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Modelling the Effects of Antiretroviral Therapy on Kidney Diseases Among HIV Infected Individuals in Tanzania

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Abstract

This study examined the role of highly active antiretroviral therapy (HAART) in the dynamics of kidney diseases among HIV-infected individuals. A deterministic model was formulated for the dynamics of kidney disease in HIV-infected people with HAART as treatment in the model. Numerical simulations showed that though HAART reduces HIV progression to the AIDS stage, there is an increase in HIV-related kidney diseases. Also, the result obtained in this study showed that reducing the effective contact rate of HIV and improving the effectiveness of HAART by 99% in preventing the progression from HIV without symptoms group to HIV-related kidney diseases can decrease the prevalence of HIV-related kidney diseases. Therefore, based on the findings obtained to reduce the population of HIV-related kidney diseases in the general population Pharmacists should focus on improving HAART which will reduce the progression of kidney diseases from HIV.

Keywords: Kidney diseases; human immunodeficiency virus; highly active antiretroviral therapy; sensitivity analysis; HIV-infected individuals.

Introduction

The human immunodeficiency virus (HIV) affects the immune system of human beings by restoring its genetic material as ribonucleic acid (RNA) (Huo and Chen 2015, Teklu and Rao 2022). According to UNAIDS (2023), by 2022, 39 million people were living with HIV/AIDS and in that particular 680,000 deaths were from AIDS-related diseases worldwide. Since the introduction of Highly Active Antiretroviral Therapy (HAART) in 1996 there has been a significant improvement in morbidity and mortality of HIV-infected patients (Lee et al. (2013)). However, the increased accessibility to HAART has led to new challenges, including a higher burden of renal and genitourinary diseases among HIV-infected individuals (Kalyesubula et al. (2014)). Kidney diseases in HIV-infected individuals can be due to HIV infection, opportunistic infections, and as a result of HAART-related toxicities (nephrotoxicity) (Kalyesubula and Perazella 2011). The Tanzanian Government started scaling up its antiretroviral treatment (ART) program from referral, regional and district hospitals to primary health care facilities in October 2004 (URT 2003)

Chronic Kidney Disease (CKD) is a condition where the kidneys are damaged and cannot function adequately and may be related to the presence of other diseases such as diabetes, high blood pressure, and kidney failure (Alfano et al. (2019), CDC 2019). In HIV-infected individuals, CKD and HIV-associated nephropathy (HIVAN) are non-infectious complications that can progress to end-stage renal disease (ESRD) if they

remain untreated (Abraham et al. (2015), Gudaz et al. (2020)). The relationship between HIV and kidney disease was first reported in New York and Miami in 1984 (Samje et al. (2020)). However, few studies have been done on kidney diseases in HIV/AIDS-infected individuals in middle and low-income countries due to lack of data. A study conducted by Diana et al. (2022) analyzed the relationship between kidney disease and HIV infection before and after the introduction of antiretroviral therapy (ART) in South Africa since they introduced ART in the year 2002. This study focused on HIV-positive individuals who received kidney biopsies from 1989 to 2014 and the results showed that ART had contributed to a reduction in HIVAN which is the most common in the pre-ART era(before 2002), but has not eliminated it.

Tanzania like many other countries in the Sub Sahara is faced with a growing burden of non-communicable diseases such as cardiovascular, diabetes, and kidney dysfunction. These non-communicable diseases have put a strain on the health system which initially was overwhelmed by managing contagious diseases (Mayige et al. (2011)). Kidney diseases have contributed significantly to increased risk and burden of cardiovascular problems as well as mortality in Tanzania and other low- and middle-income countries (Jager and Fraser 2017). Several studies conducted in Tanzania have consistently reported a high prevalence of CKD among HIV patients receiving HAART, with factors such as advanced age, male gender, hypertension, and high viral load associated with CKD (Mapesi et al. (2018), Mwemezi et al. (2020)). Also, the work by Kilonzo et al. (2016) has demonstrated a high prevalence of kidney dysfunction in adult patients which leads to mortalities in Mwanza, Tanzania.

Another study by Peck et al. (2014), showed that HIV-infected adults in Tanzania who had HAART for more than two years have a high risk of getting hypertension and kidney diseases. However, it has been shown that widespread antiretroviral treatment has reduced the incidence of opportunistic infections among HIV-infected patients, hence improving health and life expectancy to near normal(Akinyemi et al. (2017)). According to the study by Mwanjala et al. (2022), the prevalence of renal dysfunction increases by 3% for each year of age. Additionally, the study conducted by Mapesi et al. (2021) found that as age increases, the rate of kidney diseases also increases among HIV individuals.

The length of time HIV-infected individuals on HAART has been identified as a predictor of kidney diseases. According to the Tanzania HIV Impact Survey of 2022-2023, the prevalence of HIV among adults in Tanzania is 4.4% and, in 2016, Tanzania started using the WHO's plan to test and treat people infected with HIV. Based on the research conducted by Panga et al. (2022) in Tanzania, it had shown that kidney disease is a significant health problem among individuals with HIV infection and length of time on HAART is among of risk factors. Several studies (Mapesi et al. (2021), Mwanjala et al. (2022)), have shown that the prevalence of renal dysfunction and kidney disease increases with age, and the duration of time on highly active antiretroviral therapy (HAART) is a predictor of kidney diseases in this population.

A study by Wu et al. (2022) developed a mathematical model that considers three age groups, spatial diffusion, infection rates dependent on viral load, and conversion rates to analyze the global dynamics of HIV/AIDS transmission. Their results showed that implementing intervention measures targeting both individuals and general populations is highly effective in controlling the spread of the disease. Also, mathematical models have been used to study the impact of HAART on HIV-related kidney diseases. Some studies have shown that HAART can reduce the progression of kidney diseases and mortality rates among HIV/AIDS-infected individuals who are in the AIDS stage. A study by Gudaz et al. (2020) developed a mathematical model that highlighted the importance of reducing AIDS cases to lower the prevalence of HIV/AIDS-related kidney diseases. Their results indicated that the higher effectiveness

of HAART in preventing the progression to AIDS and from AIDS to HIV-related kidney disease results in fewer HIV patients with kidney diseases. Also, Hull-nye et al. (2020) developed a mathematical model to examine the effect of HAART on the dynamics of people with AIDS and HIV-related kidney diseases. Their results indicated that if HAART can reduce both the progression to AIDS and HIV-related kidney diseases at the same time, the number of HIV/AIDS patients with kidney diseases will be low, even if HAART efficacy is lower.

Due to the common occurrence of HIV-related kidney diseases in African populations and the current practice of HIV-infected individuals initiating HAART regardless of CD4 cell counts, there has been a noticeable increase in the prevalence of kidney disease among HIV-infected individuals (Alfano et al. (2019)). Therefore, to understand the impact of HAART on HIV-related kidney diseases, a mathematical model was used in this study to investigate the effects of HAART at different stages of HIV infection since kidney disease among HIV patients is due to direct renal cell injury from HIV infection associated chronic inflammation and other risk factors such as long term use of nephrotoxicity and opportunistic diseases.

Previous mathematical studies only looked at the AIDS stage because only people with AIDS could use HAART. Today, any HIV patient can use HAART, regardless of their CD4 cell counts. This study extends Gudaz et al. (2020) work by examining the impact of HAART on different groups of HIV patients and determining how effective HAART is in reducing or increasing the number of HIV/AIDS patients with kidney diseases. The study aims to provide insights into the relationship between HAART and HIV-related kidney diseases in Tanzania by using data from World Health Organization (WHO) and National AIDS Control Programme (NACP).

Materials and Methods

Model Formulation

According to the Center for Disease Control and Prevention (CDC), the transmission dynamics of HIV has three stages: acute HIV, chronic HIV, and full-blown status known as AIDS. A deterministic model is formulated in which the human population is divided into four classes to describe how individuals progress from one disease status to another. The susceptible class($S(t)$) is composed of individuals who are free from HIV infection but are capable of becoming infected if they are sufficiently exposed to the disease. HIV compartment($H(t)$) includes all HIV-infected individuals with the number of CD4 cells greater than $200 cell/mm^3$ (acute and chronic stage) and can transmit the disease to susceptible individuals at rate β. As the body's immunity weakens individuals from the acute and chronic HIV classes may progress to the AIDS compartment (A(t)) at rate ρ. Individuals in the HIV/AIDS-related kidney diseases compartment ($K(t)$) are HIV-infected patients with kidney diseases before or after entering stage 3 of HIV infection. This compartment includes individuals with HIV and AIDS who develop kidney diseases and progress to K(t) at rates of s_1 and s_2, respectively. The dotted lines represent social interactions between S, H, and A, which were also analyzed in the study by (Olaniyi et al. (2024)).

The study considers the following assumptions: the HAART is administered to all individuals in the three infection classes and the efficacy of HAART(e, j, α) may vary from 0% to 100%, It is assumed that HIV and susceptible individuals experience natural death at the rate μ since the asymptotic stage, individuals infected with HIV experience no symptoms or only mild ones. Thus, HIV-related death during this stage is assumed to be negligible (Apenteng and Ismail 2015). In AIDS and HIV-related kidney disease compartments, individuals die naturally from causes not related to AIDS and HIV-related kidney diseases at rates of μ_A and μ_K respectively (Hull-nye et al. (2020) AIDS-related mortality is denoted by c and can be reduced through HAART, which is represented by e. Similarly, mortality due to

HIV- related kidney diseases is denoted by δ and can be reduced through ART, represented by j. Other parameters and their description are represented in Table 1.

Table 1: Description of parameters and symbols used in the model (1)

Parameter	Description
Λ	Recruitment rate of susceptible individuals
β	Effective transmission rate
s_2	Progression rate from AIDS to HIV-related kidney diseases
s_1	Progression rate from HIV to HIV -related kidney diseases
r	Effect of HAART to block the progression from HIV to HIV-related kidney diseases
α	Effect of HAART to block the progression from HIV to AIDS
μ	Natural death rate of HIV and susceptible individuals
h	Effect of HAART to reduce the progress from AIDS to HIV-related kidney disease

The total population $N(t)$ at any time t is given by $N(t) = S(t) + H(t) + A(t) + K(t)$. The force of infection is represented as $\lambda_H = \frac{\beta H + \eta A}{N}$ where η is the probability of individuals in AIDS state transferring infection, but individuals in an AIDS compartment have a low probability of transferring infection ($\eta \approx 0$) due to their weakened health status and suffering opportunistic diseases (Akpa and Oyejola 2010, Habibah et al. (2020)). Therefore force of infection becomes $\lambda_H = \frac{\beta H}{N}$.

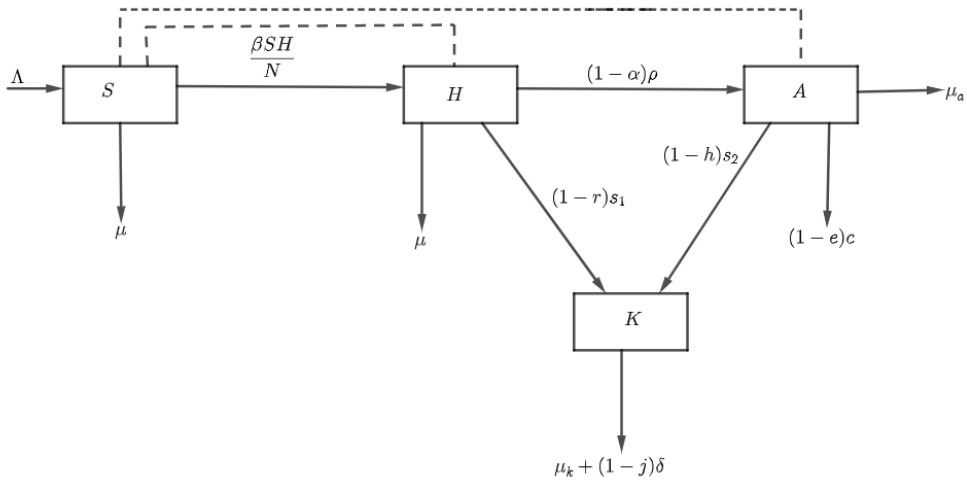


Figure 1: Flow diagram of HIV/AIDS-related kidney diseases

From Figure 1, and the model assumptions we get the following nonlinear system of differential equation:

$$\left.\begin{aligned}\frac{dS}{dt} &= \Lambda - \beta S\frac{H}{N} - \mu S\\ \frac{dH}{dt} &= \beta S\frac{H}{N} - (1-\alpha)\rho H - \mu H - (1-r)s_1 H\\ \frac{dA}{dt} &= (1-\alpha)\rho H - \mu_A A - (1-e)cA - (1-h)s_2 A\\ \frac{dK}{dt} &= (1-h)sA + (1-r)s_1 H - \mu_K K - (1-j)\delta K\end{aligned}\right\} \quad (1)$$

with initial condition $S(0) > 0, H(0) \geq 0, A(0) \geq 0, K(0) \geq 0$.

Positivity and boundedness of the model

Since the system deals with the human population the model has to be biologically well-posed, it is important to show that all state variables are always non-negative with positive initial conditions in a bounded region. It is required to show that the solution of the model system (1) is non-negative and bounded for all time $t > 0$. The following theorems are considered;

Theorem 3.1 *At initial conditions, the solutions of model system*(1) *are non-negative for all time* $t > 0$.

Proof: Suppose that the initial condition of the state variables are non-negative, then the first equation of the model (1) becomes,

$\frac{dS}{dt} = \Lambda - \beta S\frac{H}{N} - \mu S \geq -\left(\beta\frac{H}{N} + \mu\right)S$ implying that $S(t) \geq S(0)e^{-\int_0^t\left(\beta\frac{H}{N}+\mu\right)dt} > 0$

since the exponential function has a non-negative quantity. Similarly, other solutions of the model can be represented as

$$H(t) \geq H(0)e^{-\int_0^t(\mu+(1-\alpha)\rho+(1-r)s_1)dt} > 0$$
$$A(t) \geq A(0)e^{-\int_0^t((1-e)c+\mu_A+(1-h)s_2)dt} > 0$$
$$K(t) \geq K(0)e^{-\int_0^t(\mu_k+(1-j)\delta)dt} > 0$$

Hence all the solutions of the system (1) are non-negative for $\forall t > 0$.

Theorem 3.2 *All solutions of the system* (1) *are bounded in the region*

$$\Omega = \left\{(S,H,A,K) \in \mathbb{R}^4_+, \frac{\Lambda}{\mu}\right\}$$

Proof: Given that $N(t) = S(t) + H(t) + A(t) + K(t)$, adding the equations in system of equation (1) gives

$\frac{dN}{dt} = \Lambda - (S+H)\mu - (1-e)cA - \mu_A A - \mu_K K - (1-j)\delta K$. That $\frac{dN}{dt} \leq \Lambda - \mu N$. By integration $N(t) \leq \left(N(0) - \frac{\Lambda}{\mu}\right)e^{-(\mu t)} + \frac{\Lambda}{\mu}$ $\forall t \geq 0$, hence $N(t) \longrightarrow \frac{\Lambda}{\mu}$ as $t \longrightarrow \infty$. Hence, the model is bounded and the system is epidemiological meaningful and well-posed.

Existence of Equilibrium Solutions

Disease-free equilibrium point of the model

Analyzing the model to determine the conditions necessary for the existence of an equilibrium/steady state which is referred to as the HIV-related kidney disease-free steady state

(disease-free equilibrium). This is the equilibrium at which the population remains in the absence of HIV infection($H = A = K = 0$). Therefore to find the steady state, equate all equations in system (1) to zero, and solve for S^*, H^*, A^*, K^*, to get

$\Lambda - \beta SH - \mu S = 0 \quad \Rightarrow S^* = \frac{\Lambda}{\mu}$

Therefore the disease-free equilibrium point can be represented as

$$E_0 = (S^*, H^*, A^*, K^*) = \left(\frac{\Lambda}{\mu}, 0,0,0\right)$$

Reproduction Number

The effective reproduction number in the context of our model is the number of secondary cases produced by a typical infectious HIV-positive patient, regardless of whether the patient has developed kidney disease or not, and introduced into a susceptible community in the presence of HIV treatment. The effective reproduction number of the system was derived by using the next-generation matrix proposed by Van den Driessche and Watmough (2002). The matrices F and V are to be determined and evaluated at equilibrium points in the model system (1). They be obtained as follows:

$F = \left[\frac{\partial F_i}{\partial x}\right]_{E_o}$ and $V = \left[\frac{\partial V_i}{\partial x}\right]_{E_o}$

Where the infectious groups are represented by $x^T = (H, A, K)$, F_i is the appearance of new infections in a compartment i while V_i stands for the remaining transition terms given by $V_i = V_i^- - V_i^+$, with V_i^+ is a rate of transfer of individuals into a compartment i and $V_i^{-1}$is the rate of transfer of individuals out of a compartment i

$$F_i = \begin{bmatrix} \frac{\beta S}{N} \\ 0 \\ 0 \end{bmatrix} \text{ and } \quad V_i = \begin{bmatrix} (1-\alpha)\rho H + \mu H + (1-r)s_1 H \\ -(1-\alpha)\rho H + (1-e)cA + \mu_A A + (1-h)s_2 A \\ -(1-j)\delta K + \mu_K K - (1-r)s_1 H - (1-h)s_2 A \end{bmatrix}$$

The partial derivatives of F_i and V_i, evaluated at disease-free equilibrium E_0 are given as

$$F = \begin{bmatrix} \beta & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and}$$

$$V = \begin{bmatrix} (1-\alpha)\rho + \mu + (1-r)s_1 & 0 & 0 \\ -(1-\alpha)\rho & (1-e)c + \mu_A + (1-h)s_2 & 0 \\ -(1-r)s_1 & -(1-h)s_2 & -(1-j)\delta + \mu_K \end{bmatrix}$$

The inverse of V was calculated and represented as V^{-1}.

After some calculation, $FV^{-1} = \begin{bmatrix} \frac{\beta}{(1-\alpha)\rho+\mu+(1-r)s_1} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$

The eigenvalues are

$$\lambda_{1,2,3} = \left(\frac{\beta}{(1-\alpha)\rho+\mu+(1-r)s_1}, 0, 0\right) \qquad (2)$$

The effective reproduction number (R_e) of the model system (1) is the dominant eigenvalue of the next generation matrix of FV^{-1} in which from equation (2) the following is obtained.

$$R_e = \frac{\beta}{(1-\alpha)\rho+\mu+(1-r)s_1}$$

In the absence of control strategies that is, α = 0 and r = 0, then, the basic reproduction number R_0 will be $R_0 = \frac{\beta}{\rho+\mu+s_1}$. From R_e the increased effect of therapy(HAART) reducing the prevalence of HIV/AIDS-related kidney diseases.

Local stability of the Disease-Free Equilibrium

Local stability of the disease-free equilibrium point E_o is determined by first finding the Jacobian matrix of the model system (1) for each state variable (i.e *S,H,A,K*). The populations have a unique disease-free steady state E_0 whenever the infectious disease is absent. To investigate the stability of HIV-related kidney disease-free equilibrium, the Jacobian matrix is constructed

$$J = \begin{bmatrix} -\mu - \frac{\beta H}{N} & -\frac{\beta S}{N} & 0 & 0 \\ 0 & -D_1 + \frac{\beta S}{N} - \mu & 0 & 0 \\ \frac{\beta H}{N} & (1-\alpha)\rho & -(1-e)c - \mu_A + (1-h)s_2 & 0 \\ 0 & (1-r)s_1 & (1-h)s & -(1-j)\delta + \mu_K \end{bmatrix} \quad (3)$$

where $D_1 = \rho(1-\alpha) + (1-r)s_1$

For disease-free equilibrium, the Jacobian matrix of equation(3) is represented as

$$J = \begin{bmatrix} -\mu & -\beta & 0 & 0 \\ 0 & -D_1 + \beta - \mu_H & 0 & 0 \\ 0 & (1-\alpha)\rho & -(1-e)c - \mu_A - (1-h)s_2 & 0 \\ 0 & (1-r)s_1 & (1-h)s_2 & -(1-j)\delta + \mu_K \end{bmatrix}$$

which gives the eigenvalues as follows;

$$\lambda_1 = -\mu$$

$$\lambda_2 = -((1-h)s + c(1-e) + \mu_A)$$

$$\lambda_3 = -\rho(1-\alpha) + \beta - (1-r)s_1 - \mu_H$$

from equation 2, $\beta = R_e(\rho(1-\alpha) + (1-r)s_1 + \mu)$ then substitute into λ_3 and simplify

$$\lambda_3 = (R_e - 1)(\rho(1-\alpha) + (1-r)s_1 + \mu_H) < 0 \; if \; R_e < 1$$

$$\lambda_4 = -(\mu_K + (1-j)\delta).$$

The eigenvalues for the HIV-related kidney disease-free equilibrium are negative when $R_e < 1$ indicating that the dynamical system (1) is locally asymptotically stable. This implies that if $R_e < 1$, HIV can be eliminated from the community, leading to a reduction in kidney disease cases. However, when $R_e < 1$, HIV will spread within the population, leading to an increase in kidney disease cases since kidney diseases in HIV individuals can be caused by HIV infection.

Global stability of the Disease-Free Equilibrium.

To gain insights into the global stability of the disease-free equilibrium, the following results were presented.

Theorem 3.3: *The disease-free equilibrium point E_o is global asymptotically stable if $R_e < 1$ otherwise unstable.*

Proof: The direct Lyapunov method is employed to analyze the global stability of equilibrium points. By using Lyapunov function such as$L: R_+^4 \longrightarrow R_+$ which is defined as

$$L(S,H,A,K) = (S - S^* \ln S) + (H - H^* \ln H) + (A - A^* \ln A) + (K - K^* \ln K)$$

Where $E_0 = (S^*, H^*, A^*, K^*) = \left(\frac{\Lambda}{\mu}, 0,0,0\right)$

The disease-free equilibrium point E_0 will be global stability as $t \longrightarrow \infty$ if $R_e < 1$ then $\frac{dL}{dt} < 0$ and $\frac{dL}{dt} = 0$ at an equilibrium point E_0.

By derivation of Lyapunov function and using eq (1), we get

$$\Rightarrow \frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right)\frac{dS}{dt} + \left(1 - \frac{H^*}{H}\right)\frac{dH}{dt} + \left(1 - \frac{A^*}{A}\right)\frac{dA}{dt} + \left(1 - \frac{K^*}{K}\right)\frac{dK}{dt}$$

$$\Rightarrow \frac{dL}{dt} = [\beta - \mu - (1-\alpha)\rho - (1-r)s_1]H$$

Simplify the above equation in terms of R_e we get

$$\Rightarrow \frac{dL}{dt} = [\mu + (1-\alpha)\rho + (1-r)s_1](R_e - 1)H$$

Then, $\frac{dL}{dt} < 0$ if $R_e < 1$ and $\frac{dL}{dt} = 0$ only if $R_e = 1$ or $H = H^* = 0$ at E_0

Hence based on Lyapunov method, it is verified that E_0 is globally stable.

Numerical simulation

In this section numerical simulation is carried out using software Python. The parameters used in model (1) will be estimated using data from Tanzania, obtained from the WHO, NACP, and the existing literature.

Parameter estimations

In this section, the HIV data from Tanzania are used in the fitting process to estimate the parameters used in the model (1). Despite the first case of AIDS being reported in 1983, documentation in Tanzania started in 1990 due to limited records, and the HIV data from 1990 to 2022 was obtained from the UNAIDS 2023 estimates (UNAIDS 2023). In the estimation of parameters, aim at obtaining the most suitable parameters that will ensure consistency between numerically obtained data, and clinically observed data. The model parameters to be estimated can be obtained by fitting the model to real data by using the Least squares method as explained by (Gavin 2019, Ndanguza et al. (2013)). This consists of minimizing the residual sum of square (RSS) which is given as $\sum_{i=1}^{x}(Y_i - f(Y_i,\theta)^2$ where Y_i represent observed data and θ is the parameters to be estimated. The data used were for Tanzanians living with HIV/AIDS of all sexes and ages from the year 1990 − 2000 (time before HAART started to be used in Tanzania) and to determine the effect of HAART data from 2001 − 2020 were used to estimate parameters for HAART effectiveness.

The aim is to evaluate the effect of HAART on HIV/AIDS with related kidney disease populations and project prevalence. In the model natural mortality rate,μ is fixed based on the life expectancy of Tanzanians. According to a database from World Bank (Karacan et al. 2020), the average life expectancy of Tanzanian is 67.3 years, hence $\mu = \frac{1}{67.3}$. The statistical data from the NACP report by Swai et al. (2009) indicates that there were 470,000 individuals with HIV and 129,515 with AIDS in 1990. Consequently, the initial susceptible population S_o was determined by subtracting all infections from the total population in that year. Since HAART started in 2001, all intervention parameters were initially set to zero when analyzing the disease dynamics before intervention. After the introduction of HAART, the initial parameters for its effectiveness were set within the range of 0 to 1. The remaining parameters are estimated by using the Least squares method using data from the National AIDS Control Programme (NACP) and UNAIDS respectively. Hence, the model parameters to be estimated include $\theta = \Lambda, \beta, \rho, c, s_1, s_2$.

Table 2: Estimated Parameter value for HIV/AIDS model by least square method.

Parameter	Estimated before HAART	Estimated after HAART
Λ	61799	2290023
β	0.62 per year	0.28991 per year
ρ	0.4789923 per year	0.244 per year
c	0.84 per year	0.5494 per year
μ_A	1/55 per year	Marcus et al. (2016)
μ	$1/67.3$	Karacan et al. (2020)

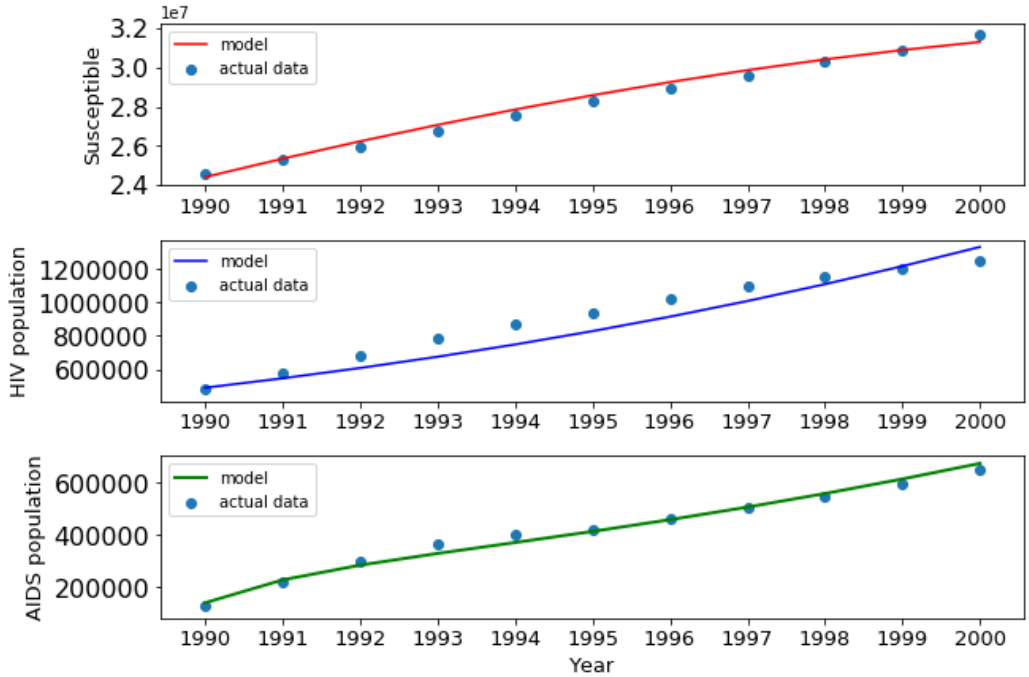
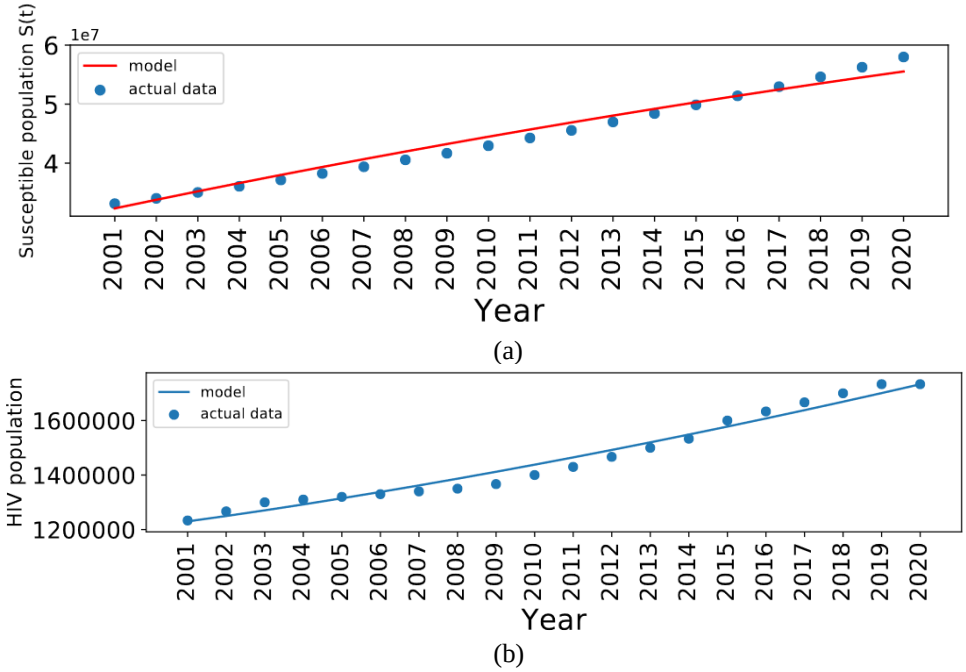
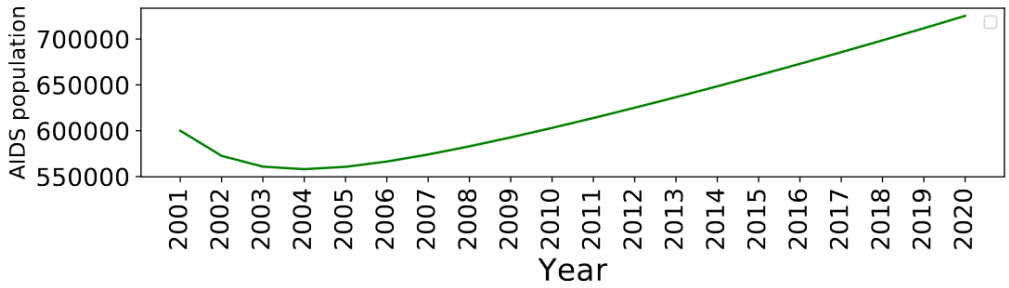


Figure 2: The prevalence of infectious groups in pre- HAART era

The data in Table (2) show that the mean time between HIV diagnosis and AIDS is about two years and one month and this occurs because most diagnoses are in more advanced stages. Also, the results show that the mean time from AIDS diagnosis to death is one year and two months.





(c)

Figure 3: Dynamics of susceptible and infected populations from 2001 to 2020

Since HIV/AIDS-related kidney disease variables started to be documented in 2018, analysis was done by considering the data from 2018 to 2020 to know the trend to reduce the disease. By using data from NACP, the following values of parameters are estimated by fitting data in the model (1).

Table 3: Parameters value for HIV/AIDS-related kidney diseases.

Parameter	**Estimated**	**source**
Λ	4000000	Estimated
β	0.9284 per year	Estimated
ρ	0.759989 per year	Estimated
c	0.1 per year	Estimated
s_1	0.087591 per year	Estimated
s_2	0.0103454 per year	Estimated
δ	0.67 per year	Gudaz et al. (2020) without treatment
μ_K	1⁄5 per year	Gudaz et al. (2020)
μ_A	1⁄55 per year	Marcus et al. (2016)

With the value in Table (3), the control reproduction number of the model (1) is $R_e \approx 1.0767 > 1$. This means that each HIV individual, on average, is spreading the infection to one individual. HAART can significantly improve the health outcomes for individuals with HIV, but $R_e > 1$ indicates that HIV transmission in the community is still high. This means that HAART alone may not be enough to slow the spread of the epidemic. Also, the population of HIV/AIDS-related kidney diseases will increase in the future.

Effect of treatment on the dynamic of diseases

To investigate the dynamic of the system(1), numerical solution by using Python the estimated parameter values were used in a simulation to project the effect of HAART on both HIV/AIDS and HIV/AIDS-related kidney disease populations in Tanzania. By using parameter values in Table 1, the simulation was done in the absence of treatment(no effect of HAART). The results show that the population of HIV individuals and AIDS individuals will increase and reach a peak point before converging to an endemic equilibrium state as time increases as shown in Figure 4.

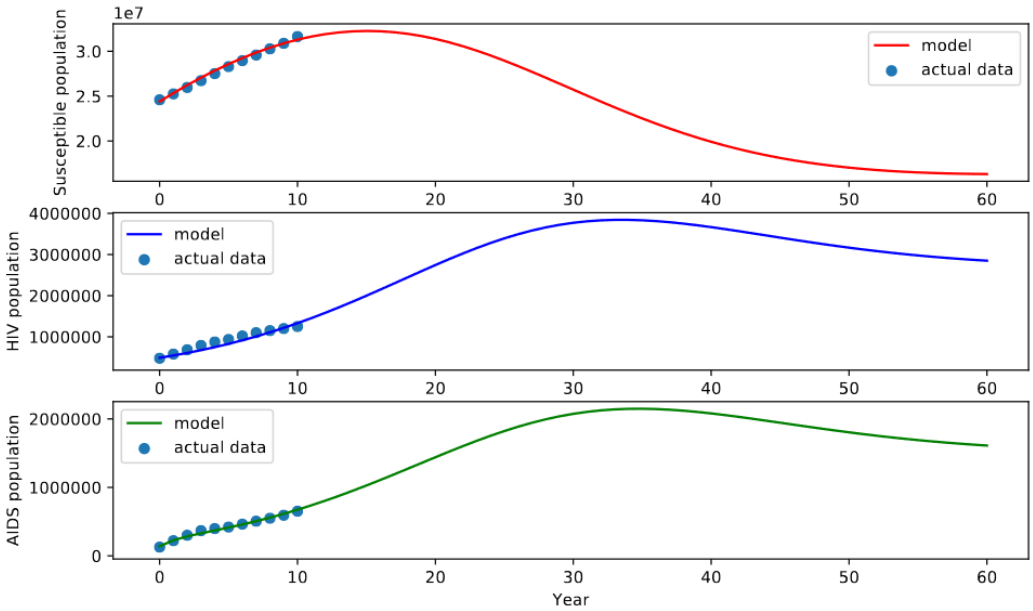


Figure 4: Projection from 2001 to 2050 with no treatment

The analysis of the effect of HAART on the HIV+ESRD population was done by considering the estimated parameter value in Table (3) with different values of the effect of HAART which vary between (0−1). The simulation of a model shows that the effect of HAART on the mortality due to HIV+ESRD is 0.403 because after diagnosis without treatment, the lifespan is 1.5 years (Gudaz et al. (2020)) and from fitted data, the lifespan is 2.7 years after diagnosis. Hence, taking HAART has led to an increased lifespan for individuals with HIV and ESRD.

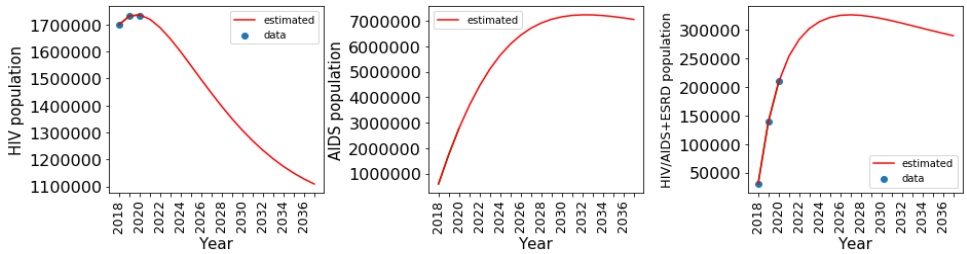


Figure 5: Dynamics of the infected population with $R_0 > 1$.

Figure (5) from the simulation shows that the prevalence of individuals who have HIV alone will decline in the upcoming years as the population of people with AIDS and HIV+ESRD will increase before reaching an endemic state.

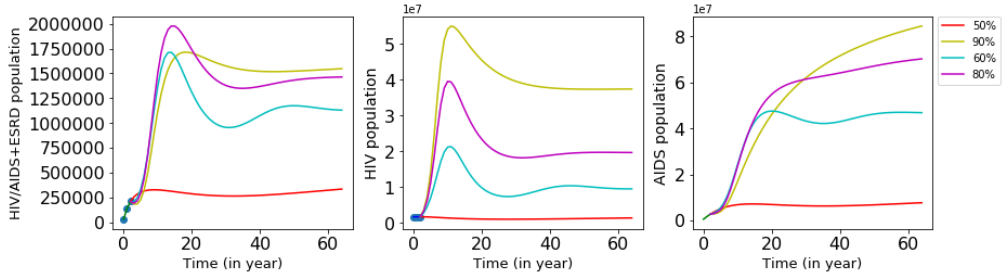


Figure 6: Simulation of the combined effect of HAART on infected individuals from 1990 to 2050.

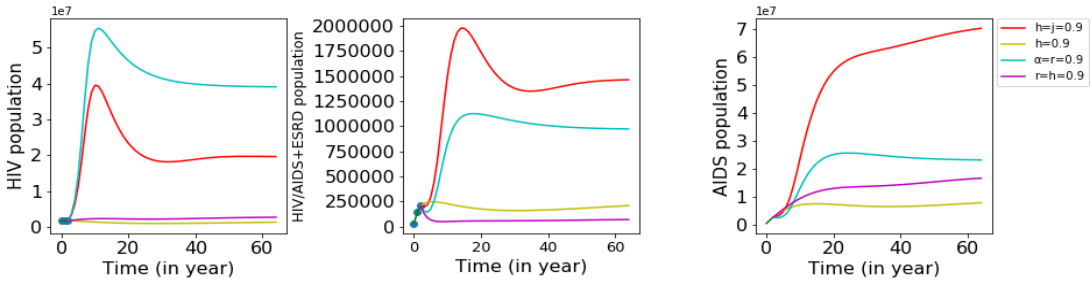


Figure 7: Variation of the effect of HAART on infected individuals.

When HAART not only blocks progression from AIDS to HIV+ ESKD (h = 0.9) but also blocks progression from HIV to HIV+ESRD(r = 0.9), the steady-state level of HIV+ ESRD is reduced to a minimum level compared to other HAART effectiveness as shown in Figure7*b*. In general, Figure 7 shows that when HAART can block progression to HIV+ESRD by 90%(h = 0.9) infected population will decrease in the future. This result is similar to other articles (Mwemezi et al. (2020), Mwanjala et al. (2022), Msango et al. (2011)) which found that renal disease does not depend on CD4 count. Therefore, as the population grows, there will be less disease-related mortality as well. The population of individuals with HIV/AIDS-associated kidney diseases will be reduced to zero once HAART is completely effective, and this will lessen the burden on society.

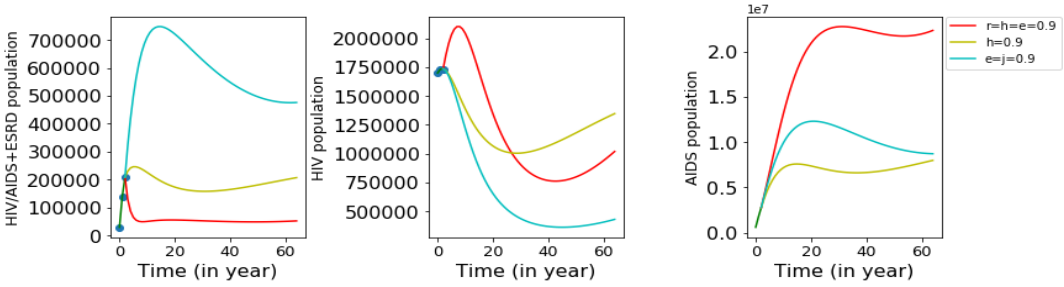


Figure 8: Different values of the effect of HAART on infected populations.

Figures 6 to 8 show the effect of varying HAART in the infected population. Figure 6 shows that after three years, the population of all infected groups will plateau when HAART has a 50% efficiency. However, when HAART efficacy is between 60% and 90%, the frequency of HIV+ESRD would grow dramatically for the first three years before declining to an endemic level. The model shows that strong gains can be

achieved when HAART can simultaneously reduce entry into the AIDS population as well as reduce progression to HIV+ESRD from infected groups, even if its effectiveness is lower (50%).

But Figure 9 shows that when the HIV transmission rate(β) decreases from 0.9 to 0.00128, the steady state of all the infected populations is reduced to zero. Regardless of parameter values to reduce/eliminate disease in society, the transmission rate/force of infection should decrease. This means that HAART only is not enough to reduce the epidemic in society but other strategies are needed to eliminate disease.

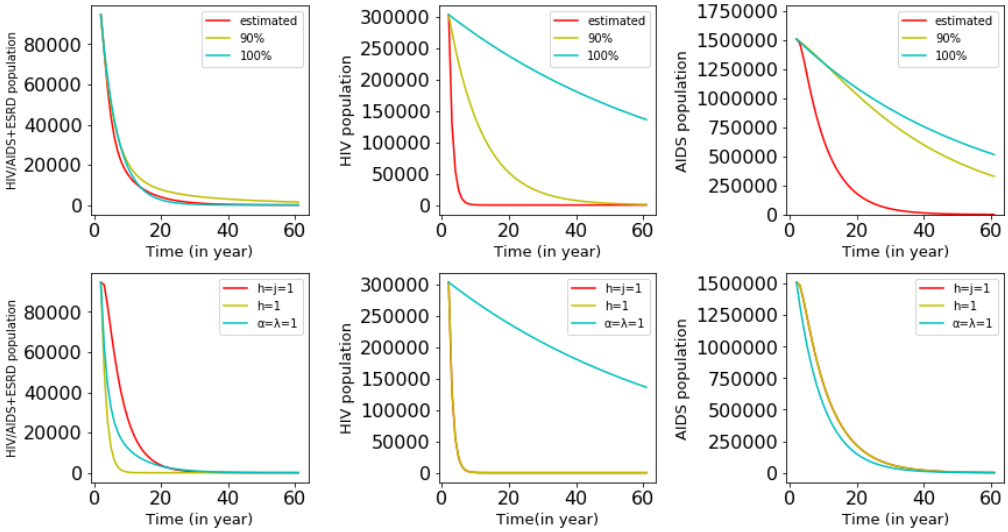


Figure 9: Effect of HAART on infected populations with β = 0.00128.

Also, the result shows that the prevalence of HIV-related kidney diseases might decrease if HAART effectively slows the progression from HIV to AIDS stage and this result is supported by research from Fiseha and Gebreweld (2021), which indicates that an increase in CD4 cell count is associated with a reduced risk of kidney diseases among HIV-positive individuals.

Sensitivity Analysis

Sensitivity analysis is a method used to assess how changes in the input model parameters of affect the output. In this section, a sensitivity analysis has been carried out to investigate the influence of parameter estimation uncertainties on the effective reproduction numbers (R_e). There are two types of sensitivity analysis methods based on local and global sensitivity analysis.

Local Sensitivity Analysis

Local sensitivity analysis evaluates how a single parameter influences the outcome while keeping all other parameters constant. The local sensitivity analysis of each parameter will be determined by using the normalized forward sensitivity index which is given as the sensitivity index of variable R_0 that depends on parameter p and is defined as $SI(p) = (\partial R_e/\partial p)*(p/R_e)$ (Chitnis et al. (2008)). For example, the sensitivity index of β is given by $SI(\beta) = \frac{\partial R_e}{\partial \beta} * \frac{\beta}{R_e} = +1$. Other indices are computed using the same approach with parameter values in Table 3. Table 5 shows the sensitivity indices of R_e to parameters.

A negative sign in sensitivity indices implies that the parameters are inversely proportional to R_e. This means that the decrease(increase) of any parameter ρ, μ and s_1 while other parameters are constant will cause an increase(decrease) in R_e and hence lead to an increase(decrease) in the spread of disease in the population. On the other hand, parameters β have a positive sensitivity index and hence

increase(decrease) while other parameters are fixed will cause an increase(decrease) in R_e.

Table 4: Sensitivity Indices for R_e

Sensitivity index	Parameters of R_e
β	+1
ρ	−0.88
μ	−0.017
s_1	−0.102
α	0.2796
r	0.906285

The result in Table 3 shows that the transmission rate(β), progression rate from HIV to AIDS(ρ), and the effect of HAART to block the progression from HIV to HIV-related kidney disease(r) have the greatest impact on the dynamic of HIV-related kidney diseases. Also, the reproduction number R_e will decrease with an increase in the effect of HAART(α and r). Therefore, to reduce the prevalence of HIV-related kidney diseases, this study recommends increasing therapy rate that will reduce the progression rate to the AIDS group and progression from HIV to HIV-related kidney diseases will reduce the prevalence of disease in the community.

Global Sensitivity Analysis

A sensitivity analysis is considered to be global when all the input parameters are varied simultaneously and the sensitivity is evaluated over the entire range of each input parameter which is given in Table 5. For analysis, we use the Latin Hypercube Sampling (LHS) method to generate sample points and Partial Rank Correlation Coefficient (PRCC) method, which uses those sample points to find out which parameters are important for the reproduction number.

Table 5: Parameters value ranges as input for LHS method

Parameter	Range
β	[0.8,1.6]
ρ	[0.3,0.9]
α	[0.0005,0.2465]
r	[0.0005,1]
s_1	[0.000257,0.7]
μ	[0.01,0.025]

A larger partial rank correlation coefficient indicates a stronger influence of the input parameter on the magnitude of R_e. The results of PRCC are shown in Table 6 and, the parameters s_1, β, and ρ are highly correlated with the threshold R_e with corresponding values 0.613454,0.551234, and 0.493451 respectively. A moderate correlation exists between parameter α and R_e with a corresponding value of 0.148508. Weak correlations have been observed between the parameters r and μ with the corresponding values 0.0469875 and −0.04033 respectively.

Therefore, the result suggests to reduce the disease is to decrease the rate of progression from HIV to HIV-related kidney diseases. Also, to increase treatment strategy to block progression from HIV to AIDS and HIV to HIV-related kidney diseases.

Table 6: Parameters and their sensitivity indices

Parameters	PRCC
β	+0.551243
ρ	−0.493451

μ	-0.04033
s_2	-0.613454
α	0.148508
r	0.0469875

Conclusion

In this study, a mathematical model of nonlinear differential equations on HIV/AIDS-related kidney diseases that incorporates treatment (HAART) at each stage of infection was developed and examined. The model is biologically meaningful and well-posed in the invariant region. Sensitivity analysis of the parameters was carried out to investigate the impact of each parameter on the infection groups. The effect of HAART on block progression from HIV to HIV-related kidney state was observed to be the second most sensitive after effective transmission rate.

The numerical results showed that HAART has a significant effect on the disease by reducing the rate at which HIV progresses to the AIDS stage and also a progression to kidney diseases. Also, the rate of progression from HIV to HIV-related kidney disease is higher compared to the rate of progression from AIDS to HIV-related kidney disease. This shows that to reduce the prevalence of HIV-related kidney diseases, efforts should be put into HIV without symptoms groups.

Based on the results, HAART treatment should be able to stop HIV/AIDS-related kidney diseases from developing and stop disease-related deaths. These findings have implications for the public. Therefore, the researchers recommend that policymakers and clinicians focus on improving HAART, which will help to reduce the progression of kidney disease associated with HIV/AIDS and lower the prevalence of HIV-related kidney diseases. A limitation of the study is the insufficient data on individuals with HIV/AIDS-related kidney diseases. Consequently, the study suggests that clinicians begin regular kidney follow-ups for individuals with HIV to help reduce the prevalence of non-communicable kidney diseases.

Conflict of Interests

The authors declare that there is no conflict of interest regarding this work.

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