptotically stable in Ω whenever

$$\mathcal{R}_0(\rho, \xi) < 1.$$

Thus, HIV infection eventually dies out independently of the initial conditions when the reproduction number is below unity. $\square$

3.4 Global stability of endemic equilibrium

Lemma 4. *The endemic equilibrium point of the model system is globally asymptotically stable if $\mathcal{R}_0^{Post} > 1$.*

Proof. We propose a Lyapunov function

$$\begin{aligned} V &= \left(S - S^* - S^* \ln \left(\frac{S}{S^*} \right) \right) + \left(I_s - I_s^* - I_s^* \ln \left(\frac{I_s}{I_s^*} \right) \right) \\ &+ \left(I_r - I_r^* - I_r^* \ln \left(\frac{I_r}{I_r^*} \right) \right) + \left(T_1 - T_1^* - T_1^* \ln \left(\frac{T_1}{T_1^*} \right) \right) \\ &+ \left(T_2 - T_2^* - T_2^* \ln \left(\frac{T_2}{T_2^*} \right) \right). \end{aligned}$$

The Lyapunov function's time derivative is thus provided by

$$\begin{aligned} \dot{V} &= \left(1 - \frac{S^*}{S} \right) \dot{S} + \left(1 - \frac{I_s^*}{I_s} \right) \dot{I}_s + \left(1 - \frac{I_r^*}{I_r} \right) \dot{I}_r + \left(1 - \frac{T_1^*}{T_1} \right) \dot{T}_1 + \left(1 - \frac{T_2^*}{T_2} \right) \dot{T}_2, \\ &= \left(1 - \frac{S^*}{S} \right) (\Pi - \lambda(\rho)S - \mu S) + \left(1 - \frac{I_s^*}{I_s} \right) (\alpha \lambda(\rho)S - Q_1 I_s) \\ &+ \left(1 - \frac{I_r^*}{I_r} \right) ((1 - \alpha) \lambda(\rho)S - Q_2 I_r) + \left(1 - \frac{T_2^*}{T_2} \right) (\rho p_r \sigma_r I_r + \epsilon T_1 - Q_4 T_2) \\ &+ \left(1 - \frac{T_1^*}{T_1} \right) (p_s \sigma_s I_s + (1 - \rho) p_r \sigma_r I_r - Q_3 T_1). \end{aligned}$$

From the model system at the steady state, we have

$$\begin{aligned} \Pi &= (\lambda(\rho)^* + \mu) S^*, \quad Q_1 = \frac{\alpha \lambda(\rho)^* S^*}{I_s^*}, \quad Q_2 = \frac{(1 - \alpha) \lambda^* S^*}{I_r^*}, \\ Q_3 &= \frac{p_s \sigma_s I_s^* + (1 - \rho) p_r \sigma_r I_r^*}{T_1^*}, \quad Q_4 = \frac{\rho p_r \sigma_r I_r^* + \epsilon T_1^*}{T_2^*}, \end{aligned}$$

and we let

$$\frac{\beta}{N} = \beta_0.$$

We substitute the above expressions into the derivative of the Lyapunov function to obtain,

$$\begin{aligned}
\dot{V} = & -\mu \left(\frac{(S - S^*)^2}{S} \right) + \beta_0 \left(1 - \frac{S^*}{S} \right) \left[I_s^* S^* \left(1 - \frac{I_s S}{I_s^* S^*} \right) + \kappa_1 I_r^* S^* \left(1 - \frac{I_r S}{I_r^* S^*} \right) \right. \\
& + \kappa_2 T_1^* S^* \left(1 - \frac{T_1 S}{T_1^* S^*} \right) + \kappa_3 \xi T_2^* S^* \left(1 - \frac{T_2 S}{T_2^* S^*} \right) \Big] \\
& + \alpha \beta_0 \left(1 - \frac{I_s^*}{I_s} \right) \kappa_3 \xi T_2^* S^* \left(\frac{T_2 S}{T_2^* S^*} - \frac{I_s}{I_s^*} \right) \\
& + \alpha \beta_0 \left(1 - \frac{I_s^*}{I_s} \right) \left[I_s^* S^* \left(\frac{I_s S}{I_s^* S^*} - \frac{I}{I_s^*} \right) + \kappa_1 I_r^* S^* \left(\frac{I_r S}{I_r^* S^*} - \frac{I_s}{I_s^*} \right) + \kappa_2 T_1^* S^* \left(\frac{T_1 S}{T_1^* S^*} - \frac{I_s}{I_s^*} \right) \right] \\
& + (1 - \alpha) \beta_0 \left(1 - \frac{I_r^*}{I_r} \right) \left[\kappa_3 \xi T_2^* S^* \left(\frac{T_2 S}{T_2^* S^*} - \frac{I_r}{I_r^*} \right) + \kappa_2 T_1^* S^* \left(\frac{T_1 S}{T_1^* S^*} - \frac{I_r}{I_r^*} \right) \right] \\
& + (1 - \alpha) \beta_0 \left(1 - \frac{I_r^*}{I_r} \right) \left[I_s^* S^* \left(\frac{I_s S}{I_s^* S^*} - \frac{I_r}{I_r^*} \right) + \kappa_1 I_r^* S^* \left(\frac{I_r S}{I_r^* S^*} - \frac{I_r}{I_r^*} \right) \right] \\
& + \left(1 - \frac{T_1^*}{T_1} \right) \left[(p_s \sigma_s I_s^* \left(\frac{I_s}{I_s^*} - \frac{T_1}{T_1^*} \right) + (1 - \rho) p_r \sigma_r I_r^* \left(\frac{I_r}{I_r^*} - \frac{T_1}{T_1^*} \right)) \right] \\
& + \left(1 - \frac{T_2^*}{T_2} \right) \left[(p_r \sigma_r I_r^* \left(\frac{I_r}{I_r^*} - \frac{T_2}{T_2^*} \right) + \rho p_r \sigma_r I_r^* \left(\frac{I_r}{I_r^*} - \frac{T_2}{T_2^*} \right)) \right]
\end{aligned}$$

Letting

$$\frac{S}{S^*} = a, \quad \frac{I_s}{I_s^*} = b, \quad \frac{I_r}{I_r^*} = c, \quad \frac{T_1}{T_1^*} = d, \quad \frac{T_2}{T_2^*} = e.$$

Then it reduces to

$$\begin{aligned}
\dot{V} = & -\mu \left(\frac{(S - S^*)^2}{S} \right) + \beta_0 \left(1 - \frac{1}{a} \right) \left[I_s^* S^* (1 - ab) + \kappa_1 I_r^* S^* (1 - ac) \right. \\
& + \kappa_2 T_1^* S^* (1 - ad) + \kappa_3 \xi T_2^* S^* (1 - ae) \Big] + \alpha \beta_0 \left(1 - \frac{1}{b} \right) \kappa_3 \xi T_2^* S^* (ae - b) \\
& + \alpha \beta_0 \left(1 - \frac{1}{b} \right) \left[I_s^* S^* (ab - b) + \kappa_1 I_r^* S^* (ac - b) + \kappa_2 T_1^* S^* (ad - b) \right] \\
& + (1 - \alpha) \beta_0 \left(1 - \frac{1}{c} \right) \left[\kappa_3 \xi T_2^* S^* (ae - c) + \kappa_2 T_1^* S^* (ad - c) \right] \\
& + (1 - \alpha) \beta_0 \left(1 - \frac{1}{c} \right) \left[I_s^* S^* (ab - c) + \kappa_1 I_r^* S^* (ac - c) \right] \\
& + \left(1 - \frac{1}{d} \right) [(p_s \sigma_s I_s^* (b - d) + (1 - \rho) p_r \sigma_r I_r^* (c - d))] \\
& + \left(1 - \frac{1}{e} \right) [(p_r \sigma_r I_r^* (c - e) + \rho p_r \sigma_r I_r^* (c - e))]
\end{aligned}$$

After expanding the brackets, we obtain

$$\begin{aligned}
\dot{V} = & -\mu \left(\frac{(S - S^*)^2}{S} \right) + \beta_0 I_s^* S^* \left(1 - ab + b - \frac{1}{a} \right) + \beta_0 \kappa_1 I_r^* S^* \left(1 - ac + c - \frac{1}{a} \right) \\
& + \beta_0 \kappa_2 T_1^* S^* \left(1 - ad + d - \frac{1}{a} \right) + \beta_0 \kappa_3 \xi T_2^* S^* \left(1 - ae + e - \frac{1}{a} \right) \\
& + \alpha \beta_0 \kappa_3 \xi T_2^* S^* \left(1 + ae - b - \frac{ae}{b} \right) + \alpha \beta_0 \kappa_2 T_1^* S^* \left(1 + ad - b - \frac{ad}{b} \right) \\
& + \alpha \beta_0 I_s^* S^* \left(1 + ab - b - a \right) + \alpha \beta_0 \kappa_1 I_r^* S^* \left(1 + ac - b - \frac{ac}{b} \right) \\
& + (1 - \alpha) \beta_0 \kappa_3 \xi T_2^* S^* \left(1 + ae - c - \frac{ae}{c} \right) + (1 - \alpha) \beta_0 I_s^* S^* \left(1 + ab - c - \frac{ab}{c} \right) \\
& + (1 - \alpha) \beta_0 \kappa_1 I_r^* S^* \left(1 + ac - a - c \right) + (1 - \alpha) \beta_0 \kappa_2 T_1^* S^* \left(1 + ad - c - \frac{ad}{c} \right) \\
& + p_s \sigma_s I_s^* \left(1 + b - d - \frac{b}{d} \right) + (1 - \rho) p_r \sigma_r I_r^* \left(1 + c - e - \frac{c}{e} \right) + \rho p_r \sigma_r I_r^* \left(1 + c - e - \frac{c}{e} \right).
\end{aligned}$$

For all $x > 0$, consider a function $y(x) = 1 - x + \ln(x) \leq 0$, where equality holds if $x = 1$. When $1 - x \leq -\ln(x)$, we get that

$$\begin{aligned}
1 + b - ab - \frac{1}{a} &= (1 - ab) + \left(1 - \frac{1}{a}\right) - (1 - b) \\
&\leq -\ln(ab) - \ln\left(\frac{1}{a}\right) + \ln(b) \\
&= \ln\left(\frac{1}{ab} \cdot a \cdot b\right) \\
&= 0,
\end{aligned}$$

$$\begin{aligned}
1 - \frac{ae}{b} - b + ae &= (1 - b) + \left(1 - \frac{ae}{b}\right) - (1 - ae) \\
&\leq -\ln(b) - \ln\left(\frac{ae}{b}\right) + \ln(ae) \\
&= \ln\left(\frac{1}{b} \cdot \frac{b}{ae} \cdot ae\right) \\
&= 0,
\end{aligned}$$

$$\begin{aligned}
1 - b + ab - a &= (1 - a) + (1 - b) - (1 - ab) \\
&\leq -\ln(a) - \ln(b) + \ln(ab) \\
&= \ln\left(\frac{1}{a} \cdot \frac{1}{b} \cdot ab\right) \\
&= 0.
\end{aligned}$$

Using the same approach, we can also show the remaining are less than or equal to zero. The term $-\mu \left(\frac{(S-S^*)^2}{S} \right) \leq 0$ is negative, then $\dot{v} \leq 0$, and $\dot{V} = 0$ if $a = b = c = d = e = 1$. The singleton E is the biggest compact invariant set given E as the endemic equilibrium. It follows that E is globally asymptotically stable if $\mathcal{R}_0^{post} > 1$ according to LaSalle's invariant principle [26]. $\square$

4 Results

4.1 Parameter estimation

Bayesian inference was implemented using Hamiltonian Monte Carlo through Stan [27]. The model was calibrated to UNAIDS data on adults receiving ART in Botswana from 2010 to 2023 [28], giving $n = 14$ annual observations. The fitted model output was $T_1(t) + T_2(t)$. The parameters $\sigma_s, \sigma_r, \gamma_s, \gamma_r, \epsilon, \nu_s, \nu_r, \beta, \kappa_1, \kappa_2, \kappa_3$, and ξ were estimated, while the remaining parameters were fixed from the literature or baseline assumptions.

Four MCMC chains were run with 2000 iterations each, including 1000 warmup iterations, resulting in 4000 post-warmup samples. All parameters had $\hat{R} < 1.01$, effective sample sizes above 2200, no divergent transitions, and no maximum tree-depth exceedances, indicating satisfactory convergence. The posterior median model fit gave $R^2 = 0.9333$. The estimated switching rate from first-line to second-line or third-line ART was $\epsilon = 0.6262$, while the progression rate to AIDS among individuals receiving advanced ART was low, with $\nu_r = 0.0253$. The infectivity-reduction parameter was estimated as $\xi = 0.5215$, and the combined infectivity contribution of the T_2 class was $\xi\kappa_3 \approx 0.61$. Although the sampler converged well, several parameters had broad credible intervals, indicating limited identifiability from the available ART data. We got the model fit 2, trace plots3 and posterior density plot 4

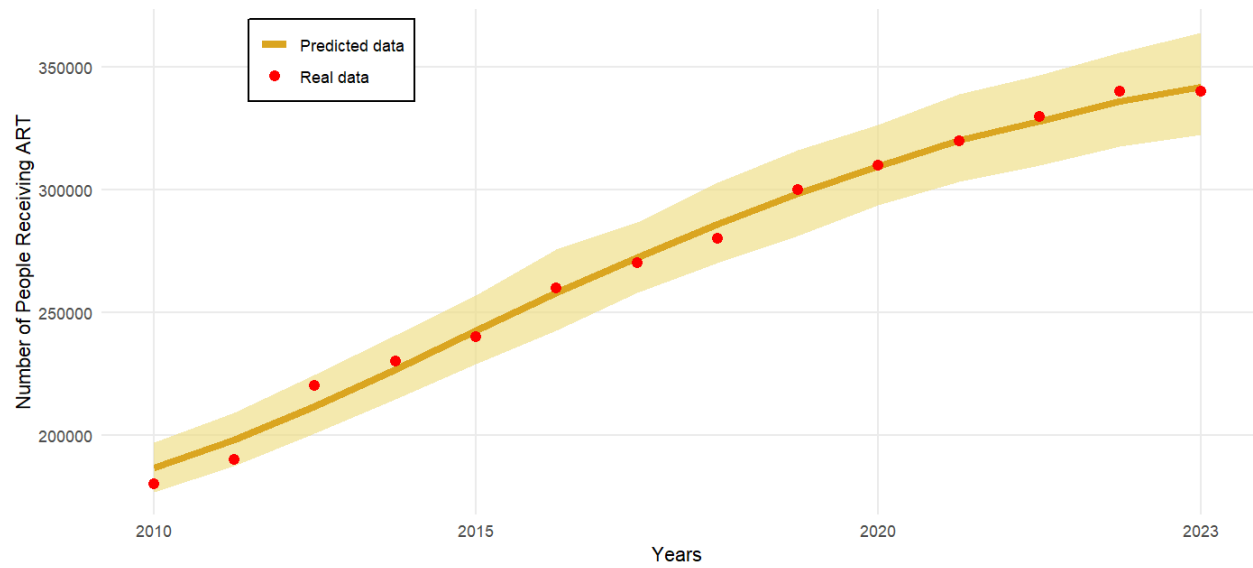


Figure 2: Model fit showing observed data against posterior median predictions for the number of people receiving ART in Botswana from 2010 to 2023.

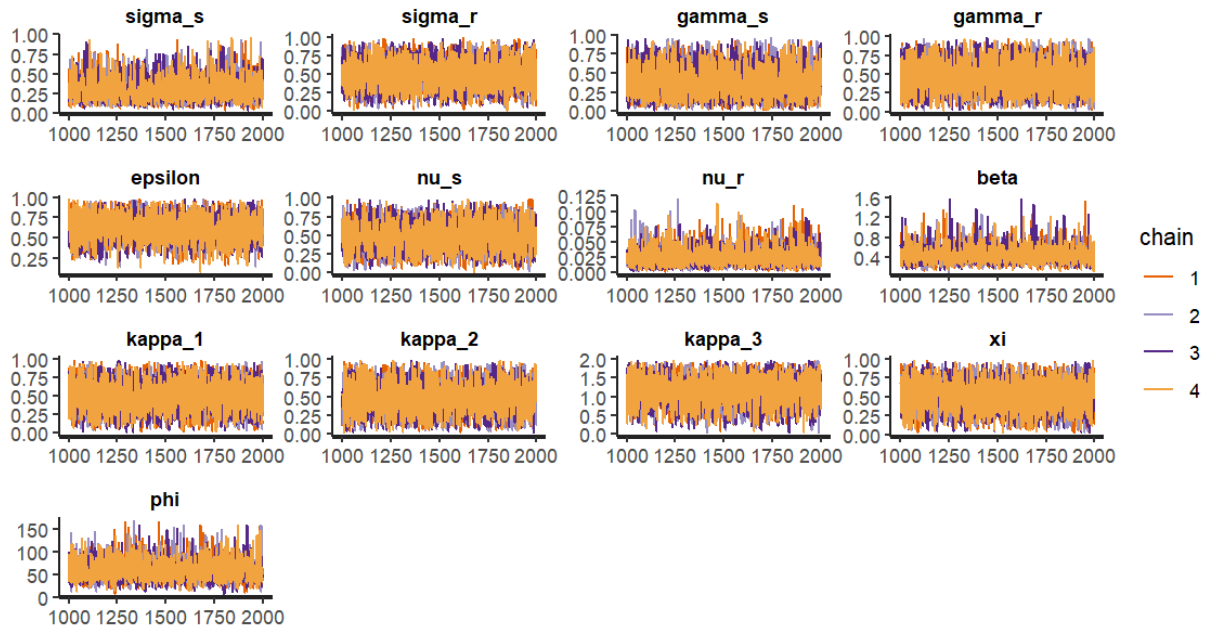


Figure 3: Trace plots

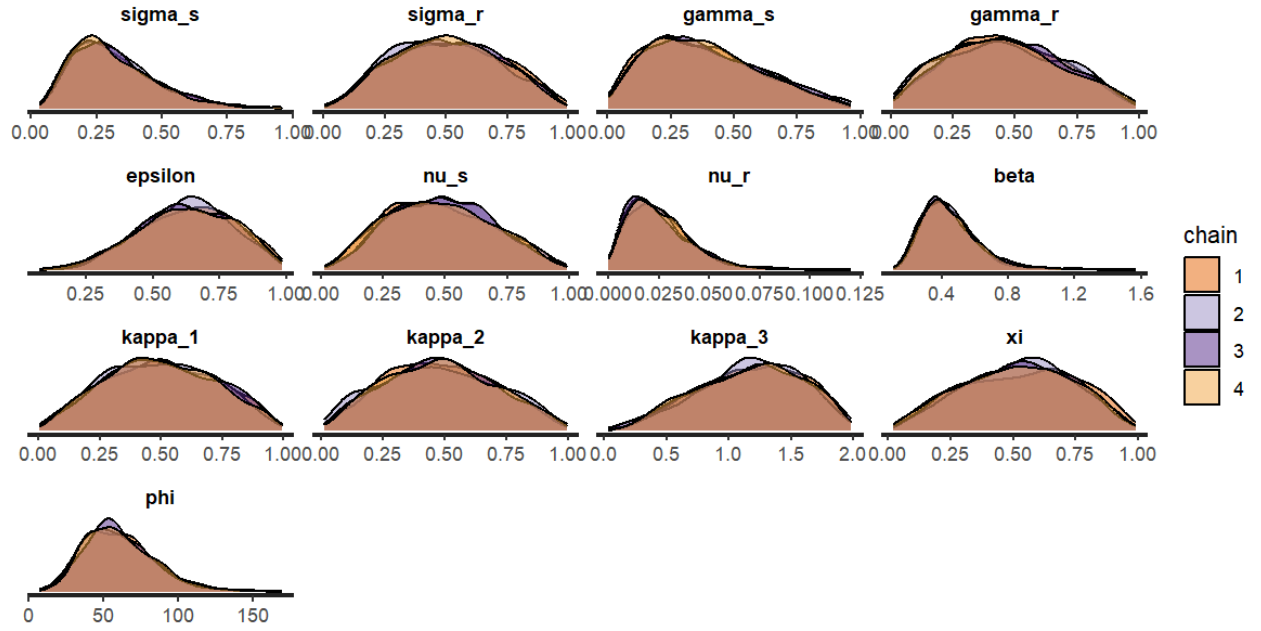


Figure 4: Posterior density plot

Parameter	Mean	SD	95% credible interval	n_{eff}	$\hat{R}$
σ_s	0.3180	0.1604	0.0920–0.6965	2228	1.0010
σ_r	0.5031	0.2134	0.1240–0.9002	3679	1.0004
γ_s	0.3847	0.2167	0.0576–0.8503	2877	1.0009
γ_r	0.4587	0.2253	0.0718–0.8885	4736	0.9998
ϵ	0.6262	0.1730	0.2887–0.9320	3593	1.0003
ν_s	0.4833	0.2067	0.1220–0.8834	2455	1.0003
ν_r	0.0253	0.0160	0.0039–0.0633	2805	1.0016
β	0.4464	0.1774	0.1911–0.8719	3170	1.0005
κ_1	0.4986	0.2215	0.0911–0.9058	4461	0.9998
κ_2	0.4807	0.2228	0.0839–0.9035	4389	0.9994
κ_3	1.1701	0.4146	0.3396–1.8607	4056	1.0003
ξ	0.5215	0.2188	0.1062–0.9029	4435	1.0003

Table 3: Posterior estimates of the model parameters obtained using Bayesian inference.

4.2 Sensitivity analysis

A global sensitivity analysis was conducted to determine the influence of model parameters on the reproduction number, $\mathcal{R}_0(\rho, \xi)$. Parameter values were sampled from their respective posterior distributions, and Partial Rank Correlation Coefficients were calculated between each parameter and $\mathcal{R}_0(\rho, \xi)$. A positive coefficient indicates that increasing the parameter increases the reproduction number, whereas a negative coefficient indicates a reduction in transmission potential. Parameters with larger absolute coefficients were considered the most influential drivers of HIV transmission and resistance-profiling effectiveness.

From Figure 5 the sensitivity analysis showed that β had the largest positive PRCC, indicating that the effective transmission rate is the most influential driver of $\mathcal{R}_0$. Positive PRCC values were also obtained for κ_3 , ξ , ϵ , κ_1 , κ_2 , and σ_r . The positive effects of κ_1 , κ_2 , and κ_3 indicate that increasing the relative infectivity of untreated resistant individuals and treated individuals increases transmission. Similarly, the positive PRCC for ξ shows that reduced treatment effectiveness in the T_2 class increases $\mathcal{R}_0$. The positive effect of ϵ suggests that, under the estimated parameter values, faster movement into T_2 does not sufficiently reduce infectivity, consistent with $\xi\kappa_3 > \kappa_2$. The positive PRCC for σ_r indicates that increased treatment initiation among resistant individuals may increase entry into treatment pathways that still contribute substantially to transmission.

Negative PRCC values were obtained for γ_s , γ_r , ν_s , ν_r , σ_s , and ρ . The negative effects of γ_s , γ_r , ν_s , and ν_r arise because these parameters increase removal from infectious compartments through progression to AIDS. The negative PRCC for σ_s indicates that faster treatment initiation among individuals with drug-sensitive HIV reduces transmission by shortening the untreated infectious period. The negative effect of ρ confirms that increasing resistance-profiling coverage reduces $\mathcal{R}_0$ by directing resistant individuals more rapidly to appropriate treatment. Overall, the results identify β , κ_3 , and ξ as the main transmission-enhancing parameters, while ρ and treatment-related removal parameters contribute to reducing transmission.

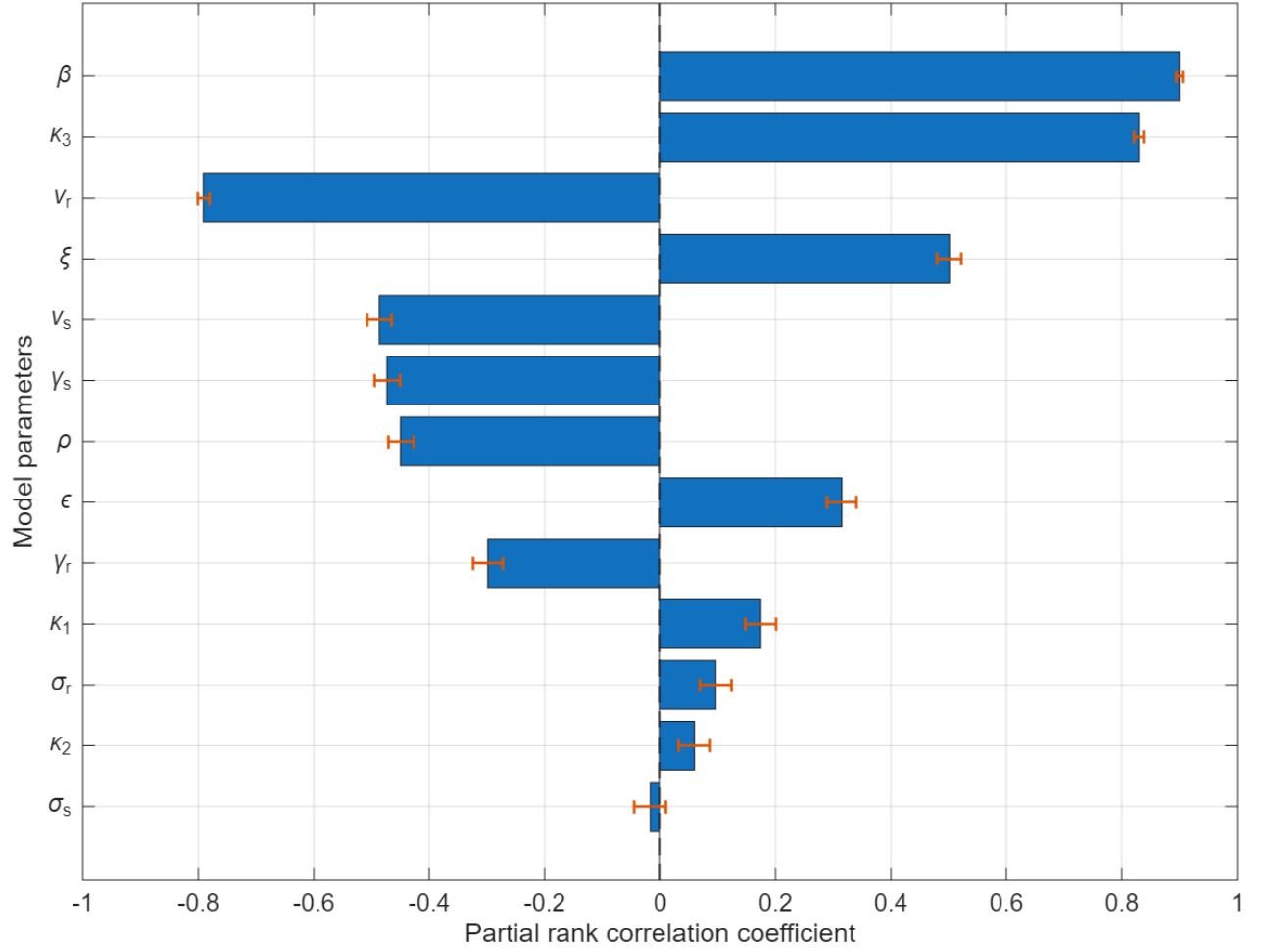


Figure 5: Tornado plot

4.3 Effect of varying ξ and ϵ on $\mathcal{R}_0^{Post}$

The heatmap shows the joint effect of infectivity reduction parameter ξ and switching rate ϵ on $\mathcal{R}_0^{post}$. For any fixed ϵ , $\mathcal{R}_0^{post}$ increases with ξ , which means that the lesser degree of suppression in T_2 leads to higher transmissibility. Similarly, for fixed ξ , larger ϵ results in a higher $\mathcal{R}_0^{post}$. The maximum $\mathcal{R}_0^{post}$ is achieved when both ξ and ϵ are large, indicating that there is a common effect between low efficacy of treatment and high rate of treatment failure. On the other hand, low values of both parameters lead to large reductions in $\mathcal{R}_0^{post}$, highlighting the importance of effective second-line therapy and better treatment adherence for controlling HIV transmission after resistance profiling.

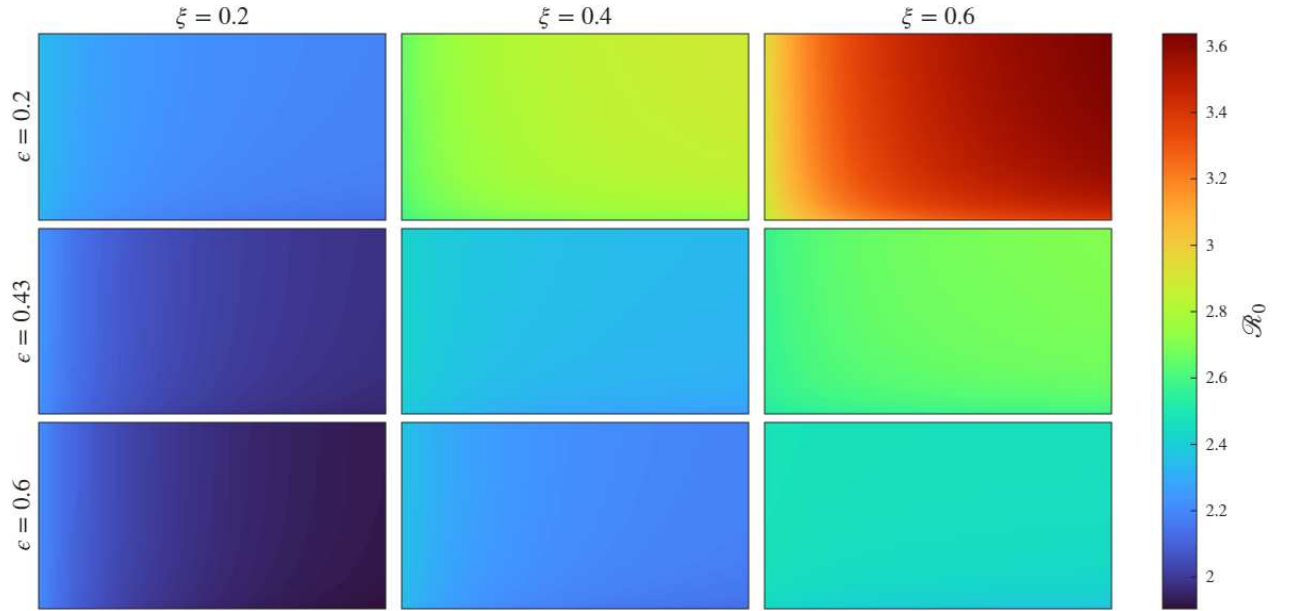


Figure 6: Heatmap showing the joint effect of the infectivity reduction parameter, ξ , and the switching rate from first-line to second-line or third-line ART, ϵ , on the post-profiling reproduction number, $\mathcal{R}_0^{\text{post}}$.

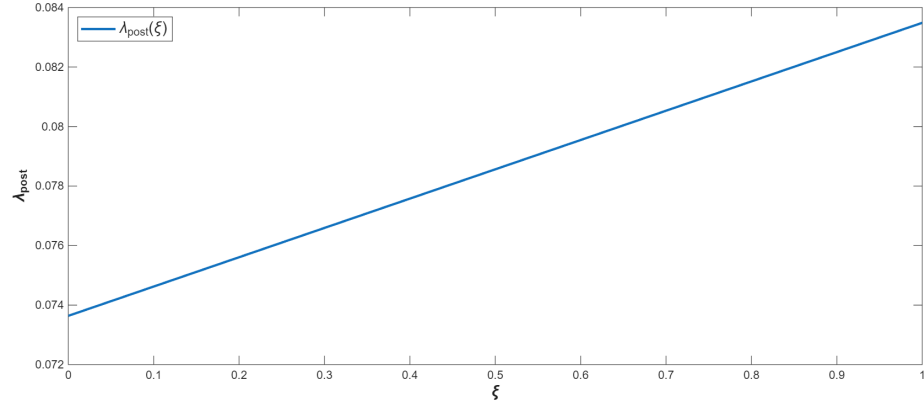


Figure 7: Effect of treatment effectiveness ξ on the post-resistance profiling force of infection λ_{post} .

From Figure 7, the post resistance profiling force of infection λ_{post} varies linearly with treatment efficacy parameter ξ . When $\xi = 1$, $\lambda_{\text{post}} = \lambda_{\text{pre}}$, indicating a situation where resistance profiling and regimen switching do not provide extra transmission benefits. Delays in resistance testing, restricted access to second- and third-line antiretroviral medicine, or inadequate adherence assistance

are all contributing factors to this issue, which keeps people who don't respond well to first-line treatment highly transmissible. λ_{post} drops proportionally as ξ decreases from 1 to 0, this captures the transmission reducing impact of Botswana's ongoing efforts in routine viral load monitoring, resistance profiling, and rapid transition to effective second and third line ART regimens. When $\xi = 0.5$, treatment optimization and adherence efforts achieve partial viral suppression among individuals in the T_2 class, leading to a significant but insufficient reduction in HIV transmission.

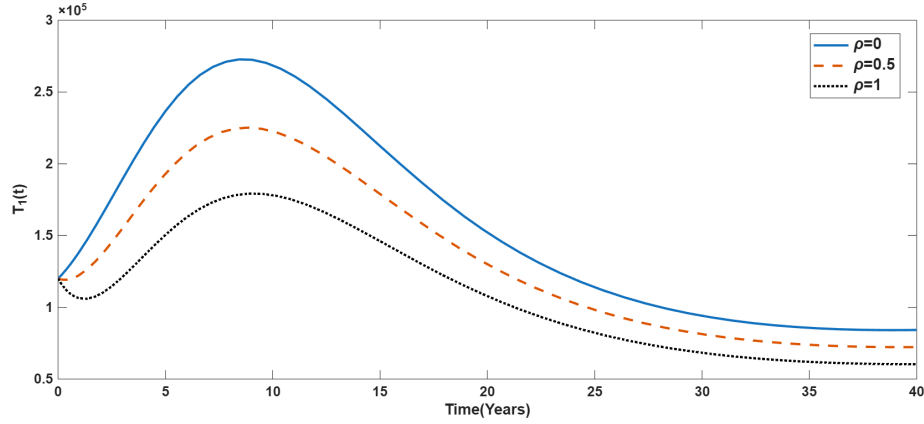


Figure 8: Effect of resistance profiling proportion ρ on the first-line treatment population $T_1(t)$

Figure 8 shows that increasing the resistance-profiling proportion reduces the population receiving first-line ART, $(T_1(t))$, because a larger proportion of individuals with drug-resistant HIV are identified before treatment allocation. Correspondingly, $(T_2(t))$ increases because more resistant individuals are initiated directly on appropriate second-line or third-line ART. This redistribution represents improved treatment allocation rather than increased treatment failure. Because individuals in (T_2) have reduced infectivity under effective advanced treatment, the shift contributes to a reduction in onward HIV transmission.

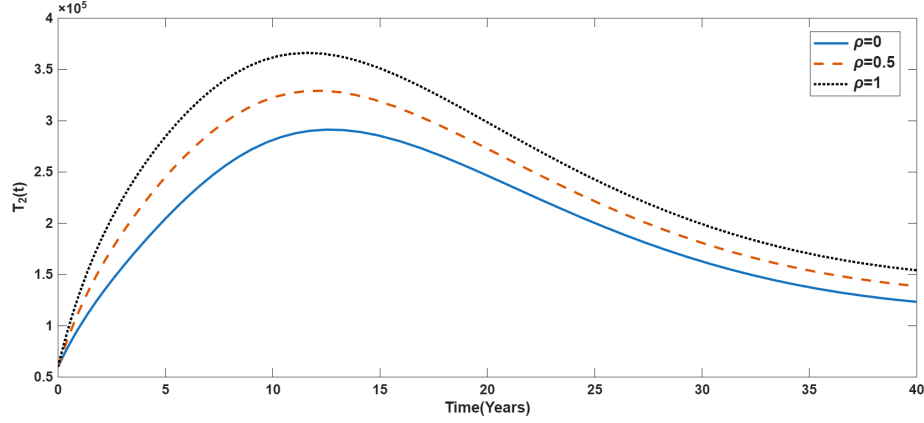


Figure 9: Effect of resistance profiling proportion ρ on the second-line treatment population $T_2(t)$

4.4 Comparison of resistant infections, advanced treatment uptake, and AIDS progression before and after profiling

Resistance profiling changes both the timing of entry into the second-line or third-line treatment compartment, $T_2(t)$, and its long-term population size. As the profiling proportion, ρ , increases, more individuals with drug-resistant HIV are identified before treatment initiation and are assigned directly to appropriate second-line or third-line ART. Consequently, resistance profiling may produce an initial increase in $T_2(t)$ because resistant cases enter this compartment earlier rather than passing through unsuccessful first-line treatment.

However, effective treatment in $T_2(t)$ reduces the infectious period, onward transmission, and progression of resistant infection. Therefore, the long-term number of individuals in $T_2(t)$ may decrease after profiling as the overall burden of drug-resistant HIV declines. Thus, an increase in early treatment allocation to $T_2(t)$ does not necessarily imply a larger long-term $T_2(t)$ population.

Figure 10 shows that the number of individuals infected with drug-resistant HIV, $I_r(t)$, is lower after resistance profiling. This reduction results from earlier identification and appropriate treatment of resistant infections, which limits their duration of infectiousness and subsequent transmission.

Figure 11 compares the population receiving second-line or third-line ART before and after profiling. The interpretation of this figure depends on the simulation period. If $T_2(t)$ is initially higher after profiling, this reflects earlier and more appropriate treatment allocation. If $T_2(t)$ becomes lower at later times, this reflects the reduction in the overall burden of resistant infection.

Figure 12 shows that progression to AIDS, $A(t)$, is reduced after profiling. Earlier allocation of individuals with drug-resistant HIV to effective treatment reduces treatment failure and slows disease progression. Overall, the results indicate that resistance profiling improves treatment allocation and

reduces resistant infections and AIDS progression.

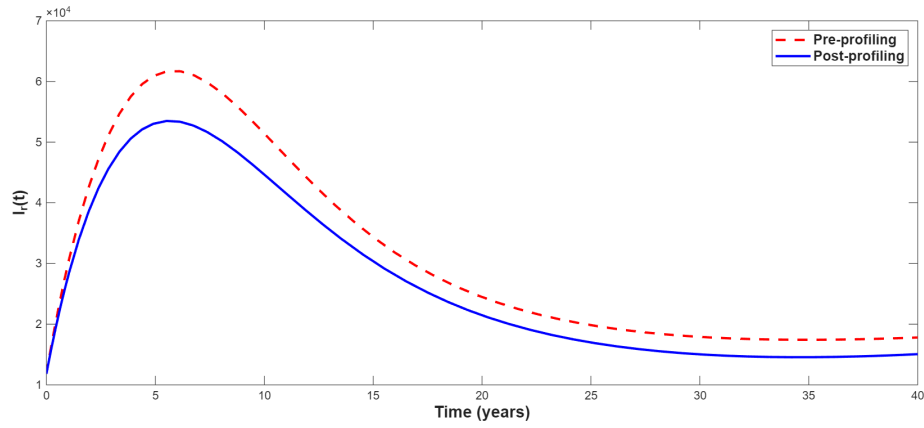


Figure 10: Comparison of $I_r(t)$ before and after resistance profiling.

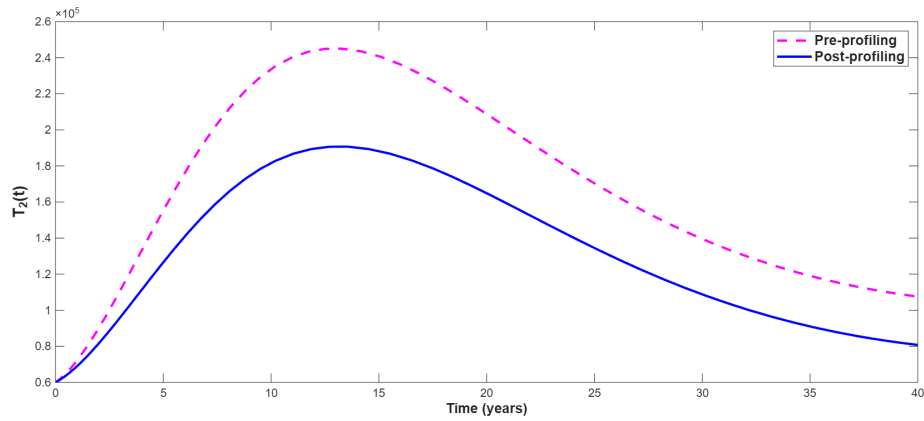


Figure 11: Comparison of $T_2(t)$ before and after resistance profiling.

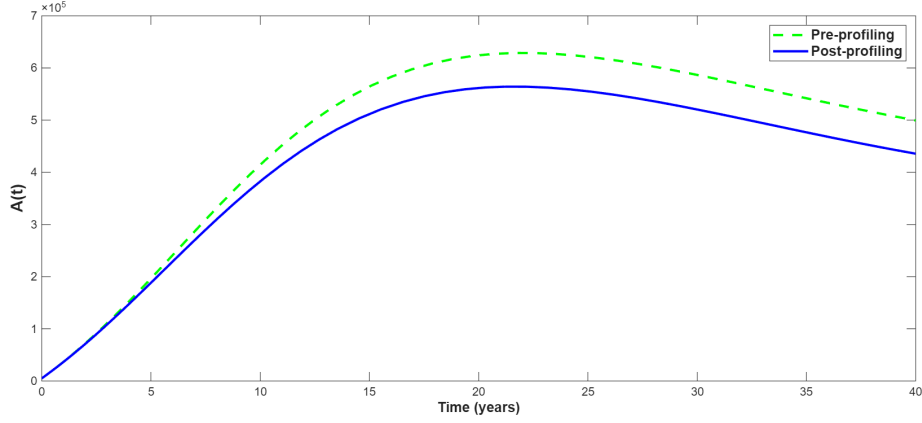


Figure 12: Comparison of $A(t)$ before and after resistance profiling.

5 Conclusion

This work developed and assessed two mathematical models to evaluate the influence of HIV medication resistance and resistance profiling on HIV/AIDS transmission dynamics in Botswana. Our modeling framework captures the critical transition from pre-resistance profiling, where all infected individuals initiate first-line ART regardless of resistance status, to post-resistance profiling, where individuals with resistant virus are identified and directed to appropriate second-line or third-line regimens. We derived expressions for the basic reproduction numbers $\mathcal{R}_0^{Pre}$ and $\mathcal{R}_0^{Post}$ using the next-generation matrix approach, demonstrating that $\mathcal{R}_0^{Post} < \mathcal{R}_0^{Pre}$ when the infectivity reduction parameter $\xi < 1$. This inequality confirms that resistance profiling provides a measurable epidemiological benefit by reducing the overall transmission potential of the population.

Numerical results revealed several critical insights for HIV program policy. First, the heatmap analysis of $\mathcal{R}_0^{Post}$ demonstrates effects between the infectivity reduction parameter ξ and the switching rate ϵ ; simultaneous improvements in both dimensions yield disproportionately large reductions in transmission potential. Second, increasing the resistance profiling proportion ρ produces a beneficial redistribution between treatment classes: the first-line treatment population $T_1(t)$ decreases while the second and third-line population $T_2(t)$ increases, reflecting more appropriate therapy allocation. Third, comparative simulations before and after profiling demonstrate reductions in resistant infections ($I_r(t)$) and AIDS progression ($A(t)$), together with more appropriate allocation of individuals with resistant HIV to second-line or third-line ART in ($T_2(t)$).

The linear correlation between λ_{Post} and ξ has significant implications for policy. When $\xi = 1$, which means that optimised regimens do not lower transmission, $\lambda_{Post} = \lambda_{Pre}$, and resistance profiling does not help. This is because health systems fail, such as when resistance testing takes

too long, access to second-line drugs is limited, or adherence support is poor. On the other hand, as ξ gets closer to zero, which means that advanced regimens are effectively suppressing the virus, the force of infection goes down by the same amount. This link measures how Botswana's continued investments in routine viral load monitoring and quick regimen switching affect the spread of the disease. Our results support multiple policy suggestions for Botswana and equivalent high-HIV-burden contexts. First, a universal resistance profile should be done before starting ART to stop the spread of resistant strains and the build-up of resistance variants. Second, it is important to improve laboratory capacity and supply chains for second-line and third-line regimens in order to get the most out of profiling. Without drug availability, the profile parameter ρ cannot be successfully improved. Third, adherence support programs that are specifically designed for those on advanced regimens will make the most of the reduction in infectivity that ξ shows. Fourth, we need to keep an eye on drug resistance that is transmitted and that people get, so that we can update profile algorithms as resistance patterns change.

Our study has some limitations that indicate possibilities for future research. Our model does not capture the heterogeneous contact patterns of key populations, including sex workers and men who have sex with men, who may have distinct resistance profiles and treatment access barriers. We did not incorporate pre-exposure prophylaxis (PrEP) or long-acting injectable antiretrovirals, which are increasingly important components of Botswana's prevention portfolio. The model also assumes that resistance testing is perfectly specific. However, in practice, incomplete sensitivity data or delays in getting results could reduce the effectiveness of the profiling.

In conclusion, our modelling study shows with numbers that HIV drug resistance profiling, when done alongside access to effective second-line and third-line therapy, lowers transmission at the community level and improves clinical outcomes. Botswana is still making progress toward the UNAIDS 95-95-95 goals and is working to keep its WHO Gold Tier certification for stopping mother-to-child transmission. Adding resistance profiling to standard care is a very effective way to deal with the growing problem of HIV drug resistance.

Conflict of interest

The authors declare that there is no conflict of interest concerning the publication of this article.

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Data Availability Statement

The dataset analysed during the current study are available in the UNAIDS repository, <https://aidsinfo.unaids.org/>

CRediT Author Statement

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