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RESEARCH PAPER

A mathematical model for the study of HIV/AIDS transmission with PrEP coverage increase and parameter estimation using MCMC with a Bayesian approach

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Abstract

In this article, we present a mathematical model for the study of HIV/AIDS considering the implementation of Pre-Exposure Prophylaxis (PrEP). As a novel element in the construction of the model, we consider the diagnosis of cases for attempting to enter the PrEP program, which allows us to study different forms of PrEP. The diagnosis of new infections helps to reduce transmission in the population because these patients are incorporated into the therapy and can achieve an undetectable viral load in blood which prevents them from infecting others. The model contains a compartment of infected persons with undetectable viral load in blood that is reached by adherence to treatment which is separated from those simply infected with the virus as they do not transmit it. Considering the structure of the model, we propose a method to study the effect of increased PrEP use and HIV incidence in a population. In the case of incidence, we took into account the stochasticity of the behavior. Besides, we find the basic reproduction number and present results that allow us to obtain the impact of the parameters associated with transmission, treatment and diagnosis on the basic reproduction number. We perform computational simulations, using demographic and HIV/AIDS data from Brazil, and utilize the Markov Chain Monte Carlo (MCMC) method with a Bayesian approach to estimate model parameters. We study two coverage increases at 25% and 35% that were selected according to the size of the Brazilian population and the daily use of PrEP. We compare the increases in coverage focused on HIV incidence, which is the number of new HIV cases infected and the number of HIV cases avoided, we conclude that by increasing PrEP coverage the incidence of HIV is reduced and the number of cases avoided increases.

Keywords: HIV; incidence; MCMC; parameter estimation; PrEP

AMS 2020 Classification: 37N25; 34A12; 60J22; 97M60

1 Introduction

HIV (human immunodeficiency virus) is a virus that attacks an individual's immune system. HIV is the cause of AIDS (Acquired Immune Deficiency Syndrome) which is an advanced stage of the disease, in which the immune system is compromised [1] and fails to cope with certain diseases. HIV-positive persons are diagnosed with AIDS if they have a CD4 count below 200 cells/mm^3 or if they contract certain opportunistic infections [1].

The HIV/AIDS virus is a problem that the world's health systems are facing, and adherence to treatment and preventive programs is an important element in controlling the pandemic. In 2021, 38.4 million [33.9 million - 43.8 million] people worldwide were living with HIV; 1.5 million [1.1 million - 2 million] people had become infected with HIV; 650,000 [510,000 - 860,000] people had died of AIDS-related illnesses; and 28.7 million people were accessing antiretroviral therapy [2–4].

HIV treatment (antiretroviral therapy, ART) is currently available in one-or two-pill daily regimens that can be initiated early in HIV infection and control HIV replication. The life expectancy of persons who have achieved immune reconstitution and remain virologically suppressed should be near normal. A suppressed or undetectable viral load in HIV-infected persons means that the person does not infect his or her sexual partner [5–7].

Oral PrEP uses antiretroviral drugs in pill form to prevent the spread of HIV/AIDS. Currently, there are two approved forms of oral PrEP in use: a combination of tenofovir and emtricitabine or TDF/FTC (brand name Truvada) and a combination of tenofovir, alafenamide, and emtricitabine or F/TAF (brand name Descovy) [8]. PrEP reduces the risk of acquiring HIV sexually by approximately 99% and the risk of acquiring HIV through injection drug use by at least 74% [9].

People using oral PrEP may have adherence problems due to daily use and forgetting to take the pill, searching for the pill over time in places where it is distributed or sold, availability of the product, etc. To counteract these complications generated by daily use, a new model of injectable PrEP has appeared, which avoids interruptions in its use because the injection would only be necessary once every two months [10, 11].

Studies of the impact of PrEP in a population with the use of mathematical models have been increasing [7, 9, 12–21]. Moya et al. [7] presented a mathematical model for studying the influence of PrEP and PEP (Post-Exposure Prophylaxis) in the presence of nondiagnostics and undetectables and Moya and Rodrigues [9] introduced a fractional order mathematical model to study the impact of the oral to the injectable Pre-Exposured Prophylaxis modality. Kim et al. [12] construct a mathematical model of HIV infection among MSM (men who have sex with men) in South Korea and simulate the effects of early antiretroviral therapy (ART), early diagnosis, PrEP, and combined interventions on the incidence and prevalence of HIV/AIDS infection. Omondi et al. [13] presented a mathematical model stratified by sex and sexual preference and included PrEP in the dynamics. Li et al. [14] presented a mathematical model to assess the impact of PrEP, biomedical interventions, and their combinations, and simulated it for a 20-year period. Silva and Torres [15] proposed a mathematical model for HIV/AIDS transmission that includes the PrEP preventive program and demonstrated that PrEP significantly reduces HIV transmission. Nabil and Hamaizia [16] presented three-dimensional discrete-time model to describe the behavior of cancer cells in the presence of healthy cells and HIV-infected cells and performed a theoretical study of the model. Bolaji et al. [17] proposed a model for HIV and tuberculosis co-infection and conclude that concentrating treatment on individuals infected with tuberculosis at the diagnosed latent infection stage could effectively reduce the incidence of HIV in the study population. Naik

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et al [18] presented a fractional order model of HIV-1 using Caputo derivatives that involves interactions between cancer cells, healthy CD4+ T cells, and virus-infected CD4+ T cells. Mustapha et al. [19] developed a mathematical model that incorporates public awareness and treatment into the dynamics of HIV/AIDS in an infected population with a detectable and undetectable viral load. Yavuz et al. [20] presented a new mathematical model for the study of the transmission of the hepatitis B virus (HBV). Moya et al. [21] presented a model for Tuberculosis with the incorporation of 3HP treatment for latent tuberculosis and use the Markov Chains Monte Carlo (MCMC) method with a Bayesian approach for the estimation of model parameters and the study in Brazil, a methodology analogous to the presented in this paper.

The aim of our work is to present a model for HIV/AIDS dynamics with the incorporation of PrEP as a compartment. The model allows studying different forms of PrEP based on adherence and variations in PrEP coverage in the population. Furthermore, with the information provided by the model, we can study the incidence of HIV for different increases in PrEP coverage and the basic number reproduction and the impact on it of parameters associated with adherence to treatment and diagnosis of cases. Based on the model structure, we perform parameter estimation using the Markov Chains Monte Carlo (MCMC) method with a Bayesian approach.

Considering the structure of the model, we propose, we can study different forms of PrEP, for example oral PrEP and injectable PrEP, and changes in PrEP coverage. Reproducing the methodology used will allow us to compare these different forms of PrEP and possible increases in coverage and make decisions based on the results of HIV incidence, HIV rate ratio, and the number of cases avoided. In addition, in the dynamics we also have important elements such as the diagnosis of cases due to the use of PrEP through HIV tests applied upon entry into the program and adherence to PrEP (which allows us to study different variants), adherence to antiretroviral treatment based on the undetectability of the viral load in the blood that we quantify in a compartment since these individuals have the virus but do not infect. Using computer simulations of the model, we will study the impact of an increase in PrEP coverage in the population based on the incidence of HIV, the HIV rate ratio and the number of cases avoided.

This paper is organized as follows: in Section 2, we present the model, study its mathematical properties, the incidence definition, and the incorporation of the PrEP program. Section 3 evaluates the basic reproduction number and investigates its sensitivity analysis. Section 4 is devoted to parameter estimation, Section 5 presents the computational simulations, and in Section 6 the conclusions of the paper are discussed.

2 Model construction

For the construction of the model, we considered the following compartments: Susceptibles (S), exposed to HIV/AIDS (E), people using PrEP (P), HIV cases (H), AIDS cases (A), and HIV/AIDS positive cases with undetectable viral load in blood (V).

We consider several parameters: Λ is the recruitment rate, so parameter Λ will represent the birth rate, while parameter α_s refers to cases of people who become infected with HIV through non-sexual routes, such as transmission from mother to child during childbirth, drug injection, blood transfusions, among others.

The parameter μ represents the death rate from natural causes (death that is not associated with the disease or its consequences). The virus transmission rate is defined as:

$$\lambda = \beta \frac{(H + \epsilon A)}{N}, \tag{1}$$

where β is the effective contact rate, ϵ is the modification parameter that adapts the AIDS condition

to contagion. and N is the total population ($N = S + E + P + H + A + V$).
We define d_H as disease-associated death in people living with HIV and AIDS. We assume that people who have undetectable viral load due to a low concentration of virus in the body die in a way associated with the disease under the rate d_H. The rate ϕ represents the movement of an HIV/AIDS-positive individual who is diagnosed in HIV status so $(1-\phi)$ is diagnosed with AIDS, ϵ_{s1} is the HIV/AIDS rate diagnosis in a risk contact.
Compartment V contains virus-infected individuals who, due to the adherence of antiretroviral treatment, reach an undetectable viral load in blood and do not transmit the virus. Parameters σ_{HI} and ν will represent HIV and AIDS cases that by adherence to therapy reach an undetectable viral load in blood and σ_H and ω will represent the loss of undetectability in viral load in blood for different reasons, such as treatment withdrawal, non-adherence to treatment, re-infection, etc, and entry into the HIV and AIDS compartments, respectively. We define the rate of progression from HIV to AIDS as τ.
The parameters ϵ_p and ϵ_f represent the rate of PrEP use (coverage of PrEP use in a population) and the rate of withdrawal and/or non-adherence to therapy. We assume that when the person does not adhere to the treatment, they become susceptible to the virus, but as long as treatment is followed properly, the person does not acquire the virus by any means. We assume that individuals entering the PrEP program are tested for HIV/AIDS so this gives a chance of diagnosing new cases. The parameter ϵ_D is related to the diagnosis of patients who were diagnosed for expressing interest in entering the PrEP program and were tested for HIV/AIDS. In the model, the diagnosis of cases for attempting to enter the PrEP program is studied. The other types of diagnosis are found in the incorporated dynamics of the exit of cases exposed to the HIV (H) and AIDS (A) compartments. Regarding the relationship between the use of PrEP and the diagnosis of new cases due to attempts to enter the PrEP program, we have to take into account factors such as the availability of both PrEP and HIV tests, which both have a cost on the market and in particular the use of PrEP is daily, dissemination of the effectiveness of PrEP and expanding its use in different social groups. These factors can be limiting to a positive impact of PrEP both in prevention and diagnosis.
The model allows the study of different forms of PrEP and also takes into account different forms of infection and the application of antiretroviral therapies.
Figure 1 shows the flow diagram of the model. The model that studies the behavior of HIV/AIDS with the presence of PrEP in a population is described as:

$$\frac{dS}{dt} = \Lambda + \epsilon_f P - (\mu + \lambda + \alpha_s + \epsilon_p)S, \tag{2}$$
$$\frac{dE}{dt} = \lambda S - (\epsilon_{s1} + \mu)E, \tag{3}$$
$$\frac{dP}{dt} = \epsilon_p S - (\mu + \epsilon_f + \epsilon_D)P, \tag{4}$$
$$\frac{dH}{dt} = \phi(\epsilon_{s1}E + \epsilon_D P) + \sigma_H V + \alpha_s S - (\mu + d_H + \tau + \sigma_{HI})H, \tag{5}$$
$$\frac{dA}{dt} = (1-\phi)(\epsilon_{s1}E + \epsilon_D P) + \omega V + \tau H - (\mu + d_H + \nu)A, \tag{6}$$
$$\frac{dV}{dt} = \sigma_{HI}H + \nu A - (\mu + d_H + \sigma_H + \omega)V, \tag{7}$$

with initial conditions:

$$S(t_0) > 0, E(t_0) > 0, P(t_0) \geq 0, H(t_0) > 0, A(t_0) > 0 \text{ and } V(t_0) > 0.$$

The initial conditions for the PrEP compartment can start with the value zero because we can make a prospective study of the epidemic after the implementation of PrEP in the population.

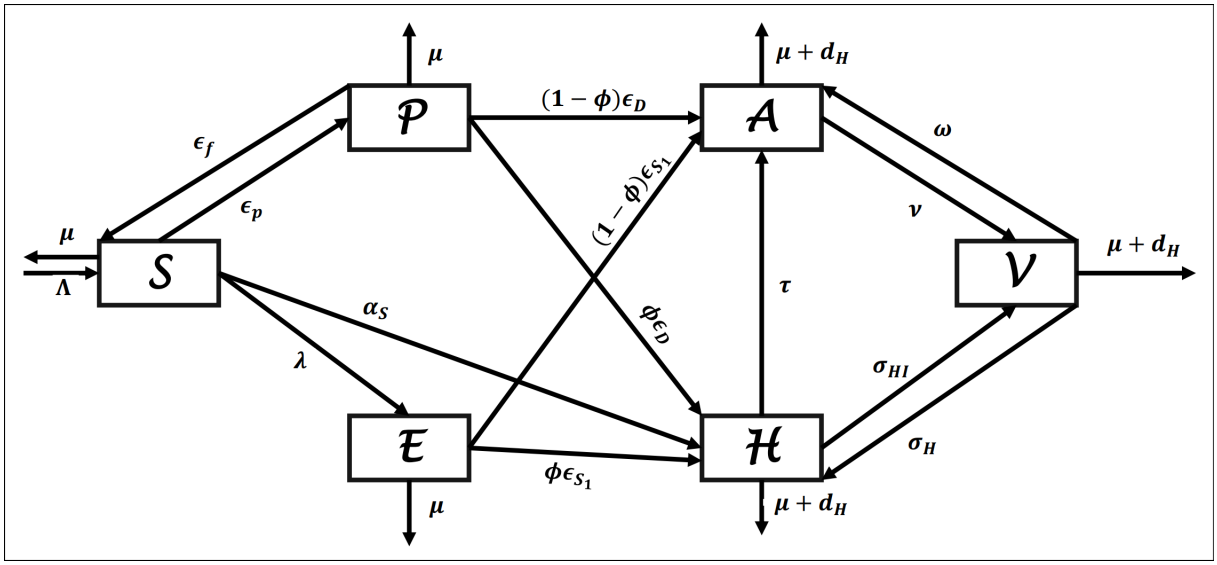

Figure 1. Flow chart of model (2)-(7). The recruitment rate is Λ and the death rate from natural causes is μ and is the same in all compartments. The use of PrEP is only admitted to those susceptible and parameters ϵ_p and ϵ_f represent the rate of PrEP use and failure to use PrEP. Before entering the PrEP program it is necessary to do HIV tests and with this, we help in the detection of new cases of HIV and AIDS, and is defined in parameter ϵ_D. Those who are susceptible are exposed to the virus with the transmission rate of virus λ. The α_s rate defines the individuals who become infected through non-sexual routes. The exposed (E compartment) who acquire the virus are diagnosed with HIV or AIDS with the diagnosis rate, ϵ_{s1}. The τ is the rate of evolution of the disease from HIV to AIDS. Parameters σ_{HI} and ν are associated with those infected with HIV (H compartment) and AIDS (A compartment) who, using retroviral treatment, achieve an undetectable viral load and enter V compartment, and parameters ω and σ_H are when undetectability is lost and depending on the disease stages enters H or A. The parameter d_H represents death associated with HIV/AIDS

The parameters and their definitions are given in Table 1.

Table 1. Definition of model parameters (2)-(7)

Parameter	Definition
Λ	Recruitment rate
ϵ	Modification parameter associated with virus transmission from AIDS patient
ϵ_p	PrEP use selection rate
ϵ_f	PrEP therapy failure rate
ϵ_D	Diagnosis rate of patients who attempted to enter the PrEP program
α_s	HIV infection rate by non-sexual routes
μ	Death rate due to natural causes
β	Effective contact rate
ν	Rate of progression from AIDS to undetectable
ϕ	Virus progression rate
ϵ_{s1}	Rate of detection and diagnosis of persons at risk contact
τ	Rate of progression from HIV to AIDS
σ_{HI}	Rate of progression from HIV to undetectable
ω	Rate of progression from undetectable to AIDS
σ_H	Rate of progression from undetectable to HIV
d_H	Death rate associated with HIV/AIDS

Basic properties of model

Now, let us prove the existence and non-negativity of the solution of model (2)-(7), and let's find the biologically feasible region.

Non-negativity and boundless of solutions

Theorem 1 *Let initial data be* $S(t_0) > 0, E(t_0) > 0, P(t_0) > 0, H(t_0) > 0, A(t_0) > 0$ *and* $V(t_0) > 0$. *Then, the solutions* $(S(t), E(t), P(t), H(t), A(t), V(t))$ *of model* (2)-(7) *are positive for all* $t > 0$. *Furthermore,*

$$\limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{\mu}. \tag{8}$$

Proof By first equation of model (2)-(7), we have that:

$$\frac{dS}{dt} = \Lambda + \epsilon_f P - (\mu + \lambda + \alpha_s + \epsilon_p)S \leq \Lambda - (\mu + \lambda + \alpha_s + \epsilon_p)S, \tag{9}$$

can be rewritten as

$$\frac{d}{dt}\left[S(t)\exp\left\{(\mu + \lambda + \alpha_s + \epsilon_p)t + \int_{t_0}^{t}\lambda(s)ds\right\}\right] \geq \Lambda\exp\left\{(\mu + \lambda + \alpha_s + \epsilon_p)t + \int_{t_0}^{t}\lambda(s)ds\right\}. \tag{10}$$

Hence, for $0 \leq t_0 \leq t^*$,

$$S(t^*)\exp\left\{(\mu + \lambda + \alpha_s + \epsilon_p)t^* + \int_{t_0}^{t^*}\lambda(s)ds\right\} - S(t_0) \geq \int_{t_0}^{t^*}\Lambda\exp\left\{(\mu + \lambda + \alpha_s + \epsilon_p)u + \int_{t_0}^{u}\lambda(w)dw\right\}du. \tag{11}$$

So that,

$$\begin{aligned} S(t^*) \geq S(t_0)\exp\left\{-\left((\mu + \lambda + \alpha_s + \epsilon_p)t^* + \int_{t_0}^{t^*}\lambda(s)ds\right)\right\} + \exp\left\{-\left((\mu + \lambda + \alpha_s + \epsilon_p)t^*\right.\right. \\ \left.\left. + \int_{t_0}^{t^*}\lambda(s)ds\right)\right\} \times \int_{t_0}^{t^*}\Lambda\exp\left\{-\left((\mu + \lambda + \alpha_s + \epsilon_p)u + \int_{t_0}^{u}\lambda(w)dw\right)\right\}du > 0. \end{aligned} \tag{12}$$

Similarly, it can be shown that $E(t), P(t), H(t), A(t)$ and $V(t) > 0$ for all $t > 0$.
Moreover, we have

$$\frac{dN}{dt} = \Lambda - \mu N - d_H(H + A + V). \tag{13}$$

Then,

$$\Lambda - (\mu + d_H)N \leq \frac{dN}{dt} \leq \Lambda - \mu N, \tag{14}$$

which gives

$$\frac{\Lambda}{\mu + d_H} \leq \liminf_{t\to\infty} N(t) \leq \limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{\mu}. \tag{15}$$

So, we have that

$$\lim_{t\to\infty} \sup N(t) \leq \frac{\Lambda}{\mu}.$$

Biologically feasible region

Now, let's define the biologically feasible region for the model (2)-(7).

Lemma 1 *The closed set* $\Omega = \left\{(S, E, P, H, A, V) \in \mathbb{R}^6_+ : N(t) \leq \frac{\Lambda}{\mu}\right\}$ *is positively-invariant and attracts all solutions of model* (2)-(7).

Proof The derivative of N (total population) is

$$\frac{dN}{dt} = \Lambda - \mu N - d_H(H + A + V). \tag{16}$$

Since $\frac{dN}{dt} \leq \Lambda - \mu N$, it follows that $\frac{dN}{dt} \leq 0$, if $N(t) \geq \frac{\Lambda}{\mu}$. Hence, the standard comparison theorem from [22] can be used to show that $N(t) \leq N(t_0)\exp\{-\mu t\} + \frac{\Lambda}{\mu}\left(1 - \exp\{-\mu t\}\right)$.
In particular, if $N(t_0) \leq \frac{\Lambda}{\mu}$, then $N(t) \leq \frac{\Lambda}{\mu}$ for all $t > 0$. Hence, the domain Ω is positively invariant.
Furthermore, if $N(t_0) > \frac{\Lambda}{\mu}$, the either the solution enters the domain Ω in finite time or $N(t)$ approaches $\frac{\Lambda}{\mu}$ asymptotically as $t \to \infty$. Hence, the domain Ω attracts all solutions in $\mathbb{R}^6_+$.

Existence of solution

Theorem 2 *The solutions of model* (2)-(7) *with non-negative initial conditions exist for all time.*

Proof The right-hand side of the model is locally Lipschitz continuous, and this proves the local existence of the solution. The global existence of the solution follows from the bound found in Theorem 1, inequality (8).

Incidence

Incidence is the number of newly diagnosed cases of a disease. The incidence rate is the number of new cases of a disease divided by the number of people at risk of contracting the disease [23, 24]. Prevalence differs from incidence in that prevalence includes all active cases, both new and pre-existing, in the population at the specified time, whereas incidence is limited to new cases only. New entries in the HIV compartment are incorporated into the model with the following differential equation respectively:

$$\frac{dI}{dt} = \phi(\epsilon_{s1}E + \epsilon_D P) + \alpha_s S. \tag{17}$$

The HIV incidence is defined as:

$$I^*(t) = I(t) - I(t-1), \tag{18}$$

where t is the current time and $t-1$ is the moment of time immediately preceding. Then, the HIV incidence rate is:

$$\text{HIV Incidence Rate } (t) = \frac{I^*(t) * 100000}{N}. \tag{19}$$

Given that this methodology is deterministic by itself, we introduce stochasticity by considering the negative binomial distribution $(Negbin)$, one of the most general for modeling count data. Its density function is given by:

$$f_Y(y) = \binom{y+v-1}{y} \left(\frac{s}{s+v}\right)^y \left(\frac{v}{s+v}\right)^v, \; y \in \mathbb{N}, \tag{20}$$

where $E(Y) = s > 0$ is the expected value and $v > 0$ is the parameter that controls for overdispersion. Let $\mathbf{Y_1}$ be a random vector representing the annual new cases. Considering stochasticity, we have that $\mathbf{Y}_1 = (Y_{11}, \ldots, Y_{1t})$ with $\mathbf{Y_{1t}} \sim Negbin(s_{1t}, v)$, where:

$$s_{1t} = I(t) - I(t-1) = I^*(t). \tag{21}$$

In this way, we are not only able to get a point estimate but also a confidence interval for allowing stochasticity.

Increased PrEP coverage

The new PrEP coverage is based on the percentage increase of the current coverage, so the parameter ϵ_p in the period 2025-2035 will have the following structure:

$$\epsilon_p(t) = \epsilon_p(t-1) + p_s\epsilon_p(t-1), \tag{22}$$

where $\epsilon_p(t)$ is the current coverage in that year, $\epsilon_p(t-1)$ is the coverage in the previous year, and p_s is the percent increase in coverage.

3 Basic reproduction number

In a population composed only of susceptible individuals, the average number of infections caused by an infected individual is defined as basic reproduction number $\mathfrak{R}_0$. In our study, we have that the compartment of undetectable infected individuals cannot be infected by the virus but upon losing undetectability they pass to the infectious state of HIV or AIDS depending on the state of the disease in which the individual is. The incorporation of these individuals in the study of the basic reproduction number allows us to study the effect of reaching a state of virus undetectability and the impact it has when it is lost.
If $0 < \mathfrak{R}_0 < 1$, the infection will disappear in the long term, and if $\mathfrak{R}_0 > 1$ the infection can spread in a population [25, 26]. The higher the $\mathfrak{R}_0$, the more difficult it will be to control the epidemic. $\mathfrak{R}_0$ can be affected by several factors, such as the duration of infectivity of the affected patients, the infectivity of the organism, and the degree of contact between susceptible and infected populations.
Our interest is to study the disease-free equilibrium point due to its relationship with the basic

reproduction number. The disease-free equilibrium point (DFE) is:

$$\epsilon_0 = \left(\frac{\Lambda}{(\mu + \alpha_s + \epsilon_p)}, 0, 0, 0, 0, 0 \right). \tag{23}$$

To find the basic reproduction number, we use the next-generation matrix method presented in [25–27], where

$$F = \begin{pmatrix} 0 & 0 & \frac{\beta\Lambda}{N(\mu+\epsilon_p+\alpha_s)} & \frac{\epsilon\beta\Lambda}{N(\mu+\epsilon_p+\alpha_s)} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} k_0 & 0 & 0 & 0 & 0 \\ 0 & k_p & 0 & 0 & 0 \\ -\phi\epsilon_{s1} & -\phi\epsilon_D & k_1 & 0 & 0 \\ -(1-\phi)\epsilon_{s1} & -(1-\phi)\epsilon_D & -\tau & k_2 & -\omega \\ 0 & -\sigma_{HI} & 0 & -\nu & k_3 \end{pmatrix},$$

are the matrices of transmission and transition terms, respectively and $k_p = \mu + \epsilon_f + \epsilon_p$, $k_0 = \mu + \epsilon_{s1}$, $k_1 = \mu + d_H + \tau + \sigma_{HI}$, $k_2 = \mu + d_H + \nu$ and $k_3 = \mu + d_H + \sigma_H + \omega$. Then, for model (2)-(7) the basic reproduction number is

$$\mathfrak{R}_0 = \rho(FV^{-1}) = \left| \frac{\Lambda\beta\epsilon_{s1}\Big(k_3(k_2\phi + \epsilon(k_1(1-\phi)+\phi\tau)) + (\epsilon\sigma_{HI} - \nu)(\sigma_H(\phi-1)+\phi\omega)\Big)}{N(\mu+\alpha_s+\epsilon_p)k_0\Big(k_2(\sigma_H\sigma_{HI} - k_1k_3) + \nu(\sigma_H\tau + k_1\omega)\Big)} \right|, \tag{24}$$

where $\rho(FV^{-1})$ is the spectral radius of matrix FV^{-1}.
To find the basic reproduction number with the next-generation matrix method, we use the infection-free equilibrium point (ϵ_0) and now we will briefly present results that relate the stability of this point with the behavior of the $\mathfrak{R}_0$.

Theorem 3 *The infection-free equilibrium point (ϵ_0) of model (2)-(7), is locally asymptotically stable (LAS) if $\mathfrak{R}_0 < 1$ and unstable if $\mathfrak{R}_0 > 1$.*

The threshold quantity $\mathfrak{R}_0$ is the basic reproduction number of HIV/AIDS model (2)-(7). It measures the average number of new diseases generated by a single infectious agent in a fully susceptible population. Consequently, the disease-free equilibrium of model (2)-(7) is locally asymptotically stable (LAS) whenever $\mathfrak{R}_0 < 1$ and unstable if $\mathfrak{R}_0 > 1$. This means that HIV/AIDS can be removed from the community (when $\mathfrak{R}_0 < 1$) if the population sizes of model (2)-(7) are in the basin of attraction of the disease-free equilibrium ϵ_0.
Now, we prove the global stability of the infection-free equilibrium point. Following [27], we can

rewrite the model (2)-(7) as

$$\begin{aligned} \frac{dX}{dt} &= f(S,I), \\ \frac{dI}{dt} &= g(S,I), \quad g(S,0_{\mathbb{R}^5_+}) = 0, \end{aligned} \tag{25}$$

where $S \in \mathbb{R}_+$ is the susceptible compartment, $I \in \mathbb{R}^5_+$ have the compartments exposed, HIV, AIDS and undetectable of model (2)-(7) and $0_{\mathbb{R}^5_+}$ is the null vector of the space $\mathbb{R}^5_+$.

The disease-free equilibrium is now denoted by $E_0 = (S_0, 0_{\mathbb{R}^5})$ where $S_0 = \dfrac{\Lambda}{\mu + \alpha_s + \epsilon_p}$.

The conditions (H_1) and (H_2) below must be satisfied to guarantee the global asymptotic stability of E_0.

$$\begin{aligned} &(H_1): \quad \text{For} \quad \frac{dS}{dt} = f(S, 0_{\mathbb{R}^5}), \quad S_0 \quad \text{is globally asymptotically stable,} \\ &(H_2): \quad g(S,I) = AI^T - g^*(S,I), \quad g^*(S,I) \geq 0, \quad \text{for} \quad (S,I) \in \Omega, \end{aligned} \tag{26}$$

where $A = D_I g(S_0, 0_{\mathbb{R}^5})$ ($D_I G(S_0, 0_{\mathbb{R}^5})$ is the Jacobian of g at $(S_0, 0_{\mathbb{R}^5})$) is a M-matrix (the off-diagonal elements of A are non-negative) and Ω is the biologically feasible region.
The following theorem shows the global stability of the infection-free equilibrium point.

Theorem 4 *The fix point E_0 is a globally asymptotically stable equilibrium (G.A.S) of model (2)-(7) provided that $\mathfrak{R}_0 < 1$ and that the conditions (H_1) and (H_2) are satisfied.*

Proof Let

$$f(S, 0_{\mathbb{R}^5}) = \Lambda - (\mu + \alpha_s + \epsilon_p).$$

As $f(S, 0_{\mathbb{R}^5})$ is linear, then S_0 is globally stable. Then, (H_1) is satisfied. Let

$$A = \begin{pmatrix} -k_0 & 0 & \beta & \epsilon\beta & 0 \\ 0 & -k_p & 0 & 0 & 0 \\ \phi\epsilon_{s1} & \phi\epsilon_D & -k_1 & 0 & \sigma_H \\ (1-\phi)\epsilon_{s1} & (1-\phi)\epsilon_D & \tau & -k_2 & \omega \\ 0 & 0 & \sigma_{HI} & \nu & -k_3 \end{pmatrix},$$

$$I = (E, P, H, A, V),$$

$$g^*(S,I) = AI^T - g(X,I),$$

$$g^*(S,I) = \begin{pmatrix} g_1^*(X,I) \\ g_2^*(X,I) \\ g_3^*(X,I) \\ g_4^*(X,I) \\ g_5^*(X,I) \end{pmatrix} = \begin{pmatrix} \beta(H + \epsilon A)\left(1 - \dfrac{S}{N}\right) \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Since $\frac{S}{N} \leq 1$ then $1 - \frac{S}{N} \geq 0$. Thus $g^*(S,I) \geq 0$ for all $(S,I) \in \Omega$. Consequently, E_0 is a globally asymptotically stable point. Analogous proofs can be found in the bibliographical references [28–30]. We will study the joint influence of parameters $\epsilon_{s1}, \sigma_{HI}, \sigma_H, \nu$ and ω on the basic reproduction number. These parameters are associated with treatment adherence and effectiveness (undetectable virus in the blood), treatment failure, and diagnosis of cases exposed to the virus. These parameters are defined in the interval $[0,1]$ and we want to study the joint behavior when they are at the extreme values of the interval. At the extremes of the interval are the critical behaviors because they may represent all individuals or none and it is of interest to study this epidemiological situation together.

Firstly, we will study the undetectability in HIV and its impact on the basic reproduction number. The following limit characterizes the increase in the number of patients with HIV who achieve undetectability of the virus in the blood and the decrease in the number of patients who lose it and pass to the HIV state:

$$\lim_{\substack{\sigma_{HI}\to 1\\ \sigma_H \to 0}} \Re_0 = \frac{\beta\Lambda\epsilon_{s1}\Big((\mu+d_H+\omega)\big(k_2\phi+\epsilon((\mu+d_H+\tau+1)(1-\phi)+\phi\tau)\big)+(\epsilon-\nu)\phi\omega\Big)}{N(\mu+\epsilon_p+\alpha_s)k_0\big(\nu(\mu+d_H+\tau+1)\omega-k_2(\mu+d_H+\tau+1)(\mu+d_H+\omega)\big)}. \quad (27)$$

The opposite case is defined as:

$$\lim_{\substack{\sigma_{HI}\to 0\\ \sigma_H \to 1}} \Re_0 = \frac{\beta\Lambda\epsilon_{s1}\Big((\mu+d_H+\omega+1)\big(k_2\phi+\epsilon((\mu+d_H+\tau)(1-\phi)+\phi\tau)\big)-\nu((\phi-1)+\phi\omega)\Big)}{N(\mu+\epsilon_p+\alpha_s)k_0\big(\nu(\tau+(\mu+d_H+\tau)\omega)-k_2(\mu+d_H+\tau)(\mu+d_H+\omega+1)\big)}. \quad (28)$$

With the expressions (27)-(28) of $\Re_0$, we can characterize the impact that the increase and decrease in the number of patients with HIV who achieve undetectable virus loads in the blood has together with the increase and decrease in the number of patients who lose undetectability and acquire detectable levels of HIV.

Now, we are going to study the case of patients with AIDS who achieve undetectability of the virus in the blood and patients who lose undetectability and enter the compartment of AIDS. The expressions that characterize this situation are:

$$\lim_{\substack{\nu\to 1\\ \omega\to 0}} \Re_0 = \frac{\beta\Lambda\epsilon_{s1}\Big((\mu+d_H+\sigma_H)\big((\mu+d_H+1)\phi+\epsilon(k_1(1-\phi)+\phi\tau)\big)+(\epsilon\sigma_{HI}-1)\sigma_H(\phi-1)\Big)}{N(\mu+\epsilon_p+\alpha_s)k_0\big((\mu+d_H+1)(\sigma_H\sigma_{HI}-k_1(\mu+d_H+\sigma_H))+\sigma_H\tau\big)}, \quad (29)$$

$$\lim_{\substack{\nu\to 0\\ \omega\to 1}} \Re_0 = \frac{\beta\Lambda\epsilon_{s1}\Big((\mu+d_H+\sigma_H+1)\big((\mu+d_H)\phi+\epsilon(k_1(1-\phi)+\phi\tau)\big)+\epsilon\sigma_{HI}(\sigma_H(\phi-1)-\phi)\Big)}{N(\mu+\epsilon_p+\alpha_s)k_0\big((\mu+d_H)(\sigma_H\sigma_{HI}-k_1(\mu+d_H+\sigma_H+1))\big)}. \quad (30)$$

We will find the expressions for the increase and decrease in cases of HIV and AIDS that achieve the virus's undetectability in the blood and when they lose it and become infectious again. The expressions for achieving the undetectability of the virus in the blood for HIV and AIDS together

are:

$$\lim_{\substack{\sigma_{HI}\to 1\\ \nu\to 1}} \Re_0 = \frac{\beta\Lambda\epsilon_{s1}\Big(k_3\big((\mu+d_H+1)\phi+\epsilon((\mu+d_H+\tau+1)(1-\phi)+\phi\tau)\big)+(\epsilon-1)(\sigma_H(\phi-1)+\phi\omega)\Big)}{N(\mu+\epsilon_p+\alpha_s)k_0\big((\mu+d_H+1)(\sigma_H-(\mu+d_H+\tau+1)k_3)+(\sigma_H\tau+(\mu+d_H+\tau+1)\omega)\big)}, \tag{31}$$

$$\lim_{\substack{\sigma_{HI}\to 0\\ \nu\to 0}} \Re_0 = \frac{\beta\Lambda\epsilon_{s1}k_3\Big((\mu+d_H)\phi+\epsilon((\mu+d_H+\tau)(1-\phi)+\phi\tau\Big)}{-N(\mu+\epsilon_p+\alpha_s)k_0(\mu+d_H)(\mu+d_H+\tau)k_3}. \tag{32}$$

For the loss of the undetectability of the virus and return to the infectious state in the HIV and AIDS compartments are:

$$\lim_{\substack{\sigma_H\to 1\\ \omega\to 1}} \Re_0 = \frac{\beta\Lambda\epsilon_{s1}\Big((\mu+d_H+2)\big(k_2\phi+\epsilon(k_1(1-\phi)+\phi\tau)\big)+(\epsilon\sigma_{HI}-\nu)(2\phi-1)\Big)}{N(\mu+\epsilon_p+\alpha_s)k_0\big(k_2(\sigma_{HI}-k_1(\mu+d_H+2))+\nu(\tau+k_1)\big)}, \tag{33}$$

$$\lim_{\substack{\sigma_H\to 0\\ \omega\to 0}} \Re_0 = \frac{\beta\Lambda\epsilon_{s1}(\mu+d_H)\Big(k_2\phi+\epsilon(k_1(1-\phi)+\phi\tau\Big)}{-N(\mu+\epsilon_p+\alpha_s)k_0k_2k_1(\mu+d_H)}. \tag{34}$$

Besides, we are interested in studying the impact of the growth and decrease of the parameters associated with HIV cases that reach AIDS (τ) and the achievement of undetectability of the virus in the blood of cases with AIDS (ν). This factor is interesting because if a case reaches the stage of AIDS and, with adherence to the treatment, we manage to have the undetectable status of the virus in the blood, we would be avoiding new infections. The expressions of the limits of $\Re_0$ for this situation are:

$$\lim_{\substack{\tau\to 1\\ \nu\to 0}} \Re_0 = \frac{\beta\Lambda\epsilon_{s1}\Big(k_3(\phi(\mu+d_H)+\epsilon((\mu+d_H+\sigma_{HI}+1)(1-\phi)+\phi))+\epsilon\sigma_{HI}(\sigma_H(\phi-1)+\phi\omega)\Big)}{N(\mu+\epsilon_p+\alpha_s)k_0\big((\mu+d_H)(\sigma_H\sigma_{HI}-(\mu+d_H+\sigma_{HI}+1)k_3)\big)}, \tag{35}$$

$$\lim_{\substack{\tau\to 0\\ \nu\to 1}} \Re_0 = \frac{\beta\Lambda\epsilon_{s1}\Big(k_3(\phi(\mu+d_H+1)+\epsilon(\mu+d_H+\sigma_{HI})(1-\phi))+(\epsilon\sigma_{HI}-1)(\sigma_H(\phi-1)+\phi\omega)\Big)}{N(\mu+\epsilon_p+\alpha_s)k_0\big((\mu+d_H+1)(\sigma_H\sigma_{HI}-(\mu+d_H+\sigma_{HI})k_3)+(\mu+d_H+\sigma_{HI})\omega\big)}. \tag{36}$$

Now, we are going to study the increase in the diagnosis of cases rate (ϵ_{S1}) in conjunction with the undetectability of the virus in the blood, which leads to the diagnosis and effectiveness in treatment in cases with HIV and AIDS. The following expressions characterize these situations:

$$\lim_{\substack{\epsilon_{s1}\to 1\\ \sigma_{HI}\to 0}} \Re_0 = \frac{\beta\Lambda\Big(k_3(k_2\phi+\epsilon((\mu+d_H+\tau+1)(1-\phi)+\phi\tau))-\nu(\sigma_H(\phi-1)+\phi\omega)\Big)}{N(\mu+\epsilon_p+\alpha_s)(\mu+1)\big(\nu(\sigma_H\tau+(\mu+d_H+\tau+1)\omega)-k_2k_3(\mu+d_H+\tau+1)\big)}. \tag{37}$$

$$\lim_{\substack{\epsilon_{s1}\to 1\\ \sigma_{HI}\to 1}} \mathfrak{R}_0 = \frac{\beta\Lambda\Big(k_3(k_2\phi+\epsilon((\mu+d_H+\tau)(1-\phi)+\phi\tau))+(\epsilon-\nu)(\sigma_H(\phi-1)-\phi\omega)\Big)}{N(\mu+\epsilon_p+\alpha_s)(\mu+1)\big(k_2(\sigma_H-k_3(\mu+d_H+\tau))+\nu(\sigma_H\tau+(\mu+d_H+\tau+1)\omega)\big)}. \tag{38}$$

Finally, we will find the expressions of the limits for the cases of the increase in the diagnosis of cases (ϵ_{s1}), the increase in the undetectability of the virus and the decrease in the loss of the undetectability of the virus in the blood (we will call the positive scenario) and the increase in the diagnosis of cases with the increase in the loss of undetectability of the virus and the decrease in cases that achieve undetectability of the virus (we will call it semi-positive because case detection is still a positive factor but here we see the infectiousness of the treatment, regarding the undetectability of the virus or adverse situations). Then we have

$$\lim_{\substack{\epsilon_{s1}\to 1\\ \sigma_{HI}\to 1\\ \nu\to 1\\ \sigma_H\to 0\\ \omega\to 0}} \mathfrak{R}_0 = \frac{\beta\Lambda(\mu+d_H)\Big((\mu+d_H+1)\phi+\epsilon((\mu+d_H+\tau+1)(1-\phi)+\phi\tau\Big)}{-N(\mu+\epsilon_p+\alpha_s)(\mu+1)(\mu+d_H+1)(\mu+d_H)(\mu+d_H+\tau+1)}, \tag{39}$$

$$\lim_{\substack{\epsilon_{s1}\to 1\\ \sigma_{HI}\to 0\\ \nu\to 0\\ \sigma_H\to 1\\ \omega\to 1}} \mathfrak{R}_0 = \frac{\beta\Lambda(\mu+d_H+2)\Big((\mu+d_H)\phi+\epsilon((\mu+d_H+\tau)(1-\phi)+\phi\tau\Big)}{-N(\mu+\epsilon_p+\alpha_s)(\mu+1)(\mu+d_H)(\mu+d_H+2)(\mu+d_H+\tau)}. \tag{40}$$

By definition, the basic reproduction number is in the closed interval $[0,1]$, then in cases where the result of the limits is negative, we use the modulus. In the next subsection, we are going to study and obtain expressions for the impact of the parameters associated with the transmission, the rate of PrEP use, the desistence of PrEP use, and contagion by means other than sexual, on the basic reproduction number.

Sensitivity index

The sensitivity analysis of the basic reproduction number determines the relative importance of the parameters present in the basic reproduction number, such as the parameters of transmission, resistance, and recovery, among others. The sensitivity index can be defined using the partial derivatives, provided that the variable is differentiable with respect to the parameter under study. Sensitivity analysis also helps to identify the vitality of the parameter values in the predictions using the model [31–33].

Definition 1 *([33]) The normalized forward sensitivity index of a variable, v, that depends on the differentiability of a parameter p is defined as:*

$$\Upsilon_p^v := \frac{\partial v}{\partial p}\times\frac{p}{v}. \tag{41}$$

The sensitivity index of $\mathfrak{R}_0$ helps to determine the parameters that have an impact on it. We can characterize the sensitivity index as follows:

- A positive value of the sensitivity index implies that an increase in the parameter value causes an increase in the basic reproduction number.

- A negative value of the sensitivity index implies that an increase in the parameter value causes a decrease in the basic reproduction number.

The expressions of the sensitivity indices of the selected parameters are:

$$\Upsilon_{\alpha_s}^{\Re_0} = -\frac{\alpha_s}{\alpha_s + \epsilon_p + \mu} < 0, \tag{42}$$

$$\Upsilon_{\epsilon_p}^{\Re_0} = -\frac{\epsilon_p}{\alpha_s + \epsilon_p + \mu} < 0. \tag{43}$$

Parameters α_s and ϵ_p have a negative sensitivity index with respect to $\Re_0$, which implies that an increase in these parameters will mean a decrease in $\Re_0$. Epidemiologically, we have that an increase in the parameters associated with cases that do not acquire the virus in a risk contact, individuals who enter the PrEP contagion preventive method cause a reduction in the basic reproduction number. In the case of α_s, it also happens that an increase in this parameter causes a decrease in the basic reproduction number because this is a different form of contagion by contact between a susceptible and an infected human. In the case of the parameters associated with deaths and entries into the susceptible community, they are logical values and associated with demographics, since if more people infected with HIV/AIDS die, it leads to fewer infected and if more elements enter the population, the number of susceptible increases, therefore, we have more elements in the dynamics with the possibility of becoming infected with the virus.

4 Parameters estimation

Parameters selection

For the estimation of the model parameters, we used the MCMC (Markov Chains Monte Carlo) with a Bayesian approach. The theory and examples of the MCMC technique with a Bayesian approach that we use can be found in [34–36].
We select to estimate six parameters, the effective contact rate β, since it influences the HIV/AIDS transmission rate; parameters σ_H and ω, which are related to the loss of undetectable viral load and entry into the HIV and AIDS compartments, respectively; τ, which is associated with disease progression to AIDS; ν, which is related to AIDS cases reaching undetectability; and d_H, which is death from the disease. These parameters are associated with treatment efficacy, progression to AIDS, disease-associated death and transmission, and were selected because we are focusing our study on HIV incidence.

Rate ratio

The a posteriori distribution of $\boldsymbol{\theta}|\mathbf{Y}_1 = (Y_{11}, \ldots, Y_{1t})^T$, is given by:

$$\pi(\boldsymbol{\theta}|\mathbf{Y}_1) \propto L(\boldsymbol{\theta}|\mathbf{Y}_1)\pi(\boldsymbol{\theta}), \tag{44}$$

with $L(\boldsymbol{\theta}|\mathbf{Y}_1)$ being the likelihood corresponding to the negative binomial distribution in (20) and $\pi(\boldsymbol{\theta})$ the independent prior structure generated by:

$$\pi(\boldsymbol{\theta}) \propto \pi(\nu) \times \pi(\sigma_H) \times \pi(\tau) \times \pi(\omega) \times \pi(d_T) \times \pi(\beta), \tag{45}$$

where $\boldsymbol{\theta}$ denote the vector of parameters to estimate, for the active tuberculosis model, this vector will be $\boldsymbol{\theta} = (\nu, \sigma_H, \tau, \omega, d_T, \beta)$ keeping the remaining parameters fixed. To forecast a new response,

we use the a posteriori predictive distribution. It is given by,

$$p\left(\mathbf{Y}_{i,pred}|\mathbf{Y}_{i,obs}\right) = \int p\left(\mathbf{Y}_{i,pred}|\boldsymbol{\theta}\right) p(\boldsymbol{\theta} \mid \mathbf{Y}_{i,obs}) d\boldsymbol{\theta}. \tag{46}$$

By sampling from (46), we can compute quantities of interest for prediction, the same way we did it with the parameters. For example, one could compute the median and the 2.5% and 97.5% quantiles of this distribution to get a point and a symmetric credibility interval for the new response.
An important element to be analyzed in this study is the rate ratio between a reference scenario which in our case is the scenario where we maintain the implementation of PrEP at this moment and the different types of PrEP studied and the increases in PrEP use. For this analysis, we use the following procedure:

- Generate M vectors $\mathbf{Y}_{i,pred}$ from $p_{\boldsymbol{\theta}_1}\left(\mathbf{Y}_{i,pred}|\mathbf{Y}_{i,obs}\right)$ and $p_{\boldsymbol{\theta}_2}\left(\mathbf{Y}_{i,pred}|\mathbf{Y}_{i,obs}\right)$, where $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta}_2$ are defined for two different scenarios, and then we have M vectors for each scenario.
- Define each vector as $\mathbf{Y}_{sc1,j}$ and $\mathbf{Y}_{sc2,j}$ for $j = 1, \ldots, M$ for each scenario.
- For $i = 1, \ldots, M$, we compute,

$$Ratio_j = \frac{\mathbf{Y}_{sc1,j}}{\mathbf{Y}_{sc2,j}} = \left(\frac{Y_{sc1,1,j}}{Y_{sc2,1,j}}, \ldots, \frac{Y_{sc1,npred,j}}{Y_{sc2,npred,j}}\right)^T,$$

  where $npred$ is the number of predicted observations.
- With the above steps, we obtain the rate ratio ($Ratio_j$) with have dimension m.

So, as done for estimation and prediction, quantities of interest such as the median and quantiles for constructing credibility intervals, can be obtained from the distribution of the rate ratio.

Estimation and prediction intervals

The algorithm was implemented in `R` through the `Rstan` package [34, 37, 38]. To solve the deterministic system, we used a predictor-corrector method based on the Runge-Kutta predictor of order 4 and corrector of order 5 [39].
Also, an extension of the Hamiltonian Monte Carlo (HMC) algorithm [35, 39–41], was used to perform the statistical analysis. Once the sample is obtained quantities of interest such as the median and the 2.5% and 97.5% quantiles can be computed to get a point and a symmetric credibility interval.
To construct the prediction intervals of HIV Incidence, we ran 20000 simulations, and for each of those solved the system of differential equations. The vector of 20000 solutions was then considered as the vector of medians and using as many values of the overdispersion parameter we were able to sample the 2.5% and 97.5% quantiles from the negative binomial distribution, such that the interval formed by these two quantiles is what we consider as the credibility region [34, 36, 37, 42].

5 Computational simulations

Parameters values and demographic data

The initial conditions for the initialization of the simulations were extracted from demographic data and for those concerning HIV, AIDS, undetectable (viral load), and incidence, we used the data reported by the Brazilian Ministry of Public Health between 2003-2019 [43–47].

For the compartment of individuals who are in the PrEP program and the parameters that are related to the use of PrEP in the population (ϵ_p, ϵ_f), we assume a value of zero until 2018, and the values for the incorporation of PrEP in 2018 of the compartment and the parameters come from [48, 49].
The initial conditions are $H(0) = 260000$, $A(0) = 150000$, $V(0) = 0.4 \times I(0)$, $P(0) = 0$, $E(0) = 100000$ and $S(0) = 1.91 \times 10^8 - V(0) - H(0) - A(0)$. We conducted simulations from 2003 until 2035 and compared with the actual data reported from 2003-2019.
For our study, we used that the probability of retention of the oral PrEP is 3 months after initiation is 72.5% and the probability of full adherence to oral PrEP is 92.3% using more than 4 pills per week [10, 49–51]. We assume that the probability of full adherence to oral PrEP is 96.3%. This information is used to give value to the parameter ϵ_f.
The data about HIV incidence was obtained from [52].
The a priori distributions for the parameters to be estimated were selected by the parameter definition space, taking a normal distribution for the parameters that can take values outside the unit interval and beta for those that are defined in $(0, 1)$ because the support of it is in that interval. Then, we picked a normal distribution $(N(\cdot, \cdot))$ for β, and ω, whose space of definition is greater than $(0, 1)$; and for other parameters a beta distribution $(Beta(a, b))$ with a and b entries defined as follows [53–55]:

$$a = Mean\left(\frac{Mean(1 - Mean)}{Var} - 1\right), \tag{47}$$

$$b = (1 - Mean)\left(\frac{Mean(1 - Mean)}{Var} - 1\right), \tag{48}$$

if $Var < Mean(1 - Mean)$ where $Mean$ is mean and Var is variance.
Table 2 shows the values of the parameters that are fixed, the intervals, and distributions a priori for the parameters to be estimated with the MCMC with a Bayesian approach.

Table 2. Parameter values and a priori distributions

Parameter	Point	Interval	A Priori Distribution	Reference
Λ	4,590,490,56	-	Fixed	[43]
α_s	0.00000001	-	Fixed	Assumed
μ	1/75.50	-	Fixed	[43]
β	-	$(0, 10)$	$N(2.5, 0.1)$	Assumed
ϵ	1.02	-	Fixed	Assumed
ϵ_D	0.00002	-	Fixed	Assumed
ϵ_{s1}	0.007	-	Fixed	[2]
ν	-	(0,0.4)	$Beta(0.021, 3.812)$	[56–59]
ϕ	0.65	-	Fixed	Assumed
τ	-	$(1/15, 1/10)$	$Beta(0.389, 4.680)$	[44, 60, 61]
σ_H	-	(0, 0.4)	$Beta(0.091, 2.549)$	[56–59]
σ_{HI}	2	-	Fixed	[61]
d_H	-	(0, 0.1)	$Beta(0.069, 3.091)$	[62]
ω	-	$(0.2, 2.5)$	$N(0.52, 0.1)$	[61, 63]

Results

In Figure 2, we can observe the posterior density functions of the parameters estimated with the MCMC with a Bayesian approach.
For our study, we used two chains and Figure 3 show the traceplots for the chains representing each parameter. In addition, the convergence of the Hamiltonian Monte Carlo (HMC) was verified by the criterion shown in [35, 39–41]. Using the expressions of the limits (27)-(40) and the mean

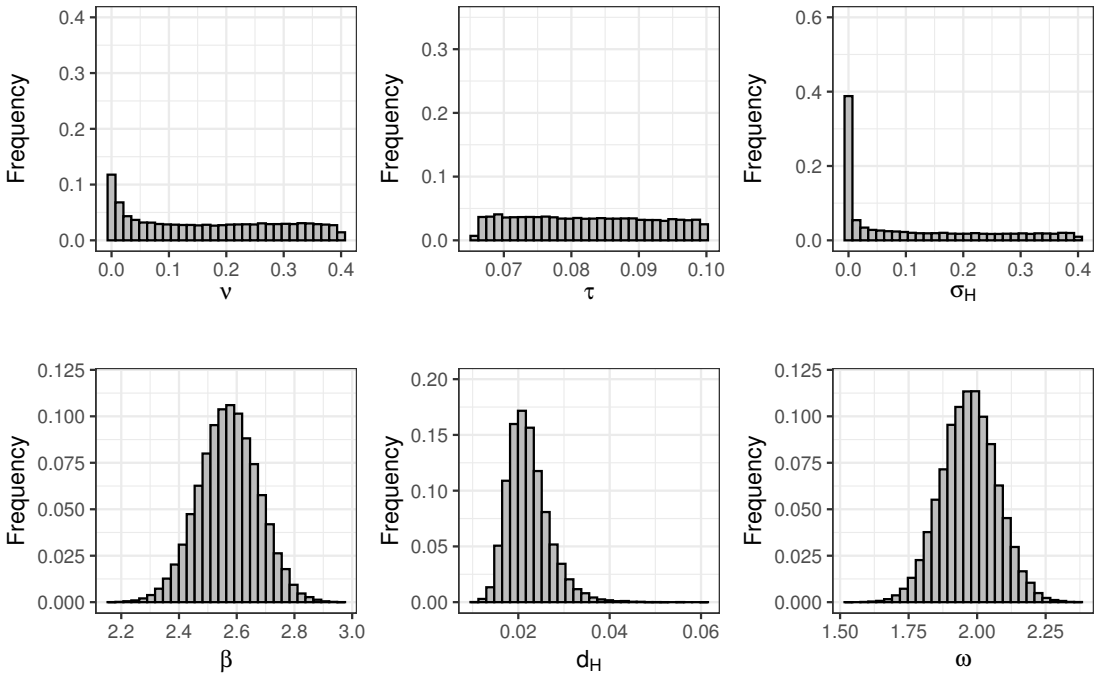

Figure 2. The posterior density functions obtained using MCMC with a Bayesian approach

of the values of the estimated parameters we have that the value obtained for the expression (27) is 0.25, and for (28) is 1.15 which means that when the parameter associated with adherence to treatment grows with HIV patients achieving the undetectability of the virus in blood the basic reproduction number is less than the unit so that the epidemic under these conditions can disappear in the population. The case when the adherence to HIV treatment tends to 0 and the number of cases that lose the undetectability and are HIV positive is higher than the unit, leads to an adverse epidemiological situation.
For expressions (29) and (30), the values obtained were 1.02 and 1.15, both greater than unity, which means that the number of AIDS cases that achieve undetectability while maintaining HIV status and other factors without intervention does not improve the epidemiological situation.
When the parameters associated with adherence to treatment and achieving undetectability of the virus in blood grow together and when the parameters associated with the loss of this undetectability for HIV and AIDS grow together, the basic reproduction number is less than unity, so we would be in a favorable situation, see expressions (31) and (34) and Table 3. In the opposite cases, by means of expressions (32) and (33), the basic reproduction number is greater than unity. In the case when the diagnosis rate increases and the parameters associated with adherence to HIV treatment increase and decrease, the basic reproduction number is less than unity but is more favorable when the latter decreases.

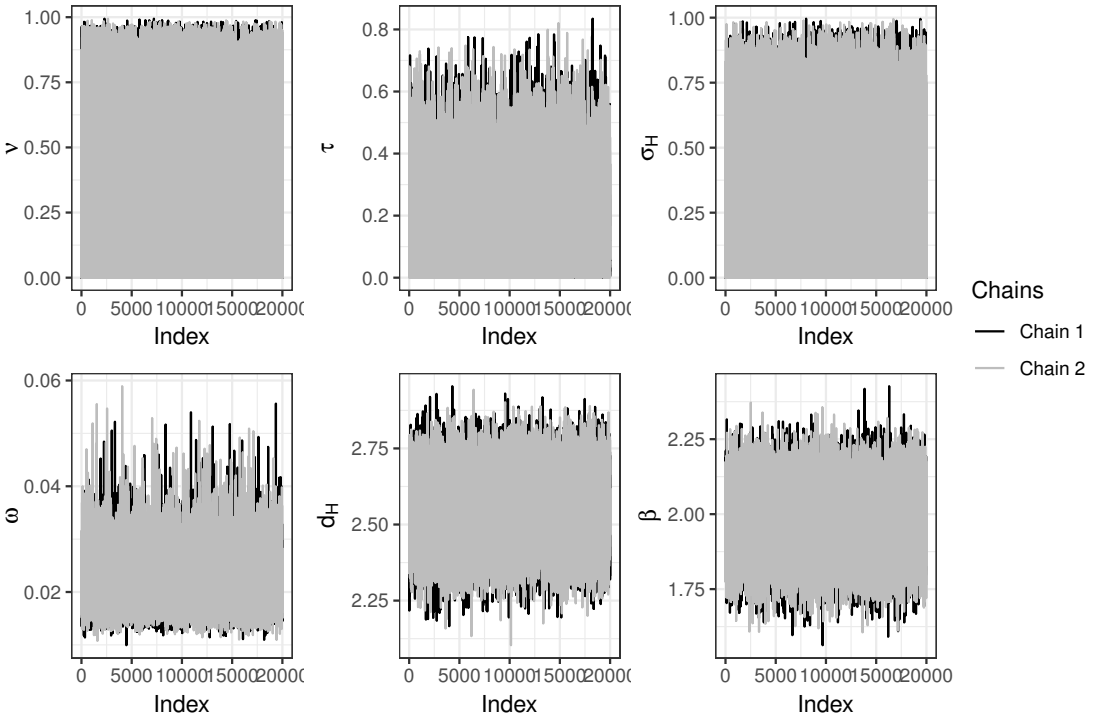

Figure 3. In this plot, each line represents an MCMC chain (2 chains), and each point represents the sampled value of a specific parameter in each MCMC iteration

When we increase the number of patients who progress from HIV to AIDS and decrease the number of AIDS cases who achieve undetectability according to formula (35), the basic reproduction number is greater than unity, which means that this epidemiological situation has a negative effect on the control of virus transmission. In the opposite situation by formula (36), the basic number reproduction is lower than unity, which we can say from the information provided by the model and the values of the parameters that if the number of cases with progression to AIDS increases, we need to increase adherence to treatment to counteract it.
In the case of increased case detection and adherence to HIV treatment according to formula (38), we have a positive impact on the basic reproduction number because it is less than unity. But if the number of diagnoses increases but adherence to treatment decreases according to formula (37), the basic reproduction number is greater than unity, so in order to have a positive effect on the decrease of HIV/AIDS cases we must have greater adherence to treatment in HIV.
Generally, when the parameters associated with the diagnosis and adherence to treatment in HIV and AIDS tend to the limit of the definition interval and the parameters of loss of the virus's undetectability in the blood tend to zero and return to the HIV and AIDS state, we are in a favorable situation for the control and future eradication of the epidemic and the opposite case we would be in an unfavorable situation because the basic reproduction number is greater than unity, see expressions (39) and (40) in Table 3.

Table 4 shows the evolution of the parameters associated with PrEP use when we implement the 25% coverage increase and 35% in 2025. Also, we assume that the health system has enough medication to cover the number of new individuals starting to use PrEP per year, which is logical taking into account the size of the Brazilian population. In the case a patient stops the PrEP use by decision or due to adverse effects, he/she can re-enter after a period of time to use the preventive method again, always remembering that our study, given the characteristics of the HIV/AIDS

Table 3. Values of the expressions (27)-(40) related to the joint variation over the $\mathfrak{R}_0$ of the parameters associated with treatment and diagnosis. The first column represents where the parameters will tend together, the second column links the respective expression of the basic reproduction number and the last column shows the value of the basic reproduction number when the parameters tend together to those values

Parameters	Expressions	Value of $\mathfrak{R}_0$
$\sigma_{HI} \to 1$ and $\sigma_H \to 0$	(27)	0.25
$\sigma_{HI} \to 0$ and $\sigma_H \to 1$	(28)	1.15
$\nu \to 1$ and $\omega \to 0$	(29)	1.02
$\nu \to 1$ and $\omega \to 0$	(30)	1.15
$\sigma_{HI} \to 1$ and $\nu \to 1$	(31)	0.16
$\sigma_{HI} \to 0$ and $\nu \to 0$	(32)	1.21
$\sigma_H \to 1$ and $\omega \to 1$	(33)	1.07
$\sigma_H \to 0$ and $\omega \to 0$	(34)	0.91
$\tau \to 1$ and $\nu \to 0$	(35)	1.01
$\tau \to 0$ and $\nu \to 1$	(36)	0.83
$\epsilon_{s1} \to 1$ and $\sigma_{HI} \to 0$	(37)	1.02
$\epsilon_{s1} \to 1$ and $\sigma_{HI} \to 1$	(38)	0.64
$\epsilon_{s1} \to 1$, $\sigma_{HI} \to 1$, $\nu \to 1$, $\sigma_H \to 0$, and $\omega \to 0$	(39)	0.11
$\epsilon_{s1} \to 1$, $\sigma_{HI} \to 0$, $\nu \to 0$, $\sigma_H \to 1$, and $\omega \to 1$	(40)	1.24

epidemic and the data, is annual. We compare two possible increases in coverage, Coverage I,

Table 4. Value of PrEP use rate with increases in coverage and number of new PrEP users per year from 2025-2035

Year	ϵ_p with Coverage I	Number of individuals who started using PrEP	ϵ_p with Coverage II	Number of individuals who started using PrEP
2025	0.000375	82136	0.000405	88707
2026	0.00046875	103273	0.00054675	120458
2027	0.0005859375	129812	0.0007381125	163525
2028	0.0007324219	163120	0.0009940063	221378
2029	0.0009155274	204914	0.0013419085	300347
2030	0.0011444093	257342	0.0018115765	407366
2031	0.0014305116	323087	0.0024462831	552355
2032	0.0017881395	394781	0.0033015982	728920
2033	0.0022235174	510597	0.0044571576	1018180
2034	0.0027939681	638246	0.0060176282	1374650
2035	0.0034921721	802668	0.0081231698	1867099

which is an increase of 25% per year, and Coverage II, an increase of 35% per year, both following formula (22), where the percentage increases are the p_s value, with respect to keeping the current rate of PrEP use fixed. We quantified the impact with the HIV incidence rate, HIV rate ratio and number of avoided cases and began implementation in 2025 to study its effect until 2035.
With Coverage I basic number that, the HIV incidence reported by the model was 17.06 ([15.96, 18.92]), which represented a decrease of 18.98% ([18.04%, 18.62%]) with respect to the scenario where we maintain the current coverage which was 20.85 ([19.61, 22.23]).
With Coverage II of HIV incidence rate was 15.15 ([14.15, 16.22]), which is a decrease of 27.66% ([27.03%, 27.84%]) with respect to the scenario where we maintain the current coverage until 2035.
Using HIV incidence as a quantification of the impact of increased coverage, we can conclude that from the values reported by the model and the estimation technique, an increase in PrEP coverage in Brazil favors the reduction of new cases of HIV, but we must take into account that given the

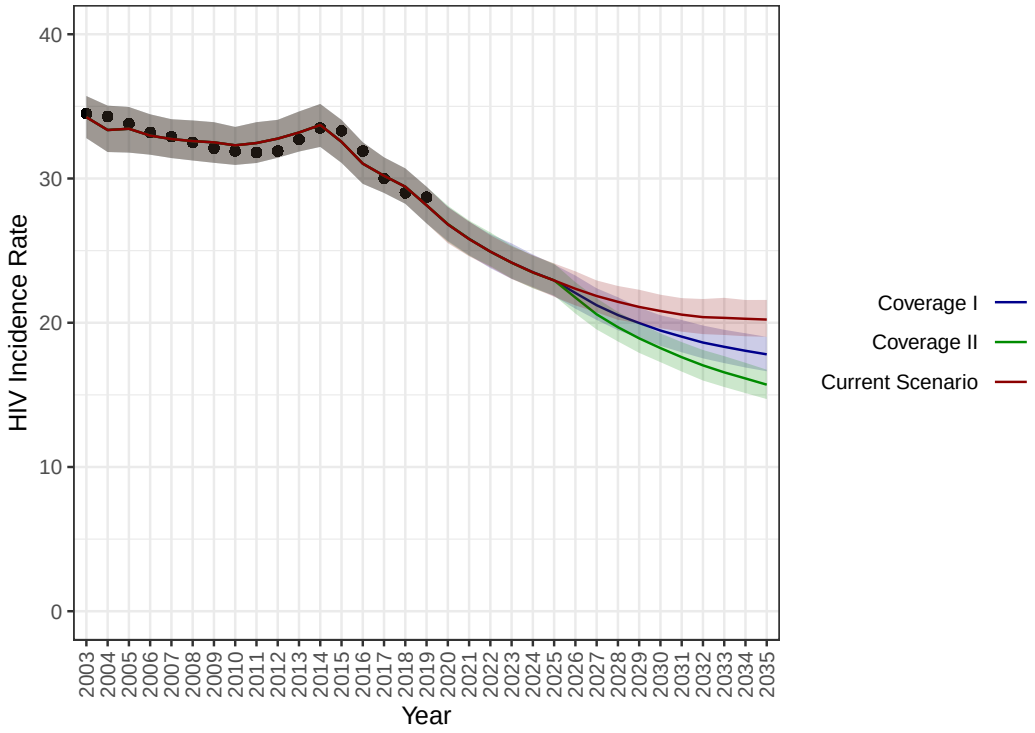

Figure 4. Behavior of the HIV incidence rate for the different increases in coverage starting in 2025 using the formula (22), and when we maintain PrEP use at current coverage (Current Scenario) until 2035. The credibility intervals between 2.5% and 97.5% are shown and the black points are the real data reported [43–46, 52]

demographics of Brazil, we need to further reduce the incidence of HIV for future eradication of the virus, see Figure 4.

The number of averted cases of HIV infection with the increased coverage is significant. The 35% annual increase in coverage (Coverage II) reported the highest number of averted cases with respect to the 25% increase in coverage, with a difference of 26790 fewer cases for 2.5%, 26390 for 50% and 26420 cases averted for 97.5%, see Table 5.

The reported values of the rate ratio show that Coverage I has at the end of the study in 2035 a value of 0.82 ([0.75, 0.89]) and Coverage II of 0.73 ([0.66, 0.80]), see Table 6, showing again that an increase in PrEP coverage in the population has a positive impact.

Based on the data reported by model (2)-(7), and the parameter estimation method, we obtained that through the HIV incidence, the number of HIV cases avoided, and the rate ratio that an increase in PrEP coverage can reduce the impact of HIV/AIDS in Brazil. In this case, two annual increases in PrEP coverage in Brazil of 25% and 35% were studied and the difference in the values obtained was significant and we recommend increasing the use of PrEP and extending its use not only to the vulnerable part of the population. to reduce the impact of the virus on the population.

Table 5. Number of cases avoided in 2035 with the different coverage increases started in 2025 and the difference in the number of cases avoided between Coverage I and Coverage II

	2.5%	50%	97.5%
Coverage I	15985	50879	85448
Coverage II	42774	77269	111868
Difference	26790	26390	26420

Table 6. Rate ratio for the different coverage increases initiated in 2025 and studying the impact until 2035

	Coverage I			Coverage II		
Year	Estimated	Lower Limit	Upper Limit	Estimated	Lower Limit	Upper Limit
2025	1.00	0.93	1.07	1.00	0.93	1.07
2026	0.98	0.91	1.05	0.97	0.90	1.04
2027	0.96	0.89	1.03	0.93	0.86	1.00
2028	0.94	0.87	1.01	0.90	0.84	0.97
2029	0.92	0.85	0.99	0.87	0.81	0.94
2030	0.90	0.83	0.97	0.85	0.78	0.92
2031	0.88	0.81	0.96	0.82	0.76	0.89
2032	0.87	0.80	0.94	0.80	0.73	0.87
2033	0.85	0.78	0.92	0.77	0.71	0.84
2034	0.83	0.76	0.91	0.75	0.68	0.82
2035	0.82	0.75	0.89	0.73	0.66	0.80

6 Conclusions

In this article, we presented a mathematical model for HIV/AIDS transmission that incorporates current PrEP programs. We presented a methodology that incorporates increasing PrEP coverage in the population into the model. The model allows for the study of different PrEP variants, different coverages and takes into account the importance of antiretroviral treatment in the transmission of the virus, in particular, adherence to treatment which leads to having an undetectable viral load in the blood and not infecting, and the diagnosis of cases due to the attempt to enter the PrEP program. We demonstrated the basic properties of the model: that it has a solution, such solution is positive, and in which region it makes epidemiological sense. We focus on the incidence of HIV cases because antiretroviral therapies allow the patient not to reach that state of the disease, in addition to being the most advanced cases of the disease. In the model, we have a compartment for people with undetectable viral load in the blood with the use of treatment because they will not represent a problem in the transmission of the virus and we can monitor the patient's health status and try to control the evolution of the disease. Using the next-generation matrix, we found the basic reproduction number and studied the joint and independent impact of parameters associated with the effectiveness of the treatment, the number of cases with HIV that reach the stage of AIDS, the use of PrEP, and contagion by other non-sexual ways.

To estimate parameters, we used the Markov Chains Monte Carlo (MCMC) with a Bayesian approach and as a value to quantify the impact we have on the HIV incidence rate ratio. The parameters selected to estimate are related to the effectiveness of antiretroviral treatment, death associated with the disease, and transmission. Using demographic data from Brazil and data from the bibliography for parameters and initial conditions, we performed computer simulations. We presented a test to observe the behavior of the estimation of the selected parameters of the model. We studied two possible increases in PrEP program coverage of 25% and 35%. With the results reported by the model, the accumulated cases of the individuals and the new individuals who enter the program are studied, since it is important that the results are logical with respect to the study population. The results obtained are acceptable, as can be seen in Table 4.

We compare the behavior after increasing coverage by 25% and 35% in 2025 compared to maintaining the current coverage with oral PrEP using as a basis the incidence of HIV, HIV rate ratio and the number of cases avoided.

The results of the study showed the potential of PrEP use to reduce the incidence of HIV in Brazil. The model, after adapting the initial conditions and parameters, can be utilized to predict HIV incidence in other regions, countries, or localities.
In future work, we intend to study the model in other scenarios and study the cost-benefit problem of implementing injectable PrEP and increasing coverage.

Declarations

Use of AI tools

The authors declare that they have not used Artificial Intelligence (AI) tools in the creation of this article.

Data availability statement

All data generated or analyzed during this study are included in this article.

Ethical approval

The authors state that this research complies with ethical standards. This research does not involve either human participants or animals.

Consent for publication

All authors authorize the publication of the work.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Author's contributions

E.M.D.M.: Conceptualization, Formal Analysis, Methodology, Software, Validation, Visualization, Data Curation, Writing-Original Draft. R.A.R and A.P.: Visualization, Validation, Writing - Review & Editing. All authors discussed the results and contributed to the final manuscript. The authors have read and agreed to the published version of the manuscript.

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