A Study on the Occurrence of HIV Eradication for Preexposure Prophylaxis Treatment with a Deterministic HIV Model

Hyeygjeon Chang*, Claude H. Moog, and Alessandro Astolfi

Abstract

We examine the HIV eradication in this paper using a mathematical model and analyse the occurrence of virus eradication during the early stage of infection. To this end we use a deterministic HIV infection model, modify it to describe the pharmacological dynamics of antiretroviral HIV drugs, and consider the clinical experimental results of preexposure prophylaxis HIV treatment. We also use numerical simulation to the model the experimental scenario, thereby supporting the clinical results with a model-based explanation. The study results indicate that the protocol employed in the experiment can eradicate HIV in infected patients at the early stage of the infection.

I. INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus to cause acquired immune deficiency syndrome (AIDS) [1]. HIV infection can cause the virus to infect CD4 T-cells and macrophages. A CD4 T-cell infected by HIV stops performing the role in the human body’s immune system and instead produces new copies of the HIV virus. Once the CD4 T-cell count reaches a certain minimum, the immune system cannot work reliably. Although HIV drug treatment has advanced,
AIDS continues to be a prevalent worldwide disease. For example, in 2009, 1.8 million patients died from AIDS and the total number of HIV infected patients was estimated to be 33.3 million [2].

A number of studies based on mathematical models have been published to better understand the dynamics of HIV infection. For example, several HIV/AIDS mathematical models have been reported in [3]–[7]. In [8]–[10] the authors have presented control systems applications for these HIV models. We investigate HIV eradication in this paper using a mathematical model and consider the clinical experiments reported in [11], which has been primarily presented to evaluate the physical effect of preexposure antiretroviral chemoprophylaxis in the prevention of HIV infection.

Preexposure antiretroviral chemoprophylaxis is regarded as a promising approach to prevent HIV infection [12]–[14]. Currently preexposure prophylaxis is rarely used for men and transgender women. However, if evidence of the effectiveness and safety becomes available, most could consider its use. In order to examine the clinical effect of preexposure prophylaxis for men and transgender women, experiments have been designed and conducted [11].

In the experiments conducted in [11], 2499 randomly assigned uninfected people received either a placebo or FTC-TDF, i.e., a combination of emtricitabine and tenofovir disoproxil fumarate, once a day. The experimenters followed the studied subjects for 3324 person-years. At the enrollment, 10 of the subjects were found to have been HIV-infected. During follow-up, 100 of the subjects became HIV-infected and of these, 64 were in the placebo group and 36 were in the FTC-TDF group. This result indicates a 44% reduction in HIV infection. Therefore the experimenters concluded that the drug FTC-TDF could prevent HIV infection in the studied subjects. For detailed information regarding the experimental data and results, see [11].

To theoretically study the experimental results we employ the extracellular deterministic HIV model used in [3], [4] and modify the model with the pharmacological dynamics studied in [15], [16]. Using this modified model we analyse the possibility of virus extinction in the HIV treatment of preexposure chemoprophylaxis and the results of the study are supported by the experiment results of [11]. In addition our research can theoretically explain the experimental results, based on the modified mathematical model.

Preliminary work relating to that in this paper has been presented in [17]. The research presented here extends our investigation of the virus eradication criterion to preexposure prophylaxis.
HIV treatment and its corresponding parameter conditions.

The main contribution of this research can be summarised as follows. We prove that our HIV infection model extended with pharmacological dynamics is realistically consistent with the results of the experiments in [11]. Particularly our mathematical model simulation study results imply that the experimental protocol eradicates the virus under some specific subject conditions.

The effect of the experiment in [11] on the cellular immune response has been studied in [18]. In contrast with [18], the mathematical model used in this paper considers no term related to immune system enhancement. The focus of this paper is on HIV eradication during the early stage of the virus infection, when no immune response or cellular latent reservoirs of HIV can be established. Based on the same reasoning, we do not model the latent HIV reservoirs, which are the main reason that HIV eradication is impossible in the later stage of virus infection [19]. It is notable that the experiment in [11] was intended to address HIV preexposure prophylaxis, i.e., drug treatment (and prevention of infection) immediately before or after the contact with HIV. If this treatment works effectively, then the infection remains at the early infection stage, preventing further infection and suppressing the virus load to a sufficiently low level. Note that preexposure and postexposure prophylaxis for HIV have been studied by stochastic HIV eradication analysis in [20]–[22].

We organise this paper as follows. Section II introduces the HIV infection model of [3], [4], which we extend to include pharmacological dynamics to numerically simulate the experiments in [11]. In section III we describe the simulation studies performed with the modified model of HIV infection. In section IV we discuss our results and draw our conclusions.

II. HIV Dynamic Model Including Pharmacological Dynamics

In this section we describe our extension of the HIV model used in [3], [4] to include the pharmacological dynamics of FTC-TDF.
A. Three-dimensional HIV Dynamics

The model of [3], [4] is as follows:

\[
\begin{align*}
\dot{x} &= \lambda - dx - \beta xv, \\
\dot{y} &= \beta xv - ay, \\
\dot{v} &= ky - cv.
\end{align*}
\]  

(1)

Note that the states, \(x\), \(y\), and \(v\), are the concentrations of specific cells. That is, \(x\), \(y\), and \(v\) describe the concentrations of healthy CD4 T-cells (CD4/mm\(^3\)), CD4 T-cells infected by HIV (CD4/mm\(^3\)), and virions (RNA copies/ml), respectively.

In order to model the drug effect on \(\beta\), we introduce \(\eta\), \(0 \leq \eta \leq 1\), presenting to the drug efficacy, to be the control input. Then the parameter \(\beta\) is given by:

\[
\beta = (1 - \eta) \bar{\beta}.
\]

(2)

From a control systems perspective, the control input \(\eta\) corresponds particularly to the efficiency of reverse transcriptase inhibitors (RTIs). It is notable that FTC and TDF are classified in this category of antiretroviral drugs. The value \(\eta = 1\) implies a perfect HIV infection block by the drug, whereas \(\eta = 0\) implies there being no effect by the drug. In subsection II-B we further model the control input \(\eta\) to describe the effect by the drug FTC-TDF. For additional details on the model see [3], [4].

As stated above, compared to the research in [18], the mathematical model (1) in this paper does not consider the immune response. It is notable that the experiments of [11] were intended for HIV preexposure chemoprophylaxis, which sought virus extinction during the early stage of HIV infection, thus any boost in the immune response was neglected. Practically, such an approach (i.e., with no suppression effect by the immune response considered) can produce more conservative results regarding HIV eradication, because the immune response always acts suppressing the virus and the infected cells. For the same reason, model (1) does not consider terms related to a latent HIV reservoir. As long as the treatment works properly and the infection is prevented, we assume that the infection process remains at the early stage, with no immune response or development of any latent virus reservoir.

The parameters of model (1) are positive, as estimated in [9] on the basis of clinical data. Table I provides the model’s median parameter values. For additional studies on parameter estimation for HIV models see [23]–[25] and the references therein.
TABLE I
ESTIMATED VALUES OF HIV MODEL PARAMETERS [9]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median Value</th>
<th>Parameter</th>
<th>Median Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda$</td>
<td>5.36 mm$^{-3}$/day</td>
<td>$d$</td>
<td>0.012 / day</td>
</tr>
<tr>
<td>$\beta$</td>
<td>$8.38 \times 10^{-8}$ ml / day</td>
<td>$a$</td>
<td>0.041 / day</td>
</tr>
<tr>
<td>$k$</td>
<td>6.85 mm$^3$ ml$^{-1}$/day</td>
<td>$c$</td>
<td>0.280 / day</td>
</tr>
</tbody>
</table>

The parameter estimation in [9] has been performed during HIV drug treatment. As such, Table I suggests that the estimated value of $\beta$ has been associated with full medication, rather than the value of $\bar{\beta}$. Meanwhile the parameter estimations in [10] have been made based on the pretreatment and posttreatment data of six volunteer patients. From the study in [10], based on the pretreatment data, the $\bar{\beta}$ median value is estimated to be $9.34 \times 10^{-7}$ (ml / day).

Table I presents the estimated value of $\lambda$ for HIV-infected patients. In general the CD4 T-cell count for HIV-free subjects is known to be approximately 1000/mm$^3$ [3]. Therefore it is generally assumed that the median value of $\lambda$ for uninfected individuals is 12, i.e., $d \times 1000$.

B. Pharmacological Dynamics for FTC-TDF

Currently most control schemes for the HIV drug treatment, e.g., the schemes of the studies in [26]–[28], cannot be applied to HIV-infected patients. This is because the widely considered control input for HIV models is the efficacy of the drug in the human body, not the drug dosage. The efficacy of the drug, which ranges between zero and one, is not accurately described by the drug amount.

Now we investigate the relationship between the control input of model (1) and the HIV drug dose with additional pharmacokinetic and pharmacodynamic modeling. By doing so we obtain an extended model that uses the drug dosage as the control input, which is more practical than previous models for biomedical applications. It is notable that different HIV infection models have been employed to research the relationship between the virus dynamics and the concentration of HIV drugs [18], [29]–[31]. In particular an extended HIV infection model has been presented in [18] based on the HIV infection model with immune response modeling of [6], [28].
The drug administration process into the human body has two phases [15]. The first is the pharmacokinetic phase, corresponding to the profiles of the drug level and time, and involves the drug dose, administration route, and intake frequency. The second phase is the pharmacodynamic phase, corresponding to the effects realised by the drug. The results of this phase depend on the concentration of the drug in the action compartments.

1) Pharmacological Dynamics Modeling: Typically drugs are prescribed to be taken at a constant interval and at a constant dose. In this research we assume that the drug is absorbed instantaneously and completely, is distributed in the human body as one compartment, and is eliminated by first-order kinetics. The elimination rates of FTC and TDF are modelled by:

\[ \dot{\sigma}_F = -k_F \sigma_F, \]  
\[ \dot{\sigma}_T = -k_T \sigma_T. \]  

(3) \hspace{1cm} (4)

\( \sigma_F \) and \( \sigma_T \) are the intracellular amounts of FTC and TDF, respectively. \( k_F \) and \( k_T \) are the constant rates of elimination of the first-order FTC and TDF, respectively. Note that these elimination rates are related to the drug half-life intracellularly. For example, the half-life of FTC, \( t_{1/2} \), is \( \log 2/k_F \). The HIV-drug intake can be regarded to be an impulsive control input.

A number of studies have empirically fit dose-response curves [16]. The Hill function is one class of models employed in these studies and is given by:

\[ \eta(t) = \eta_{max} \frac{C(t)^\gamma}{C(t)^\gamma + \frac{1}{Q}}. \]  

(5)

\( \eta(t) \) corresponds to the drug efficiency response by the drug plasma concentration \( C(t) \). \( \gamma \) and \( Q \) are constants, and \( \eta_{max} \) is the maximum response level.

As in [16] we let \( Q = 1/C_{50} \). The parameter \( C_{50} \) is the drug plasma concentration reducing the drug efficiency to 50% of \( \eta_{max} \). As in [32]–[34] we assume that \( \gamma = 1 \) since the drug considered in this paper is a combination of FTC and TDF, which are classified as nucleoside reverse transcriptase inhibitor (NRTI). Note that in this subsection we consider the human body to be one-compartment.

At time \( t \) we obtain the drug amount in the human body as the product of the plasma concentration (\( C(t) \)), the human body mass (\( M \)), and the apparent volume of distribution (\( V_d \)).
That is,
\[ \eta(t) = \eta_{\text{max}} \frac{\sigma(t)}{\sigma(t) + \sigma_{50}}, \]
where \( \sigma(t) = C(t)V_d M \) and \( \sigma_{50} = C_{50}V_d M \). For an additional description of the pharmacological dynamic model, see [10].

2) Pharmacological model parameters: In this paper we consider FTC-TDF as it has been employed in [11]. One tablet of FTC-TDF contains a total of 500 \( mg \), combining with 200 \( mg \) of FTC and 300 \( mg \) of TDF. This tablet is also known by the brand name Truvada\textsuperscript{®} [35]. To describe the simultaneous effects of FTC and TDF we exploit two pharmacological models.

We consider the representative pharmacological parameters to be \( k_F = 0.0178 /h \) i.e., 0.4266 /day, \( k_T = 0.0042 /h \) i.e., 0.1014 /day, \( \sigma_{50,F} = 0.6762 \) \( mg \), and \( \sigma_{50,T} = 20.5744 \) \( mg \). Note that the subscript \( F \) stands for FTC whilst the subscript \( T \) stands for TDF. For a study involving the detailed estimation of these parameters, see [18].

While here we suggest representative values of the pharmacological parameters, in subsection III-B we consider a range of parameters.

C. Integration of Models with Control Input

Model (1) including (2) is now combined with (3) and (6), to yield:
\[ \dot{x} = \lambda - dx - (1 - \eta_F) (1 - \eta_T) \beta x v, \]
\[ \dot{y} = (1 - \eta_F) (1 - \eta_T) \beta x v - ay, \]
\[ \dot{v} = ky - cv, \]
\[ \dot{\sigma}_F = -k_F \sigma_F, \]
\[ \dot{\sigma}_T = -k_T \sigma_T, \]

where
\[ \eta_F = \eta_{\text{max},F} \frac{\sigma_F}{\sigma_F + \sigma_{50,F}}, \]
\[ \eta_T = \eta_{\text{max},T} \frac{\sigma_T}{\sigma_T + \sigma_{50,T}}. \]

Note that we assume that the drug effects by FTC and TDF are totally independent of each other.
Now we set $X(t) := [x(t)\ y(t)\ v(t)\ σ_F(t)\ σ_T(t)]^T$. Then we represent model (7) by the following:

$$
\dot{X} = F(X).
$$

(8)

Using model (8) we can simulate the experiment of [11]. To this end we use the impulsive control inputs in model (8) to describe the drug intake and the HIV exposure for the protocol of the experiment. These can be approximately modeled by the instantaneous changes in $σ_F$, $σ_T$, and $v$, respectively. We also assume that at an instance of discrete time the drug is administrated. HIV drugs are generally delivered as extended release formulations [36], while the drug intake is treated as an impulsive input in the HIV model.

Although in [37] an impulsive control input has been modelled as Dirac-delta-function on $\dot{X}$, here we exploit the equivalent description of a hybrid system. The system is described with a discontinuity on $X$, given by:

$$
\begin{align*}
\dot{X}(t) &= F(X(t)), & \text{if } t \notin S_d \cup S_v, \\
X^+ &= X + V_d, & \text{if } t \in S_d, \\
X^+ &= X + V_v, & \text{if } t \in S_v,
\end{align*}
$$

(9)

where $V_d$ and $V_v$ are the vectors describing the instantaneous changes in the medicine states (i.e., $σ_F$ and $σ_T$) and for the virus state $v$, respectively. Note that $S_d$ is the set, at each element of which the instantaneous changes occur on the states $σ_F$ and $σ_T$ while $S_v$ is the set, at each element of which the instantaneous changes occur on the state $v$.

With respect to the instantaneous changes of $σ_F$ and $σ_T$ we consider the oral bioavailability for $V_d$. Oral bioavailability is a pharmacokinetic parameter used to describe the fraction of an oral dose reaching the system, namely:

$$
V_d = [0\ 0\ 0\ 200(mg) \times B_F\ 300(mg) \times B_T]^T.
$$

(10)

The bioavailability of FTC is $B_F$ while the bioavailability of TDF is $B_T$. The median values of $B_F$ and $B_T$ are 0.92 and 0.25, respectively [38]. Additionally it is assumed that if a fraction of the administered drug reaches the system, then it is completely converted into the intracellular activation form.

Following the experimental protocol of [11], we set $S_d := \{1, 2, 3, 4, \ldots, T_d\}$, where the treatment period $T_d$ is 450 (days). It is assumed that the contacts with HIV occur at instants,
that are the elements of the set $S_v$. In a later section we determine the $M_v$ value of $V_v = [0 \ 0 \ M_v \ 0 \ 0]^T$.

**D. Consideration of the Virus Eradication Cases**

As model (1) is deterministic and continuous-time, it is impossible for the state $v$ (or the infected CD4 T-cell $y$) to be reduced to 0 [4], [39]. It is notable that viruses and cells are countable objects in biological systems, whereas the state variables of the model (1) are positive real.

In this paper it can be assumed that HIV is eradicated if the HIV and infected CD4 T-cells are reduced to sufficiently low levels, because we consider preexposure prophylaxis HIV treatment, not need to consider latent HIV reservoir. In [4], [39], for example, the elimination of HIV has been discussed with a threshold corresponding to a virus population of less than 1 particle. Thus, to study virus extinction in an HIV patient in this simulation study, threshold conditions for the virus and infected CD4 T-cells are required. To this end we consider the following criterion as characterising the virus eradication.

**Virus Eradication Criterion for Preexposure Prophylaxis HIV Treatment (VEC_PrEP)**

In the model (1) the virus is considered to be eradicated during the experimental protocol if there exists a time instant $T$ ($T_m \leq T \leq T_d$) such that $k_y y(T) < 0.5$ and $k_v v(T) < 0.5$, where $k_y = 5 \times 10^6$, $k_v = 5 \times 10^3$, and $T_m = \max(S_v)$. Otherwise the virus is not considered to be eradicated.

Note that in this work we consider the total volume of human blood *i.e.*, 5,000 ml, instead of the extracellular fluid volume, considered in [40]. Then $k_y y(\cdot)$ and $k_v v(\cdot)$ are the subject’s infected CD4 T-cells count and the HIV virion count.

We assume that the virus eradication case, based on the VEC_PrEP, corresponds to the HIV prevention cases of the experiment performed in [11]. The assumption is reasonable because we consider only the early HIV infection stage and not the immune response or cellular latent HIV reservoirs. Note that the preexposure prophylaxis HIV treatment given in the experiment of [11] can prevent infection, suppress the viral load, and keep the infection at the early stage. For the later stage of HIV infection, this approximation would not be reasonable due to the
presence of latent HIV reservoirs, which are not considered in model (1), and would result in HIV persistence. For studies similar to our research based on the stochastic analysis of HIV eradication during the early stage of HIV infection, see [20], [21].

**Remark 1:** In the absence of drug treatment the HIV-free equilibrium point \((\lambda/d, 0, 0)\) of model (1) with the given parameter set of Table I is unstable [3], [4]. However, by applying the VEC_PrEP, the equilibrium point becomes locally stable because the states \(y\) and \(v\) are considered to be zero when \(y < 0.5/k_y\) and \(v < 0.5/k_v\), respectively. The basin of attraction of the point is computed to be: \(x > 0, y < 0.5/k_y, \) and \(v < 0.5/k_v\).

In [41] the stability of the HIV-free equilibrium point of the HIV model when using periodic multidrug therapy has been analysed with the so-called basic reproduction number. Compared with [41] this paper deals with virus eradication during drug treatment, rather than whether or not the virus increases during treatment. Note that even in cases in which the virus decreases by drug therapy the VEC_PrEP can remain unsatisfied for \(T_m \leq T \leq T_d\).

Even with the VEC_PrEP and a stable equilibrium point \((i.e.,\) HIV-free status), this does not necessarily imply that we can control the state rendered into the point’s basin of attraction. In the following section we investigate this possibility based on the experiment protocol of [11] and the parameters of model (7).

### III. Numerical Simulations

For the simulations of this paper the initial condition is considered to be \(X(0) = [1000 0 0 0 0]^T\) corresponding to HIV-free status, since the normal CD4 T-cell count of HIV uninfected subjects is approximately 1000 /mm\(^3\) [3].

It is assumed that \(S_v = \{10, 50\}\) which implies that contacts with the virus occur on the 10th and 50th days. Also it is assumed that \(M_v = 0.002\) implying that a small number of the HIV virions are infused into the human body. Note that this value, \(M_v = 0.002\), corresponds to 10 virion particles in the 5,000 (ml), total blood volume of one patient. By the experimental protocol, \(\max(S_v) < T_d\), which implies that the contacts with the virus occur during the FTC-TDF administration days.
A. Three Cases with Different Values of $\eta_{\text{max},F}$ and $\eta_{\text{max},T}$

Since drug-resistant HIV species for the 2 NRTIs (i.e., FTC and TDF) are ideally assumed not to exist in the patient, we can set $\eta_{\text{max},F} = 1$ and $\eta_{\text{max},T} = 1$ (see [32]–[34]). Nevertheless antiretroviral HIV drug treatment does not succeed frequently because of the emergence of a resistant virus [4]. This resistant emergence is often owing to the preexistence of resistant HIV [42].

Although we can reasonably assume $\eta_{\text{max},F}$ and $\eta_{\text{max},T}$ to be equal to 1 because FTC and TDF are recognised as effective antiretroviral HIV drugs [32]–[34], the emergence of drug resistant HIV can result in reduced drug efficiency. Thus in this section we consider variations in the values of $\eta_{\text{max},F}$ and $\eta_{\text{max},T}$ to demonstrate the effect of HIV resistance on HIV treatment. We present three scenarios with three different pairs of parameter values, for $\eta_{\text{max},F}$ and $\eta_{\text{max},T}$.

In the first scenario we assume that both $\eta_{\text{max},F}$ and $\eta_{\text{max},T}$ are equal to 0.9. Fig.1 depicts the computer simulation results following the experimental protocol of [11]. We employ the integrated system (9) and the parameter values for $k_F$, $k_T$, $\sigma_{50,F}$, and $\sigma_{50,T}$ that are provided in subsection II-B. The upper two graphs of Fig.1 show the time histories of $\eta_F$ and $\eta_T$, respectively. Note that the time scales of these two graphs differ from the lower three.

This simulation shows that the $y$ and $v$ states continuously converge to 0. Using the VEC_PrEP, HIV is eradicated in the simulation of Fig.1. For example, at Day 450, $k_yy(450) = 4.2567 \times 10^{-6} < 0.5$ and $k_vv(450) = 7.3357 \times 10^{-6} < 0.5$.

In the second scenario we assume that both $\eta_{\text{max},F}$ and $\eta_{\text{max},T}$ are equal to 0.8. Fig.2 presents the result of the computer simulation. In the upper two graphs of Fig.2, note that the time scales also differ from those of the lower three. In the simulation in Fig.2, the states $v$ and $y$ do not converge to 0. Instead the states continue to increase in the latter part of the simulation. However, based on the VEC_PrEP one can conclude that HIV is eradicated in the simulation of Fig.2. For example, at Day 250, $k_yy(250) = 0.0549 < 0.5$ and $k_vv(250) = 0.0492 < 0.5$.

Note that we apply the VEC_PrEP to the data from the simulation results, once the simulation is completed. Then we determine whether there exists any time instant in which the condition of the VEC_PrEP is satisfied during the entire simulation period. As such, any virus rebound in the latter part of the simulation is irrelevant to the conclusion based on the VEC_PrEP.

For the third simulation we set both $\eta_{\text{max},F}$ and $\eta_{\text{max},T}$ to be equal to 0.7. Fig.3 presents the result of computer simulation. Note that the lower three time scales in this figure differ
Fig. 1. Computer simulation results following the protocol of the experiment in [11] using model (8) with $\eta_{max,F} = 0.9$ and $\eta_{max,T} = 0.9$. The simulation employs $S_c = \{10, 50\}$ and $M_c = 0.002$ to implement the impulsive change of the virus. Note that the time scale of the upper two graphs, in which the time histories of $\eta_F$ and $\eta_T$ are represented, respectively, differ from the lower three. Also note the third graph shows the time history of $x - x(0)$ rather than $x$, because the $x$ state remains close to $x(0)$.
Fig. 2. Computer simulation results of the protocol of the experiment in [11] using model (8) with $\eta_{\text{max}, F} = 0.8$ and $\eta_{\text{max}, T} = 0.8$. The simulation employs $M_v = 0.002$ and $S_v = \{10, 50\}$ to describe the impulsive virus infusion. The time scale of the upper two graphs differ from the lower three. The third graph shows the time history of $x - x(0)$ rather than $x$. 
Fig. 3. Computer simulation results of the protocol of the experiment in [11] using model (8) with $\eta_{\text{max},F} = 0.7$ and $\eta_{\text{max},T} = 0.7$. Note that the lower three time scales differ from those in the other figures. We employ $M_c = 0.002$ and $S_c = \{10, 50\}$ in this simulation.
from those of Fig.1 and Fig.2. In the simulation $k_y \min_{T_m \leq t \leq T_d} y(t) = 1.0444 > 0.5$ and $k_v \min_{T_m \leq t \leq T_d} v(t) = 0.6600 > 0.5$. Thus the minimum cell number of the infected CD4 T-cells and the minimum HIV virion number in the subject are both greater than 0.5 over the time period from the occurrence of the last virus infusion to the end of the experiment. Thus, by the VEC_PrEP, HIV eradication is not achieved.

**B. Parameter Plane for $\eta_{max,F}$ and $\eta_{max,T}$**

In this subsection we use a parameter plane $(\eta_{max,F}, \eta_{max,T})$ to study the range of $\eta_{max,F}$ and $\eta_{max,T}$ between zero and one. All other parameters are as described in subsection III-A. 31 parameter values are considered along the axis of the plane. Thus we have $31 \times 31$ pairs of parameter values and we have performed simulations for each pair for 450 days, as described in subsection III-A.

Fig. 4. Three-dimensional plot with $\eta_{max,F}$, $\eta_{max,T}$, and $\omega_m$ where $\omega_m = k_v \min_{T_m \leq t \leq T_d} v(t)$. The figure is based on the simulation results in the $(\eta_{max,F}, \eta_{max,T})$ parameter plane ranging between 0 and 1. All other system parameters are described in subsection III-A.
Let

\[
\psi_m = k_y \min_{T_m \leq t \leq T_d} \ y(t), \\
\omega_m = k_v \min_{T_m \leq t \leq T_d} \ v(t),
\]

where \( k_y = 5 \times 10^6 \), \( k_v = 5 \times 10^3 \), and \( T_m = \max \ S_v \). Thus \( \psi_m \) and \( \omega_m \) are the minimum cell count of the infected CD4 T-cells and the minimum HIV virion count in the subject (i.e., 5,000 ml of blood) over the time period from the occurrence of the last virus infusion to the end of the experiment. Based on the simulation results in the \((\eta_{max,F}, \eta_{max,T})\) parameter plane, Fig.4 shows a 3-dimensional plot with \( \eta_{max,F}, \eta_{max,T}, \) and \( \omega_m \).

To apply the VEC\_PrEP, Fig.4 is not sufficient to determine whether the conditions of the VEC\_PrEP are satisfied in each simulation.

Thus we plot the results in Fig.5 with circles, crosses, and dot symbols. After each simulation, if the HIV is considered to be extinguished with reference to the VEC\_PrEP, then we mark the corresponding \((\eta_{max,F}, \eta_{max,T})\) point with a circle on the plane. As shown in the case described in subsection III-A, the experimental protocol could lead to HIV eradication for these subjects.

If the VEC\_PrEP conditions are not met, we investigate how the simulation result deviated from these conditions. If \( \psi_m \geq 0.5 \) and \( \omega_m \geq 0.5 \), then we mark the corresponding point with a cross on the plane. The dot marks reflect cases in which \( \omega_m < 0.5 \) but \( \psi_m \geq 0.5 \), i.e. those for which the \( y \) state could be considered to generate multiple copies of HIV, resulting in HIV persistence. Note that no other cases are identified.

IV. CONCLUSIONS

In this study we have used a mathematical model approach to investigate HIV eradication in the early HIV-infection stage. First we have considered the clinical experimental results of [11]. To perform computer simulation experiments we have employed the three-dimensional HIV model of [3], [4] and we have modified it to include the pharmacology dynamics of antiretroviral HIV drugs. We then have performed numerical simulation experiments.

In comparison with the study in [18] in the mathematical model of this study we have not considered any immune response effect. This is because we have been only interested in the phenomenon of HIV eradication during the early stage of the virus infection prior to any boost in the immune response. By doing so (i.e., in the absence of any suppression effect by an immune
response) we have realised more conservative simulation results and parameter conditions, since the immune term always suppresses the virus and infected cells. It is notable that the experiment of [11] has been intended for HIV preexposure chemoprophylaxis. Eventually mathematical model-based studies on the experiment of [11] (e.g., [18] and this paper) could help to make a plan for further experiments.

Using the extended HIV mathematical model, We have revisited the experimental results via the computer simulation, and our study results have provided insight for better understanding the implications of those results. Our study result has suggested that the experimental protocol could lead to HIV eradication during the early stage of HIV-infection. Our study also provides some parameter conditions to achieve virus extinction by preexposure prophylaxis treatment for HIV.

Fig. 5. Simulation results in the plane of parameters, $(\eta_{\text{max},F}, \eta_{\text{max},T})$, with decision by the VEC\_PrEP. When HIV is considered to be extinguished based on the VEC\_PrEP, we mark the corresponding point with a circle on this plane. The dots and the crosses on the plane correspond to the cases with $\psi_m \geq 0.5$ and $\omega_m < 0.5$, and to the cases with $\psi_m \geq 0.5$ and $\omega_m \geq 0.5$, respectively.
It is notable that in July 2012 the U.S. Food and Drug Administration approved the usage of the drug FTC-TDF for the first time as a treatment for reducing the risk of HIV infection [43].

To extend the investigation of this paper we are considering several future research directions. In this paper we have employed the model (1) for the preexposure prophylaxis for HIV. However, for postexposure prophylaxis for HIV, a different HIV model must be considered that describes latent reservoirs of the virus. Latent reservoir makes it very difficult to extinguish the virus in an infected patient by postexposure prophylaxis for HIV. Also while we have employed a deterministic model for the HIV infection problem in this paper, stochastic models could be considered for future investigation.

In this paper we have focused on the experiment protocol of [11], i.e., with patients taking one tablet of FTC-TDF once a day. In the simulation studies of section III that follows the protocol, the decision by VEC_PrEP stems from the inter-patient parameters, i.e., $\eta_{\text{max},F}$ and $\eta_{\text{max},T}$, which correspond to the patients sensitivity to the drugs. In order to satisfy the VEC_PrEP we could adjust the amount of the drug taken, rather than imposing a fixed daily dosage protocol. For example, we might increase the amount of drug for a non-sensitive patient to eradicate the virus. This type of study will be considered in future work.

REFERENCES


