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Periodic Trajectories for HIV Dynamics in a Seasonal Environment With a General Incidence Rate

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Abstract. In this paper, we propose a five-dimensional nonlinear system of differential equations for the human immunodeficiency virus (HIV) including the B-cell functions with a general nonlinear incidence rate. The compartment of infected cells was subdivided into three classes representing the latently infected cells, the short-lived productively infected cells, and the long-lived productively infected cells. The basic reproduction number was established, and the local and global stability of the equilibria of the model were studied. A sensitivity analysis with respect to the model parameters was undertaken. Finally, some numerical simulations are presented to illustrate the theoretical findings.

1. Introduction

Human immunodeficiency virus (HIV) is a type of virus that attacks the body's immune system [1]. Although HIV infection is a manageable chronic condition, if left untreated, it can weaken the immune system or progress to acquired immune deficiency syndrome (AIDS). Some people may have no symptoms after contracting HIV so the infection is not diagnosed until symptoms of AIDS appear. It can take up to 10 years. Symptoms of an HIV infection can last for a few days or weeks. They can go away on their own. It is common for HIV infection to be misdiagnosed as another illness first.

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Historically, mathematics (in this context, we refer in particular to mathematical modeling and analysis) has been used to better understand the dynamics of the transmission of infectious diseases and to learn how to control them. This application of mathematics dates back to the work of Daniel Bernoulli, who used mathematical and statistical methods to study the potential impact of the smallpox vaccine in 1760 [2]. In the 1920s, Sir Ronald Ross, a physician by training, used mathematical modeling to propose effective methods of malaria control. In particular, he showed that the disease can be eradicated if the mosquito population is kept below a certain threshold, a discovery that won him the Nobel Prize in medicine. More recently, mathematics has helped shape effective public health policies against the spread of emerging and re-emerging diseases that pose a significant threat to public health, such as HIV/AIDS, influenza (e.g., the recent pandemics of bird flu and swine flu), malaria, severe acute respiratory syndrome (SARS) and tuberculosis. The mathematical modelling in epidemiology is a way to study how a disease is spread, predict the future behaviour, and propose control strategies. Several works qualitatively proposed and studied some mathematical models describing the dynamical behaviour of infectious disease transmission (see, for example, [3–9]). In particular, the HIV epidemic models with constant coefficients have been analysed in several works (see, for example, [10–13]). However, seasonality is very repetitive in each of the ecological, biological, and human systems [14]. In particular, in the climate variation patterns repeated every year by the same way, bird migration is repeated according to the repeated season variation, schools open and close almost periodically each year, etc. Among other things, these seasonal factors affect the pathogens' survival in the environment, host behaviour, and the abundance of vectors and non-human hosts. Therefore, several diseases show seasonal behaviours. Taking into account the seasonality in mathematical modelling becomes very important. Note that even the simplest mathematical models that take into account seasonality present many difficulties to study [5]. In [15], Bacaër and Gomes discussed the periodic S-I-R model, a simple generalization of the classical model of Kermack and McKendrick [16]. In [17], the authors studied a SEIRS epidemic model with periodic fluctuations. They calculated the basic reproduction number $\mathcal{R}_0$ of the time-averaged system (autonomous). Then, they proved a sufficient but not necessary condition ($\mathcal{R}_0 < 1$) such that the disease could not persist in the population in a seasonal environment. In [18], Guerrero-Flores et al. considered a class of SIQRS models with periodic variations in the contact rate. They proved the existence of periodic orbits by using Leray–Schauder degree theory. Zhang and Teng [19] studied an alternative SEIRS epidemic model in a seasonal environment and established some sufficient equivalent conditions for the persistence and the extinction of the disease. These results were improved by Nakata and Kuniya in [3] by giving a threshold value between the uniform persistence and the extinction of the disease. In [6], Bacaër and Guernaoui gave the definition of the basic reproduction number in seasonal environments. In 2008, Wang and Zhao [20] defined $\mathcal{R}_0$ for several compartmental epidemic models in seasonal environments. All these definitions were different, in several cases, from the basic reproduction number defined for the time-averaged system. By considering general compartmental epidemic models in seasonal environments, Wang and Zhao [20] showed that $\mathcal{R}_0$ was the threshold value for proving or not the local stability of the disease-free periodic trajectory. In [21], the authors studied the periodic behaviour of an "SVEIR" epidemic in a seasonal environment with vaccination.

As seasonality is very repetitive in the environment, which affects several diseases that show seasonal behaviours, taking seasonality into account in mathematical modelling becomes a necessity. In this paper, we proposed an extension of the HIV model proposed in [10, 11] by reducing the system from six-dimensional to five-dimensional system and by taking into account the seasonal environment. The mathematical model includes the B-cell functions for HIV dynamics with a general nonlinear incidence rate. The infected compartment was subdivided into two classes, namely the latently infected class and the productively infected class. We studied, in a first step, the autonomous system by investigating the global stability of the steady states. In a second step, we showed that the disease-free periodic solution is globally asymptotically stable if $\mathcal{R}_0$ is less than 1, and, if $\mathcal{R}_0$ is greater than 1, the disease persists. The rest of the paper is organized as follows. In Section 2, we introduced the mathematical model. In Section 3, we studied the case of an autonomous system, where all parameters are supposed to be constants. In Section 4, we considered the non-autonomous system, gave some basic results, and gave the definition of $\mathcal{R}_0$. We showed that the value of $\mathcal{R}_0$ around one was a threshold value between the disease's extinction and the disease's uniform persistence. We gave numerical examples that supported the theoretical findings in Section 5. Section 6 provided a brief conclusions of our obtained results.

2. Mathematical Model for HIV Dynamics

In this paper, we generalized the mathematical model studied in [10, 11]. The mathematical model is compartmental model since it describes the transfer of molecules through different compartments of the body. Let X_u, X_l, X_i, X_p, and X_c to be the number of uninfected cells, latently infected cells, productively infected cells, free virions, and B cells, respectively. The change in the number or concentration of CD4$^+$ T lymphocytes (dX_u) over a small time interval (dt) is a function of a constant (rate of de novo cell production ϱ), the rate of cell death (d_u) proportional to the number of cells present (X_u), and the number of infected cells that leave this "compartment" to join the compartment of infected cells (X_l, X_i). The number of infected cells is distributed into two compartments depending on the type of infected cell (X_l, X_i).

The number of infected cells is, therefore, a function of the number of target cells, the number of circulating virions (X_p), and the incidence rate of infection $(f_1(X_p)X_u)$, also called infectivity. The incidence rate of infection is very important for understanding the dynamics of the system. The variation in the number of virions (dX_p) per unit of time depends on the number of virions produced

$(d_i r_1 X_i)$, the clearance d_p of the virus, and the neutralized part of the HIV particles, $f_2(X_p)X_c$.

$$\begin{cases} \dot{X}_u(t) = \varrho(t) - (p_1(t) + p_2(t)) f_1(X_p(t)) X_u(t) - d_u(t) X_u(t), \\ \dot{X}_l(t) = p_1(t) f_1(X_p(t)) X_u(t) - (d_l(t) + \nu(t)) X_l(t), \\ \dot{X}_i(t) = p_2(t) f_1(X_p(t)) X_u(t) + \nu(t) X_l(t) - d_i(t) X_i(t), \\ \dot{X}_p(t) = d_i(t) r_1(t) X_i(t) - d_p(t) X_p(t) - f_2(X_p(t)) X_c(t), \\ \dot{X}_c(t) = \varepsilon(t) X_p(t) - d_c(t) X_c(t) - \upsilon(t) f_2(X_p(t)) X_c(t), \end{cases} \tag{2.1}$$

with positive initial condition $(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in \mathbb{R}_+^5$. The B-cell immune response is assumed to be proportional to the free virions' population (εX_p). The B cell impairment rate is assumed to be proportional to the contact with the free virions' population ($\upsilon f_2(X_p)X_c$, where υ is a positive constant).

$(p_1 + p_2) f_1(X_p) X_u$ is the incidence rate of infection and $f_2(X_p)X_c$ is the neutralization rate of HIV particles. Note that the incidence rate (f_1) and the neutralization rate (f_2), increase once the free viruses increase and are neutral in the absence of the virus. Thus, the functions f_1 and f_2 satisfy the following assumption.

The model's parameters are positive and are given hereafter as in Table 1.

Parameter	**Description**
p_1	Incidence rate between X_p and X_l
p_2	Incidence rate between X_p and X_i
ϱ	Generation rate of X_u
d_u, d_l, d_i, d_p, d_c	Death rates
ν	Conversion rate from the X_l compartment to the X_i compartment
r_1	Generated HIV in the lifetime of the short-lived productively infected cells
ε	B-cell immune rate (proportional to the free virions' quantity)
$f_2(X_p)X_c$	Neutralization rate of HIV particles
$\upsilon f_2(X_p)X_c$	B-cell impairment rate

Table 1. Model's parameters.

Assumption 2.1. *f_1 and f_2 are increasing, concave and continuous functions that satisfy $f_1(0) = f_2(0) = 0$.*

Lemma 2.1. (1) $f_1'(X_p)X_p \le f_1(X_p) \le f_1'(0)X_p,\ \forall X_p \in \mathbb{R}_+$;

(2) $\left(\frac{f_1(X_p)}{f_1(X_p^*)} - \frac{X_p}{X_p^*}\right)\left(1 - \frac{f_1(X_p^*)}{f_1(X_p)}\right) \le 0,\ \forall X_p, X_p^* \in \mathbb{R}_+$.

Proof. (1) For $X_p \in \mathbb{R}_+$, let $h_1(X_p) = f_1(X_p) - X_p f_1'(X_p)$. Since f_1 is a concave increasing function, then $f_1'(X_p) \ge 0$ and $f_1''(X_p) \le 0$. Therefore, $h_1'(X_p) = -X_p f_1''(X_p) \ge 0$ and

$h_1(X_p) \geq h_1(0) = 0$ or also $f_1(X_p) \geq X_p f_1'(X_p)$. Similarly, let $h_2(X_p) = f_1(X_p) - X_p f_1'(0)$, then $h_2'(X_p) = f_1'(X_p) - f_1'(0) \leq 0$ since f_1 is concave. Then, $h_2(X_p) \leq h_2(0) = 0$ and $f_1(X_p) \leq X_p f_1'(0)$.

(2) For $X_p, X_p^* \in \mathbb{R}_+$, let $h_3(X_p) = \dfrac{f_1(X_p)}{X_p}$, $h_3'(X_p) = \dfrac{f_1'(X_p)X_p - f_1(X_p)}{X_p^2} \leq 0$; thus, the function h_3 is decreasing. If the function, f_1, is increasing, then the quantity $\Big(h_3(X_p) - h_3(X_p^*)\Big)(f_1(X_p) - f_1(X_p^*))$ is negative. Thus,

$$\begin{aligned}\Big(h_3(X_p) - h_3(X_p^*)\Big)(f_1(X_p) - f_1(X_p^*)) &= \Big(\frac{f_1(X_p)}{X_p} - \frac{f_1(X_p^*)}{X_p^*}\Big)(f_1(X_p) - f_1(X_p^*)) \\ &= \frac{f_1(X_p^*)f_1(X_p)}{X_p}\Big(\frac{f_1(X_p)}{f_1(X_p^*)} - \frac{X_p}{X_p^*}\Big)\Big(1 - \frac{f_1(X_p^*)}{f_1(X_p)}\Big) \\ &\leq 0.\end{aligned}$$

□

3. Autonomous system

Consider the case where all parameters of dynamics (2.1) are constant and the system becomes autonomous and takes the following form

$$\begin{cases} \dot{X}_u = \varrho - (p_1 + p_2)f_1(X_p)X_u - d_u X_u, \\ \dot{X}_I = p_1 f_1(X_p)X_u - (d_I + \nu)X_I, \\ \dot{X}_i = p_2 f_1(X_p)X_u + \nu X_I - d_i X_i, \\ \dot{X}_p = d_i r_1 X_i - d_p X_p - f_2(X_p)X_c, \\ \dot{X}_c = \varepsilon X_p - d_c X_c - \upsilon f_2(X_p)X_c, \end{cases} \tag{3.1}$$

with positive initial condition $(X_u^0, X_I^0, X_i^0, X_p^0, X_c^0) \in \mathbb{R}_+^5$.

3.1. **Basic Results.**

It is necessary that the state variables $X_u(t), X_I(t), X_i(t), X_p(t)$ and $X_c(t)$ remain non-negative for all $t \geq 0$. Let $p = p_1 + p_2$, $d_1 = \min(d_u, d_I, d_i)$ and $d_2 = \min(\dfrac{d_p}{2}, d_c)$.

Lemma 3.1.

$$\Gamma = \left\{(X_u, X_I, X_i, X_p, X_c) \in \mathbb{R}_+^5 \ ; \ X_u + X_I + X_i \leq \frac{\varrho}{d_1} \ , \ X_p + \frac{d_p}{2\varepsilon}X_c \leq \frac{\varrho(d_i r_1)}{d_1 d_2}\right\}$$

is a positively invariant attractor set for the dynamics (3.1).

Proof. $\mathbb{R}^5_+$ is positively invariant set for (3.1), since we have

$$\begin{aligned}
\dot{X}_u \mid_{X_u=0} &= \varrho > 0,\\
\dot{X}_l \mid_{X_l=0} &= p_1 f_1(X_p) X_u \geq 0,\\
\dot{X}_i \mid_{X_i=0} &= p_2 f_1(X_p) X_u + \nu X_l \geq 0,\\
\dot{X}_p \mid_{X_p=0} &= r_1 d_i X_i \geq 0,\\
\dot{X}_c \mid_{X_c=0} &= \varepsilon X_p \geq 0.
\end{aligned}$$

In order to prove that the solution is bounded, let us define $T_1(t) = X_u(t) + X_l(t) + X_i(t) - \dfrac{\varrho}{d_1}$ and $T_2(t) = X_p(t) + \dfrac{d_p}{2\varepsilon} X_c(t)$. From equation (3.1), we have

$$\dot{T}_1(t) = \varrho - (d_u X_u(t) + d_l X_l(t) + d_i X_i(t)) \leq -d_1 T_1(t).$$

Therefore, $T_1(t) \leq T_1(0) e^{-d_1 t}$, then $X_u(t)+X_l(t)+X_i(t) \leq \dfrac{\varrho}{d_1} + \Big(X_u(0)+X_l(0)+X_i(0) - \dfrac{\varrho}{d_1}\Big) e^{-d_1 t}$. Similarly, we have

$$\begin{aligned}
\dot{T}_2(t) &= d_i r_1 X_i + \frac{d_p}{2\varepsilon}\varepsilon X_p - d_p X_p - \frac{d_p}{2\varepsilon} d_c X_c - f_2(X_p) X_c - \frac{d_p}{2\varepsilon}\upsilon f_2(X_p) X_c\\
&= d_i r_1 X_i - \frac{d_p}{2} X_p - \frac{d_p}{2\varepsilon} d_c X_c - f_2(X_p) X_c - \frac{d_p}{2\varepsilon}\upsilon f_2(X_p) X_c\\
&\leq d_i r_1 X_i - \frac{d_p}{2} X_p - \frac{d_p}{2\varepsilon} d_c X_c\\
&\leq d_i r_1 X_i - d_2 T_2(t)\\
&\leq \frac{\varrho}{d_1}(d_i r_1) - d_2 T_2(t).
\end{aligned} \tag{3.2}$$

Therefore, $T_2(t) \leq e^{-d_2 t}\Big(T_2(0) - \dfrac{\varrho}{d_1 d_2}(d_i r_1)\Big) + \dfrac{\varrho}{d_1 d_2}(d_i r_1)$, thus

$$X_p(t) + \frac{d_p}{2\varepsilon} X_c(t) \leq e^{-d_2 t}\Big(X_p(0) + \frac{d_p}{2\varepsilon} X_c(0) - \frac{\varrho}{d_1 d_2}(d_i r_1)\Big) + \frac{\varrho}{d_1 d_2}(d_i r_1).$$

Now if

$$X_u(0) + X_l(0) + X_i(0) \leq \frac{\varrho}{d_1}$$

then,

$$X_u(t) + X_l(t) + X_i(t) \leq \frac{\varrho}{d_1}$$

and if

$$X_p(0) + \frac{d_p}{2\varepsilon} X_c(0) \leq \frac{\varrho}{d_1 d_2}(d_i r_1)$$

then,

$$X_p(t) + \frac{d_p}{2\varepsilon} X_c(t) \leq \frac{\varrho}{d_1 d_2}(d_i r_1),$$

therefore, Γ is positively invariant for system (3.1). □

3.2. **Basic reproduction number and steady states.** Let $\mathcal{R}_0$ to be the basic reproduction number, describing the average number of new cases of a disease that a single infected and contagious person will generate on average in a susceptible population. Diekmann et al. [22] were the first to propose the next-generation matrix method to calculate $\mathcal{R}_0$. Late, Van den Driessche and Watmough [23] elaborated this method. Let , $F = \begin{pmatrix} 0 & 0 & p_1 f_1'(0)\dfrac{\varrho}{d_u} \\ \nu & 0 & p_2 f_1'(0)\dfrac{\varrho}{d_u} \\ 0 & r_1 d_i & 0 \end{pmatrix}$ and $V = \begin{pmatrix} (d_l+\nu) & 0 & 0 \\ 0 & d_i & 0 \\ 0 & 0 & d_p \end{pmatrix}$. Then, the next-generation matrix is given by $FV^{-1} = \begin{pmatrix} 0 & 0 & \dfrac{\varrho p_1 f_1'(0)}{d_u d_p} \\ \dfrac{\nu}{(d_l+\nu)} & 0 & \dfrac{\varrho p_2 f_1'(0)}{d_u d_p} \\ 0 & r_1 & 0 \end{pmatrix}$ and its characteristic polynomial is given by:

$$\begin{aligned} X_p(\lambda) &= \begin{vmatrix} -\lambda & 0 & \dfrac{\varrho p_1 f_1'(0)}{d_u d_p} \\ \dfrac{\nu}{(d_l+\nu)} & -\lambda & \dfrac{\varrho p_2 f_1'(0)}{d_u d_p} \\ 0 & r_1 & -\lambda \end{vmatrix} \\ &= -\lambda \begin{vmatrix} -\lambda & \dfrac{\varrho p_2 f_1'(0)}{d_u d_p} \\ r_1 & -\lambda \end{vmatrix} - \frac{\nu}{(d_l+\nu)} \begin{vmatrix} 0 & \dfrac{\varrho p_1 f_1'(0)}{d_u d_p} \\ r_1 & -\lambda \end{vmatrix} \\ &= -\lambda \left((\lambda^2 - r_1 \frac{\varrho p_2 f_1'(0)}{d_u d_p} \right) + \frac{\nu}{(d_l+\nu)} r_1 \frac{\varrho p_1 f_1'(0)}{d_u d_p} \\ &= -\lambda^3 + (r_1 p_2)\frac{\varrho f_1'(0)}{d_u d_p}\lambda + \frac{\nu r_1 p_1}{(d_l+\nu)}\frac{\varrho f_1'(0)}{d_u d_p}. \end{aligned}$$

Therefore, the spectral radius representing the basic reproduction number is:

$$\mathcal{R}_0 = (r_1 p_2)\frac{\varrho f_1'(0)}{d_u d_p} + \frac{\nu r_1 p_1}{(d_l+\nu)}\frac{\varrho f_1'(0)}{d_u d_p} = \frac{(r_1 p_2)(d_l+\nu) + \nu r_1 p_1}{(d_l+\nu) d_p}\frac{\varrho f_1'(0)}{d_u}.$$

Lemma 3.2.
- *If $\mathcal{R}_0 \le 1$, then the model (3.1) admits a unique equilibrium point given by $\mathcal{E}_0 = (\frac{\varrho}{d_u}, 0, 0, 0, 0)$.*
- *If $\mathcal{R}_0 > 1$, then the model (3.1) admits two equilibrium points $\mathcal{E}_0$ and $\mathcal{E}^* = (X_u^*, X_l^*, X_i^*, X_p^*, X_c^*)$.*

Proof. Let $(X_u, X_l, X_i, X_p, X_c)$ be any equilibrium point of the model (3.1) satisfying:

$$\begin{cases} 0 = \varrho - (p_1+p_2) f_1(X_p) X_u - d_u X_u, \\ 0 = p_1 f_1(X_p) X_u - (d_l+\nu) X_l, \\ 0 = p_2 f_1(X_p) X_u + \nu X_l - d_i X_i, \\ 0 = r_1 d_i X_i - d_p X_p - f_2(X_p) X_c, \\ 0 = \varepsilon X_p - d_c X_c - \upsilon f_2(X_p) X_c. \end{cases} \tag{3.3}$$

By solving equation (3.3), we obtain a steady state given by the HIV-free steady state $\mathcal{E}_0 = (\frac{\varrho}{d_u}, 0, 0, 0, 0)$. Moreover, we have:

$$\begin{cases} X_u &= \dfrac{\varrho}{(p_1+p_2)f_1(X_p)+d_u}, \\ X_i &= \dfrac{d_pX_p + f_2(X_p)X_c}{r_1 d_i} = \dfrac{d_pX_p + \dfrac{\varepsilon X_p f_2(X_p)}{d_c+\upsilon f_2(X_p)}}{r_1 d_i}, \\ X_l &= = \dfrac{p_1 f_1(X_p)}{(d_l+\nu)} X_u = \dfrac{p_1 f_1(X_p)}{(p_1+p_2)f_1(X_p)+d_u}\dfrac{\varrho}{(d_l+\nu)}, \\ X_c &= \dfrac{\varepsilon X_p}{d_c+\upsilon f_2(X_p)}. \end{cases} \tag{3.4}$$

Using the third equation of the dynamics (3.3), we obtain

$$\begin{aligned} 0 &= p_2 f_1(X_p)X_u + \nu X_l - d_i X_i \\ &= \frac{\varrho p_2 f_1(X_p)}{(p_1+p_2)f_1(X_p)+d_u} + \frac{\nu\varrho p_1 f_1(X_p)}{(d_l+\nu)\Big[(p_1+p_2)f_1(X_p)+d_u\Big]} - \frac{d_p d_c + d_p\upsilon f_2(X_p) + \varepsilon f_2(X_p)}{r_1(d_c+\upsilon f_2(X_p))} \end{aligned} \tag{3.5}$$

Therefore, $X_p = 0$ is a solution and then $X_u = \frac{\varrho}{d_u}$ and $X_l = X_i = X_p = X_c = 0$, called the HIV-free steady state $\mathcal{E}_0 = (\frac{\varrho}{d_u}, 0, 0, 0, 0)$. Furthermore, assume that $X_p \neq 0$, and divide the equation (3.5) by X_p, we obtain

$$\frac{\varrho\Big[p_2(d_l+\nu)+\nu p_1\Big]}{(d_l+\nu)\Big[(p_1+p_2)f_1(X_p)+d_u\Big]}\frac{f_1(X_p)}{X_p} - \frac{d_p d_c + d_p\upsilon f_2(X_p) + \varepsilon f_2(X_p)}{r_1(d_c+\upsilon f_2(X_p))} = 0 \tag{3.6}$$

Consider the function g defined by

$$g(X_p) = \frac{\varrho\Big[p_2(d_l+\nu)+\nu p_1\Big]}{(d_l+\nu)\Big[(p_1+p_2)f_1(X_p)+d_u\Big]}\frac{f_1(X_p)}{X_p} - \frac{d_p d_c + d_p\upsilon f_2(X_p) + \varepsilon f_2(X_p)}{r_1(d_c+\upsilon f_2(X_p))}. \tag{3.7}$$

One can easy obtain

$$\lim_{X_p\to 0^+} g(X_p) = \frac{\varrho p_2 f_1'(0)}{d_u} + \nu\frac{\varrho p_1 f_1'(0)}{(d_l+\nu)d_u} - \frac{d_p}{r_1} = \frac{d_p}{r_1}(\mathcal{R}_0 - 1) > 0 \text{ if } \mathcal{R}_0 > 1.$$

Since

$$g(X_p) \leq \frac{\varrho p_2\dfrac{f_1(X_p)}{X_p}}{p_2 f_1(X_p)} + \nu\frac{\varrho p_1\dfrac{f_1(X_p)}{X_p}}{\nu p_1 f_1(X_p)} - \frac{d_p}{r_1} \leq \frac{2\varrho}{X_p} - \frac{d_p}{r_1}, \tag{3.8}$$

therefore, $g(\frac{2\varrho r_1}{d_p}) \leq 0$. Furthermore, the derivative of g is given by

$$\begin{aligned} g'(X_p) &= \frac{X_p f_1'(X_p) - f_1(X_p)}{X_p^2}\left(\frac{\varrho\Big[p_2(d_l+\nu)+\nu p_1\Big]}{(d_l+\nu)\Big[(p_1+p_2)f_1(X_p)+d_u\Big]}\right) \\ &\quad -\frac{f_1(X_p)}{X_p}\left(\varrho\Big[p_2(d_l+\nu)+\nu p_1\Big]\left(\Big[(p_1+p_2)f_1(X_p)+d_u\Big]\right)^{-2}\frac{(p_1+p_2)}{(d_l+\nu)}f_1'(X_p)\right) \\ &\quad -\frac{\varepsilon\dfrac{(d_c+\upsilon f_2(X_p))f_2'(X_p)-\upsilon f_2'(X_p)f_2(X_p)}{(d_c+\upsilon f_2(X_p))^2}}{r_1} \\ &= \frac{X_p f_1'(X_p) - f_1(X_p)}{X_p^2}\left(\frac{\varrho\Big[p_2(d_l+\nu)+\nu p_1\Big]}{(d_l+\nu)\Big[(p_1+p_2)f_1(X_p)+d_u\Big]}\right) \\ &\quad -\frac{f_1(X_p)}{X_p}\left(\frac{\varrho\Big[p_2(d_l+\nu)+\nu p_1\Big](p_1+p_2)}{(d_l+\nu)\left(\Big[(p_1+p_2)f_1(X_p)+d_u\Big]\right)^2}f_1'(X_p)\right) - \frac{\dfrac{\varepsilon d_c f_2'(X_p)}{(d_c+\upsilon f_2(X_p))^2}}{r_1}. \end{aligned}$$

By Lemma 2.1, the first term of $g'(X_p)$ is negative and since the second and the third terms are negative then $g'(X_p) < 0$, and thus, g is a decreasing function. Then, the existence and uniqueness of $X_p^* \in (0, \frac{2\varrho r_1}{d_p})$ such that $g(X_p^*) = 0$. Therefore,

$$\begin{cases} X_u^* = \dfrac{\varrho}{(p_1+p_2)f_1(X_p^*)+d_u}, \\ X_i^* = \dfrac{d_p X_p^* + \dfrac{\varepsilon X_p f_2(X_p^*)}{d_c+\upsilon f_2(X_p^*)}}{r_1 d_i}, \\ X_l^* = \dfrac{p_1 f_1(X_p^*)}{(p_1+p_2)f_1(X_p^*)+d_u}\dfrac{\varrho}{(d_l+\nu)}, \\ X_c^* = \dfrac{\varepsilon X_p^*}{d_c+\upsilon X_p^*}. \end{cases} \tag{3.9}$$

Then, the persistence equilibrium point $\mathcal{E}^* = (X_u^*, X_l^*, X_i^*, X_p^*, X_c^*)$ exists and is unique if $\mathcal{R}_0 > 1$. □

3.3. **Local Stability.** In this section, we aim to investigate the local stability of the steady states of system (3.1) using the linearization approach. Recall that the value of $\mathcal{R}_0$ with respect to the unit is important in concluding if the disease persists or not. Hereafter, we give the results concerning the local stability of the equilibrium points $\mathcal{E}_0$ and $\mathcal{E}^*$.

Theorem 3.1. *If $\mathcal{R}_0 < 1$, then the steady state $\mathcal{E}_0$ is locally asymptotically stable.*

Proof. The Jacobian matrix of the linear approximation of system (3.1) at the trivial steady state $\mathcal{E}_0$ is:

$$J_0 = \begin{pmatrix} -d_u & 0 & 0 & -(p_1+p_2)\frac{\varrho}{d_u}f_1'(0) & 0 \\ 0 & -(d_l+\nu) & 0 & \frac{p_1\varrho}{d_u}f_1'(0) & 0 \\ 0 & \nu & -d_i & \frac{p_2\varrho}{d_u}f_1'(0) & 0 \\ 0 & 0 & r_1 d_i & -d_p & 0 \\ 0 & 0 & 0 & \varepsilon & -d_c \end{pmatrix}$$

J_0 admits five eigenvalues. The first two eigenvalues are given by $\lambda_1 = -d_u < 0$ and $\lambda_2 = -d_c < 0$. The other three eigenvalues are the roots of:

$$\begin{aligned}
X_p(\lambda) &= \begin{vmatrix} -(d_l+\nu+\lambda) & 0 & \frac{p_1\varrho}{d_u}f_1'(0) \\ \nu & -(d_i+\lambda) & \frac{p_2\varrho}{d_u}f_1'(0) \\ 0 & r_1 d_i & -(d_p+\lambda) \end{vmatrix} \\
&= -(d_l+\nu+\lambda)\begin{vmatrix} -(d_i+\lambda) & \frac{p_2\varrho}{d_u}f_1'(0) \\ r_1 d_i & -(d_p+\lambda) \end{vmatrix} - \nu \begin{vmatrix} 0 & \frac{p_1\varrho}{d_u}f_1'(0) \\ r_1 d_i & -(d_p+\lambda) \end{vmatrix} \\
&= -(d_l+\nu+\lambda)\Big[(d_i+\lambda)(d_p+\lambda) - r_1 d_i\frac{p_2\varrho}{d_u}f_1'(0)\Big] - \nu\Big[-r_1 d_i\frac{p_1\varrho}{d_u}f_1'(0)\Big] \\
&= -(d_l+\nu+\lambda)\Big[(d_i d_p + d_i\lambda + d_p\lambda + \lambda^2) - r_1 d_i\frac{p_2\varrho}{d_u}f_1'(0)\Big] + \nu r_1 d_i\frac{p_1\varrho}{d_u}f_1'(0) \\
&= -(d_l+\nu+\lambda)\Big[(\lambda^2 + (d_i+d_p)\lambda + d_p d_i) - r_1 d_i\frac{p_2\varrho}{d_u}f_1'(0)\Big] + \nu r_1 d_i\frac{p_1\varrho}{d_u}f_1'(0) \\
&= -(\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0)
\end{aligned}$$

where

$$\begin{aligned}
a_2 &= d_l + \nu + d_i + d_p \\
a_1 &= (d_l+\nu)(d_i+d_p) - r_1 d_i\frac{p_2\varrho}{d_u}f_1'(0) + d_i d_p \\
&\geq (d_l+\nu)(d_i+d_p) - r_1 d_i\frac{p_2\varrho}{d_u}f_1'(0) + d_i d_p - \nu r_1 d_i\frac{p_1\varrho}{(d_l+\nu)d_u}f_1'(0) \\
&= (d_l+\nu)(d_i+d_p) + d_i d_p(1-\mathcal{R}_0) \\
a_0 &= (d_l+\nu)\Big[d_p d_i - r_1 d_i\frac{p_2\varrho}{d_u}f_1'(0)\Big] - \nu r_1 d_i\frac{p_1\varrho}{d_u}f_1'(0) \\
&= d_i d_p(d_l+\nu)\Big(1 - \frac{(r_1p_2)(d_l+\nu) + \nu r_1 p_1}{(d_l+\nu)d_p}\frac{\varrho f_1'(0)}{d_u}\Big) \\
&= d_i d_p(d_l+\nu)\Big(1-\mathcal{R}_0\Big) \\
a_2a_1 - a_0 &= (d_l+\nu+d_i+d_p)\Big((d_l+\nu)(d_i+d_p) - r_1 d_i\frac{p_2\varrho}{d_u}f_1'(0) + d_i d_p\Big) \\
&\quad -(d_l+\nu)\Big[d_p d_i - r_1 d_i\frac{p_2\varrho}{d_u}f_1'(0)\Big] + \nu r_1 d_i\frac{p_1\varrho}{d_u}f_1'(0) \\
&= (d_i+d_p)\Big((d_l+\nu)(d_i+d_p) - r_1 d_i\frac{p_2\varrho}{d_u}f_1'(0) + d_i d_p\Big)
\end{aligned}$$

$$
\begin{aligned}
&+(d_I+\nu)^2(d_i+d_p)+\nu r_1 d_i \frac{p_1\varrho}{d_u} f_1'(0)\\
\geq\ & (d_i+d_p)\Big((d_I+\nu)(d_i+d_p)+d_i d_p(1-\mathcal{R}_0)\Big)\\
&+(d_I+\nu)^2(d_i+d_p)+\nu r_1 d_i \frac{p_1\varrho}{d_u} f_1'(0)
\end{aligned}
$$

It is easy to see that for $\mathcal{R}_0 < 1$, we have

$$a_2 > 0, a_1 > 0, a_0 > 0, a_2 a_1 > a_0.$$

Then, by using the Routh-Hurwitz criteria [24, 25], the eigenvalues have negative real parts. Then, the trivial steady state $\mathcal{E}_0$ is locally asymptotically stable once $\mathcal{R}_0 < 1$; however, it is a saddle point once $\mathcal{R}_0 > 1$. □

Theorem 3.2. *The infected steady state $\mathcal{E}^*$ is locally asymptotically stable once $\mathcal{R}_0 > 1$.*

Proof. The value of the Jacobian matrix at the infected equilibrium point $\mathcal{E}^*$ is:

$$
J^* = \begin{pmatrix}
-(p_1+p_2)f_1(X_p^*)-d_u & 0 & 0 & -(p_1+p_2)f_1'(X_p^*)X_u^* & 0\\
p_1 f_1(X_p^*) & -(d_I+\nu) & 0 & p_1 f_1'(X_p^*)X_u^* & 0\\
p_2 f_1(X_p^*) & \nu & -d_i & p_2 f_1'(X_p^*)X_u^* & 0\\
0 & 0 & r_1 d_i & -d_p - f_2'(X_p^*)X_c^* & -f_2(X_p^*)\\
0 & 0 & 0 & \varepsilon - \upsilon f_2'(X_p^*)X_c^* & -d_c - \upsilon f_2(X_p^*)
\end{pmatrix}
$$

The eigenvalues of J^* are the roots of:

$$
X_p^*(\lambda) = \begin{vmatrix}
-(p_1+p_2)f_1(X_p^*)-d_u-\lambda & 0 & 0 & -(p_1+p_2)f_1'(X_p^*)X_u^* & 0\\
p_1 f_1(X_p^*) & -(d_I+\nu+\lambda) & 0 & p_1 f_1'(X_p^*)X_u^* & 0\\
p_2 f_1(X_p^*) & \nu & -d_i-\lambda & p_2 f_1'(X_p^*)X_u^* & 0\\
0 & 0 & r_1 d_i & -d_p - f_2'(X_p^*)X_c^* - \lambda & -f_2(X_p^*)\\
0 & 0 & 0 & \varepsilon - \upsilon f_2'(X_p^*)X_c^* & -d_c - \upsilon f_2(X_p^*) - \lambda
\end{vmatrix}.
$$

The characteristic polynomial $X_p^*(\lambda)$ can be written in the form $X_p^*(\lambda) = \lambda^5 + a_4\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0$. Then, by using the Maple software, we can prove that for $\mathcal{R}_0 < 1$, we have

$$a_5 > 0, a_4 > 0, a_3 > 0, a_2 > 0, a_1 > 0, a_0 > 0, a_1 a_2 a_3 > a_3^2 + a_1^2 a_4,$$

$$(a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 + a_1^2 a_4) > a_5(a_1 a_2 - a_3)^2 + a_1 a_4^2.$$

Therefore, the roots of X_p^* (eigenvalues) have negative real parts by the Routh-Hurwitz criteria [24,25]. The steady state, $\mathcal{E}^*$, is then locally asymptotically stable if $\mathcal{R}_0 > 1$. □

3.4. **Global Stability.** Define G to be the function $G(z) = z - 1 - \ln z$ and the constant:

$$\Lambda = \frac{(r_1 p_2)(d_I+\nu)+\nu r_1 p_1}{(d_I+\nu)(p_1+p_2)}.$$

Note that

$$\begin{aligned}\Lambda\left(1-\frac{\frac{\varrho}{d_u}}{X_u}\right)\left(\varrho-d_uX_u\right) &= \Lambda\left(\frac{X_u-\frac{\varrho}{d_u}}{X_u}\right)d_u\left(\frac{\varrho}{d_u}-X_u\right)\\ &= -\frac{d_u}{X_u}\Lambda\left(X_u-\frac{\varrho}{d_u}\right)^2.\end{aligned}$$

Theorem 3.3. *The trivial equilibrium point $\mathcal{E}_0$ is globally asymptotically stable once $\mathcal{R}_0 \leq 1$.*

Proof. Assume that $\mathcal{R}_0 \leq 1$, and let define the Lyapunov function $\mathcal{L}_0(X_u, X_l, X_i, X_p, X_c)$ by

$$\mathcal{L}_0(X_u, X_l, X_i, X_p, X_c) = \Lambda\frac{\varrho}{d_u}G\big(X_u/\frac{\varrho}{d_u}\big) + \frac{\nu r_1}{d_l+\nu}X_l + r_1X_i + X_p + \frac{d_p}{\varepsilon}(1-\mathcal{R}_0)X_c.$$

Clearly, $\mathcal{L}_0(X_u, X_l, X_i, X_p, X_c) > 0$ for all $X_u, X_l, X_i, X_p, X_c > 0$ and $\mathcal{L}_0(\frac{\varrho}{d_u}, 0, 0, 0, 0) = 0$. The derivative of $\mathcal{L}_0$ along Model (3.1) is:

$$\begin{aligned}\frac{d\mathcal{L}_0}{dt} &= \Lambda\left(1-\frac{\varrho}{d_uX_u}\right)\left(\varrho-(p_1+p_2)f_1(X_p)X_u-d_uX_u\right)+\frac{\nu r_1}{d_l+\nu}\Big(p_1f_1(X_p)X_u-(d_l+\nu)X_l\Big)\\
&\quad +r_1\Big(p_2f_1(X_p)X_u+\nu X_l-d_iX_i\Big)+d_ir_1X_i-d_pX_p-f_2(X_p)X_c\\
&\quad +\frac{d_p}{\varepsilon}(1-\mathcal{R}_0)(\varepsilon X_p-d_cX_c-\upsilon f_2(X_p)X_c)\\
&= \Lambda\left(1-\frac{\varrho}{d_uX_u}\right)\left(\varrho-d_uX_u\right)-\Lambda(p_1+p_2)\left(1-\frac{\varrho}{d_uX_u}\right)f_1(X_p)X_u\\
&\quad +\Big(\frac{\nu r_1p_1}{d_l+\nu}+r_1p_2\Big)f_1(X_p)X_u-\Big(1+\frac{d_p\upsilon}{\varepsilon}(1-\mathcal{R}_0)\Big)f_2(X_p)X_c-d_p\mathcal{R}_0X_p\\
&\quad -\frac{d_pd_c}{\varepsilon}(1-\mathcal{R}_0)X_c\\
&= \Lambda\left(1-\frac{\varrho}{d_uX_u}\right)\left(\varrho-d_uX_u\right)+\frac{r_1p_2(d_l+\nu)+\nu r_1p_1}{(d_l+\nu)}f_1(X_p)X_u\\
&\quad -\Big(1+\frac{d_p\upsilon}{\varepsilon}(1-\mathcal{R}_0)\Big)f_2(X_p)X_c-d_p\mathcal{R}_0X_p-\frac{d_pd_c}{\varepsilon}(1-\mathcal{R}_0)X_c\\
&= -\frac{d_u}{X_u}\Lambda\left(X_u-\frac{\varrho}{d_u}\right)^2+\frac{\nu r_1p_1+r_1p_2(d_l+\nu)}{(d_l+\nu)}f_1(X_p)X_u\\
&\quad -d_p\mathcal{R}_0X_p-\Big(1+\frac{d_p\upsilon}{\varepsilon}(1-\mathcal{R}_0)\Big)f_2(X_p)X_c-\frac{d_pd_c}{\varepsilon}(1-\mathcal{R}_0)X_c\\
&= -\frac{d_u}{X_u}\Lambda\left(X_u-\frac{\varrho}{d_u}\right)^2+d_p\mathcal{R}_0\left[\frac{\nu r_1p_1+r_1p_2(d_l+\nu)}{(d_l+\nu)d_p}\frac{X_u}{\mathcal{R}_0}\frac{f_1(X_p)}{X_p}-1\right]X_p\\
&\quad -\Big(1+\frac{d_p\upsilon}{\varepsilon}(1-\mathcal{R}_0)\Big)f_2(X_p)X_c-\frac{d_pd_c}{\varepsilon}(1-\mathcal{R}_0)X_c\\
&\leq -\frac{d_u}{X_u}\Lambda\left(X_u-\frac{\varrho}{d_u}\right)^2+d_p\mathcal{R}_0\left[\frac{\nu r_1p_1+r_1p_2(d_l+\nu)}{(d_l+\nu)d_p}\frac{\varrho}{d_u\mathcal{R}_0}f_1'(0)-1\right]X_p\\
&\quad -\Big(1+\frac{d_p\upsilon}{\varepsilon}(1-\mathcal{R}_0)\Big)f_2(X_p)X_c-\frac{d_pd_c}{\varepsilon}(1-\mathcal{R}_0)X_c\\
&= -\frac{d_u}{X_u}\Lambda\left(X_u-\frac{\varrho}{d_u}\right)^2-\Big(1+\frac{d_p\upsilon}{\varepsilon}(1-\mathcal{R}_0)\Big)f_2(X_p)X_c-\frac{d_pd_c}{\varepsilon}(1-\mathcal{R}_0)X_c.\end{aligned}$$

If $\mathcal{R}_0 \leq 1$, then $\frac{d\mathcal{L}_0}{dt} \leq 0$ for all $X_u, X_l, X_i, X_p, X_c > 0$. Let $W_0 = \{(X_u, X_l, X_i, X_p, X_c) : \frac{d\mathcal{L}_0}{dt} = 0\}$. It can be easily shown that $W_0 = \{\mathcal{E}_0\}$. Using LaSalle's invariance principle [26] (see [8, 11, 12, 27] for some examples), one deduces that $\mathcal{E}_0$ is globally asymptotically stable once $\mathcal{R}_0 \leq 1$. □

Theorem 3.4. *By considering System (3.1), if $\mathcal{R}_0 > 1$, then $\mathcal{E}^*$ is globally asymptotically stable.*

Proof. Let a function $\mathcal{L}^*(X_u, X_l, X_i, X_p, X_c)$ be defined as:

$$\begin{aligned}\mathcal{L}^*(X_u, X_l, X_i, X_p, X_c) &= \Lambda X_u^* G\Big(\frac{X_u}{X_u^*}\Big) + \frac{\nu r_1}{d_l + \nu} X_l^* G\Big(\frac{X_l}{X_l^*}\Big) + r_1 X_i^* G\Big(\frac{X_i}{X_i^*}\Big) + X_p^* G\Big(\frac{X_p}{X_p^*}\Big) \\ &\quad + \frac{1}{2(\varepsilon - \upsilon X_c^*)}(X_c - X_c^*)^2.\end{aligned}$$

Clearly, $\mathcal{L}^*(X_u, X_l, X_i, X_p, X_c) > 0$ for all $X_u, X_l, X_i, X_p, X_c > 0$ and $\mathcal{L}^*(X_u^*, X_l^*, X_i^*, X_p^*, X_c^*) = 0$. Calculating $\dfrac{d\mathcal{L}^*}{dt}$ along the trajectories of (3.1) and using the fact that $\varrho = d_u X_u^* + (p_1 + p_2) f(X_p^*) X_u^*$, we obtain:

$$\begin{aligned}\frac{d\mathcal{L}^*}{dt} &= \Lambda\left(1 - \frac{X_u^*}{X_u}\right)\Big(\varrho - (p_1 + p_2) f_1(X_p) X_u - d_u X_u\Big) + \frac{\nu r_1}{d_l + \nu}\left(1 - \frac{X_l^*}{X_l}\right)\Big(p_1 f_1(X_p) X_u - (d_l + \nu) X_l\Big) \\ &\quad + r_1\left(1 - \frac{X_i^*}{X_i}\right)\Big(p_2 f_1(X_p) X_u + \nu X_l - d_i X_i\Big) + \left(1 - \frac{X_p^*}{X_p}\right)(d_i r_1 X_i - d_p X_p - f_2(X_p) X_c) \\ &\quad + \frac{1}{(\varepsilon - \upsilon X_c^*)}(X_c - X_c^*)(\varepsilon X_p - d_c X_c - \upsilon f_2(X_p) X_c) \\ &= d_u \Lambda\left(1 - \frac{X_u^*}{X_u}\right)(X_u^* - X_u) + \frac{r_1 p_2 (d_l + \nu) + \nu r_1 p_1}{(d_l + \nu)}\left(f_1(X_p^*) X_u^* - f_1(X_p^*) X_u^* \frac{X_u^*}{X_u} + f_1(X_p) X_u^*\right) \\ &\quad - \frac{\nu r_1 p_1}{d_l + \nu}\frac{X_l^*}{X_l} f_1(X_p) X_u + \nu r_1 X_l^* - r_1 p_2 f_1(X_p) X_u \frac{X_i^*}{X_i} - \nu r_1 X_l \frac{X_i^*}{X_i} + d_i r_1 X_i^* - d_p X_p - f_2(X_p) X_c \\ &\quad - d_i r_1 X_i \frac{X_p^*}{X_p} + d_p X_p^* + \frac{X_p^*}{X_p} f_2(X_p) X_c + \frac{1}{(\varepsilon - \upsilon X_c^*)}(X_c - X_c^*)\Big(\varepsilon X_p - (d_c + \upsilon f_2(X_p)) X_c\Big).\end{aligned}$$

Now, since:

$$\begin{aligned}&\frac{\nu r_1 p_1}{d_l + \nu} f_1(X_p^*) X_u^* = \nu r_1 X_l^*,\ d_i r_1 X_i^* = r_1 p_2 f_1(X_p^*) X_u^* + \nu r_1 X_l^*, \\ &d_p X_p^* + f_2(X_p^*) X_c^* = d_i r_1 X_i^*, \text{ and } \varepsilon X_p^* = d_c X_c^* + \upsilon f_2(X_p^*) X_c^*,\end{aligned}$$

then

$$\begin{aligned}\frac{d\mathcal{L}^*}{dt} &= d_u \Lambda\left(1 - \frac{X_u^*}{X_u}\right)(X_u^* - X_u) + r_1 p_2 f_1(X_p^*) X_u^* + \frac{\nu r_1 p_1}{(d_l + \nu)} f_1(X_p^*) X_u^* + r_1 p_2 f_1(X_p) X_u^* \\ &\quad + \frac{\nu r_1 p_1}{(d_l + \nu)} f_1(X_p) X_u^* - r_1 p_2 f_1(X_p^*) X_u^* \frac{X_u^*}{X_u} - \frac{\nu r_1 p_1}{(d_l + \nu)} f_1(X_p^*) X_u^* \frac{X_u^*}{X_u} \\ &\quad - \frac{\nu r_1 p_1}{d_l + \nu}\frac{X_l^*}{X_l} f_1(X_p) X_u + \nu r_1 X_l^* - r_1 p_2 f_1(X_p) X_u \frac{X_i^*}{X_i} - \nu r_1 X_l \frac{X_i^*}{X_i} + d_i r_1 X_i^* \\ &\quad - d_p X_p - f_2(X_p) X_c - d_i r_1 X_i \frac{X_p^*}{X_p} + d_i r_1 X_i^* - f_2(X_p^*) X_c^* \\ &\quad + \frac{X_p^*}{X_p} f_2(X_p^*) X_c^* + \frac{1}{(\varepsilon - \upsilon X_c^*)}(X_c - X_c^*)\Big(\varepsilon X_p - (d_c + \upsilon f_2(X_p)) X_c\Big) \\ &= -\frac{d_u}{X_u}\Lambda(X_u - v X_u^*)^2 - \frac{(d_c + \upsilon f_2(X_p))}{(\varepsilon - \upsilon X_c^*)}(X_c - X_c^*)^2 \\ &\quad + \nu r_1 X_l^*\Big(5 - \frac{X_u^*}{X_u} - \frac{X_l^* f_1(X_p) X_u}{X_l f_1(X_p^*) X_u^*} - \frac{X_l X_i^*}{X_l^* X_i} - \frac{X_p^* X_i}{X_p X_i^*} - \frac{X_p f_1(X_p^*)}{X_p^* f_1(X_p)}\Big) \\ &\quad + r_1 p_2 f_1(X_p^*) X_u^*\Big(4 - \frac{X_u^*}{X_u} - \frac{X_i^* f_1(X_p) X_u}{X_i f_1(X_p^*) X_u^*} - \frac{X_p^* X_i}{X_p X_i^*} - \frac{X_p f_1(X_p^*)}{X_p^* f_1(X_p)}\Big) \\ &\quad + (d_i r_1 X_i^*)\Big(\frac{f_1(X_p)}{f_1(X_p^*)} - \frac{X_p}{X_p^*}\Big)\Big(1 - \frac{f_1(X_p^*)}{f_1(X_p)}\Big).\end{aligned}$$

Based on the rule:

$$\frac{1}{n}\sum_{i=1}^{n} a_i \geq \sqrt[n]{\prod_{i=1}^{n} a_i}, \tag{3.10}$$

and the Lemma 2.1, we obtain $\frac{d\mathcal{L}^*}{dt}(X_u, X_l, X_i, X_p, X_c) \leq 0$ for all $X_u, X_l, X_i, X_p, X_c > 0$ and $\frac{d\mathcal{L}^*}{dt}(X_u, X_l, X_i, X_p, X_c) = 0$ if and only if $(X_u, X_l, X_i, X_p, X_c) = (X_u^*, X_l^*, X_i^*, X_p^*, X_c^*)$. From LaSalle's invariance principle [26], we deduce the global stability of $\mathcal{E}^*$ (see [11, 28, 29] for other applications). □

4. Periodic System

Return now to the main model (2.1) where all parameters are continuous and T-periodic positive functions:

$$\begin{cases} \dot{X}_u(t) &= \varrho(t) - (p_1(t) + p_2(t))f_1(X_p(t))X_u(t) - d_u(t)X_u(t), \\ \dot{X}_l(t) &= p_1(t)f_1(X_p(t))X_u(t) - (d_l(t) + \nu(t))X_l(t), \\ \dot{X}_i(t) &= p_2(t)f_1(X_p(t))X_u(t) + \nu(t)X_l(t) - d_i(t)X_i(t), \\ \dot{X}_p(t) &= d_i(t)r_1(t)X_i(t) - d_p(t)X_p(t) - f_2(X_p(t))X_c(t), \\ \dot{X}_c(t) &= \varepsilon(t)X_p(t) - d_c(t)X_c(t) - \upsilon(t)f_2(X_p(t))X_c(t). \end{cases} \tag{4.1}$$

with positive initial condition $(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in \mathbb{R}_+^5$.

Let $(\mathbb{R}^m, \mathbb{R}_+^m)$ to be the ordered m-dimensional Euclidean space associated with norm $\|\cdot\|$. For $X_1, X_2 \in \mathbb{R}^m$, we denote by $X_1 \geq X_2$ if $X_1 - X_2 \in \mathbb{R}_+^m$. We denote by $X_1 > X_2$ if $X_1 - X_2 \in \mathbb{R}_+^m \backslash \{0\}$. We denote by $X_1 \gg X_2$ if $X_1 - X_2 \in \mathrm{Int}(\mathbb{R}_+^m)$. Consider a T-periodic $m \times m$ matrix function denoted by $C(t)$ which is continuous, irreducible and cooperative. Let us denote by $\phi_C(t)$ the fundamental matrix, solution of the following system

$$\dot{x}(t) = C(t)x(t). \tag{4.2}$$

Let denote the spectral radius of the matrix $\phi_C(T)$ by $r(\phi_C(T))$. Therefore, all entries of $\phi_C(t)$ are positive for each $t > 0$. Let apply the theorem of Perron-Frobenius to deduce that $r(\phi_C(T))$ is the principal eigenvalue of $\phi_C(T)$ (simple and admits an eigenvector $y^* \gg 0$). For the rest of the paper, the following lemma will be useful.

Lemma 4.1. *[30]. There exists a positive T-periodic function $y(t)$ such that $x(t) = y(t)e^{kt}$ will be a solution of system (4.2) where $k = \frac{1}{T}\ln(r(\phi_C(T)))$.*

Let start by proving the existence (and uniqueness) of the disease free periodic trajectory of model (4.1). Let consider the following equation

$$\dot{X}_u(t) = \varrho(t) - d_u(t)X_u(t), \tag{4.3}$$

with initial condition $X_u^0 \in \mathbb{R}+$. (4.3) admits a unique T-periodic solution $X_u^*(t)$ with $X_u^*(t) > 0$ which is globally attractive in $\mathbb{R}+$ and hence, system (4.1) has a unique disease free periodic solution $(0, 0, 0, 0, X_u^*(t))$. For a continuous, positive T-periodic function $g(t)$, we set $g^u = \max_{t\in[0,T)} g(t)$, $g^l = \min_{t\in[0,T)} g(t)$, and $\bar{d}_1 = \min(d_u^l, d_l^l, d_i^l)$ and $\bar{d}_2 = \min(\frac{d_p^l}{2}, d_c^l)$.
Let $S_1(t) = X_u(t) + X_l(t) + X_i(t)$, $S_2(t) = X_p(t) + \frac{d_p}{2\varepsilon}X_c(t)$, $\bar{S}_1 = \frac{\varrho^u}{d_u^l}$ and $\bar{S}_2 = \frac{\rho^u d_i^u r_1^u}{\bar{d}_1\bar{d}_2}$. Then, we obtain

Lemma 4.2. $\Omega^u = \{(X_l, X_i, X_p, X_c, X_u) \in \mathbb{R}_+^5; 0 \le X_u + X_l + X_i \le \bar{S}_1,\ 0 \le X_p + \frac{d_p^l}{2\varepsilon^u}X_c \le \bar{S}_2\}$ *is a positively invariant attractor set for system (4.1). Furthermore, we have*

$$\lim_{t\to\infty}\Big(X_u(t) + X_l(t) + X_i(t) - X_u^*(t)\Big) = \lim_{t\to\infty}\Big(X_u(t) - X_u^*(t)\Big) = 0. \tag{4.4}$$

Proof. From system (4.1), we have

$$\begin{aligned} \dot{X}_u(t) + \dot{X}_l(t) + \dot{X}_i(t) &= \varrho(t) - d_u(t)X_u(t) - d_l(t)X_l(t) - d_i(t)X_i(t) \\ &\le \varrho^u - \bar{d}_1\left(X_u(t) + X_l(t) + X_i(t)\right) \\ &\le 0 \text{ once } \frac{\varrho^u}{d_1} \le X_u(t) + X_l(t) + X_i(t). \end{aligned} \tag{4.5}$$

and

$$\begin{aligned} \dot{X}_p(t) + \frac{d_p(t)}{2\varepsilon(t)}\dot{X}_c(t) &= d_i(t)r_1(t)X_i(t) - d_p(t)X_p(t) - f_2(X_p(t))X_c(t) + \frac{d_p(t)}{2}X_p(t) \\ &\quad -\frac{d_p(t)}{2\varepsilon(t)}d_c(t)X_c(t) - \frac{d_p(t)}{2\varepsilon(t)}\upsilon(t)f_2(X_p(t))X_c(t) \\ &\le d_i(t)r_1(t)X_i(t) - \frac{d_p(t)}{2}X_p(t) - \frac{d_p(t)}{2\varepsilon(t)}d_c(t)X_c(t) \\ &\le d_i(t)r_1(t)X_i(t) - \bar{d}_2(X_p(t) + \frac{d_p(t)}{2\varepsilon(t)}X_c(t)) \\ &\le d_i^u r_1^u \bar{S}_1 - \bar{d}_2(X_p(t) + \frac{d_p(t)}{2\varepsilon(t)}X_c(t)) \\ &\le 0 \text{ once } \bar{S}_2 \le X_p(t) + \frac{d_p(t)}{2\varepsilon(t)}X_c(t). \end{aligned} \tag{4.6}$$

This means that Ω^u is a forward invariant compact absorbing set of all solutions of system (4.1). Let $y(t) = X_u(t) + X_l(t) + X_i(t) - X_u^*(t)$ for $t \ge 0$. Therefore, we obtain $\dot{y}(t) = -d_l(t)X_l(t) - d_i(t)X_i(t) \le -\bar{d}_1 y(t)$, and this means that $\lim_{t\to\infty} y(t) = \lim_{t\to\infty}(X_u(t)+X_l(t)+X_i(t)-X_u^*(t)) = 0$. □

Next, in subsection 4.1, we define $\mathcal{R}_0$, the basic reproduction number and we will prove that the disease free periodic trajectory $(0, 0, 0, 0, X_u^*(t))$ is globally asymptotically stable (and therefore, the disease dies out) once $\mathcal{R}_0 < 1$. Then, in subsection 4.2, we will prove that $X_i(t)$ is uniform persistence (and then the disease persists) once $\mathcal{R}_0 > 1$. Therefore, we deduce that $\mathcal{R}_0$ is the threshold parameter between the uniform persistence and the extinction of the disease.

4.1. **Disease Free Periodic Solution .** We start by giving the definition of the basic reproduction number of model (4.1), by using the theory given in [20] where $\mathcal{F}(t,X) = \begin{pmatrix} p_1(t)f_1(X_p(t))X_u(t) \\ p_2(t)f_1(X_p(t))X_u(t)+\nu(t)X_l(t) \\ d_i(t)r_1(t)X_i(t) \\ \varepsilon(t)X_p(t) \\ 0 \end{pmatrix}$,

$$\mathcal{V}^-(t,X) = \begin{pmatrix} (d_l(t)+\nu(t))X_l(t) \\ d_i(t)X_i(t) \\ d_p(t)X_p(t)+f_2(X_p(t))X_c(t) \\ d_c(t)X_c(t)+\upsilon(t)f_2(X_p(t))X_c(t) \\ (p_1(t)+p_2(t))f_1(X_p(t))X_u(t)+d_u(t)X_u(t) \end{pmatrix} \text{ and } \mathcal{V}^+(t,X) = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ \varrho(t) \end{pmatrix}$$

with $X = \begin{pmatrix} X_l \\ X_i \\ X_p \\ X_c \\ X_u \end{pmatrix}$.

Our aim is to check the conditions (A1)-(A7) in [20, Section 1]. Note that system(4.1) can have the following form

$$\dot{X} = \mathcal{F}(t,X) - \mathcal{V}(t,X) = \mathcal{F}(t,X) - \mathcal{V}^-(t,X) + \mathcal{V}^+(t,X). \tag{4.7}$$

The first five conditions (A1)-(A5) are fulfilled.

The system (4.7) admits a disease free periodic trajectory $X^*(t) = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ X_u^*(t) \end{pmatrix}$. Let $f(t,X(t)) = \mathcal{F}(t,X) - \mathcal{V}^-(t,X) + \mathcal{V}^+(t,X)$ and $M(t) = \left(\dfrac{\partial f_i(t,X^*(t))}{\partial X_j}\right)_{3\le i,j\le 4}$ where $f_i(t,X(t))$ and X_i are the i-th component of $f(t,X(t))$ and X, respectively. By an easy calculus, we get $M(t) = -(p_1(t)+p_2(t))f_1(X_p(t)) - d_u(t)$ and then $r(\phi_M(T)) < 1$. Therefore $X^*(t)$ is linearly asymptotically stable in the subspace $\Gamma_s = \left\{(0,0,0,0,X_u) \in R_+^5\right\}$. Thus, the condition (A6) in [20, Section 1] is satisfied.

Now, let us define $\mathbf{F}(t)$ and $\mathbf{V}(t)$ to be four by four matrices given by $\mathbf{F}(t) = \left(\dfrac{\partial \mathcal{F}_i(t,X^*(t))}{\partial X_j}\right)_{1\le i,j\le 4}$ and
$\mathbf{V}(t) = \left(\dfrac{\partial \mathcal{V}_i(t,X^*(t))}{\partial X_j}\right)_{1\le i,j\le 4}$ where $\mathcal{F}_i(t,X)$ and $\mathcal{V}_i(t,X)$ are the i-th component of $\mathcal{F}(t,X)$ and

$\mathcal{V}(t, X)$, respectively. By an easy calculus, we obtain from system (4.7)

$$\mathbf{F}(t) = \begin{pmatrix} 0 & 0 & p_1(t)f_1'(0)X_u^*(t) & 0 \\ \nu(t) & 0 & p_2(t)f_1'(0)X_u^*(t) & 0 \\ 0 & d_i(t)r_1(t) & 0 & 0 \\ 0 & 0 & \varepsilon(t) & 0 \end{pmatrix} \text{ and } \mathbf{V}(t) = \begin{pmatrix} d_l(t)+\nu(t) & 0 & 0 & 0 \\ 0 & d_i(t) & 0 & 0 \\ 0 & 0 & d_p(t) & 0 \\ 0 & 0 & 0 & d_c(t) \end{pmatrix}.$$

Consider $Z(t_1, t_2)$ to be the two by two matrix solution of the system $\frac{d}{dt}Z(t_1, t_2) = -\mathbf{V}(t_1)Z(t_1, t_2)$ for any $t_1 \geq t_2$, with $Z(t_1, t_1) = I$, the two by two identity matrix. Thus, condition (A7) was satisfied. Let define C_T to be the ordered Banach space of T-periodic functions defined on $\mathbb{R} \mapsto \mathbb{R}^2$, associated to the maximum norm $\|.\|_\infty$ and the positive cone $C_T^+ = \{\psi \in C_T : \psi(s) \geq 0, \text{ for any } s \in \mathbb{R}\}$. Define the linear operator $K : C_T \to C_T$ by

$$(K\psi)(s) = \int_0^\infty Z(s, s-w)\mathbf{F}(s-w)\psi(s-w)dw, \quad \forall s \in \mathbb{R}, \psi \in C_T \tag{4.8}$$

Let now define the basic reproduction number, $\mathcal{R}_0$, of model (4.1) by $\mathcal{R}_0 = r(K)$.
Therefore, we conclude the local asymptotic stability of the disease free periodic solution $\mathcal{E}_0(t) = (0, 0, 0, 0, X_u^*(t))$ for (4.1) as follows.

Theorem 4.1. *[20, Theorem 2.2]. The following statements are satisfied:*

- $\mathcal{R}0 < 1$ *if and only if* $r(\phi F - V(T)) < 1$.
- $\mathcal{R}0 = 1$ *if and only if* $r(\phi F - V(T)) = 1$.
- $\mathcal{R}0 > 1$ *if and only if* $r(\phi F - V(T)) > 1$.

Therefore, $\mathcal{E}_0(t)$ is unstable if $\mathcal{R}_0 > 1$ and it is asymptotically stable if $\mathcal{R}_0 < 1$.

Theorem 4.2. *$\mathcal{E}_0(t)$ is globally asymptotically stable if $\mathcal{R}_0 < 1$. It is unstable if $\mathcal{R}_0 > 1$.*

Proof. Using the Theorem 4.1, we have $\mathcal{E}_0(t)$ is locally stable once $\mathcal{R}_0 < 1$ and it is unstable once $\mathcal{R}_0 > 1$. Therefore, it remains to prove the global attractivity of $\mathcal{E}_0(t)$ when $\mathcal{R}_0 < 1$. Consider the case where $\mathcal{R}_0 < 1$. Using the limit (4.4) in Lemma 4.2, for any $\delta_1 > 0$, there exists $T_1 > 0$ satisfying $X_u(t) + X_l(t) + X_i(t) \leq X_u^*(t) + \delta_1$ for $t > T_1$. Then $X_u(t) \leq X_u^*(t) + \delta_1$ and we deduce that

$$\begin{cases} \dot{X}_l(t) & \leq & p_1(t)f_1(X_p(t))(X_u^*(t)+\delta_1) - (d_l(t)+\nu(t))X_l(t), \\ \dot{X}_i(t) & \leq & p_2(t)f_1(X_p(t))(X_u^*(t)+\delta_1) + \nu(t)X_l(t) - d_i(t)X_i(t), \\ \dot{X}_p(t) & = & d_i(t)r_1(t)X_i(t) - d_p(t)X_p(t) - f_2(X_p(t))X_c(t), \\ \dot{X}_c(t) & = & \varepsilon(t)X_p(t) - d_c(t)X_c(t) - \upsilon(t)f_2(X_p(t))X_c(t) \end{cases} \tag{4.9}$$

for $t > T_1$. Let $M_2(t)$ to be the following 2×2 matrix function

$$M_2(t) = \begin{pmatrix} 0 & 0 & p_1(t)f_1'(0) & 0 \\ 0 & 0 & p_2(t)f_1'(0) & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}. \tag{4.10}$$

By Theorem 4.1, we have $r(\varphi_{F-V}(T)) < 1$. Let chose $\delta_1 > 0$ such that $r(\varphi_{F-V+\delta_1 M_2}(T)) < 1$. Consider the system hereafter system

$$\begin{cases} \dot{\bar{X}}_l(t) &= p_1(t)f_1(\bar{X}_p(t))(X_u^*(t)+\delta_1) - (d_l(t)+\nu(t))\bar{X}_l(t), \\ \dot{\bar{X}}_i(t) &= p_2(t)f_1(\bar{X}_p(t))(X_u^*(t)+\delta_1) + \nu(t)\bar{X}_l(t) - d_i(t)\bar{X}_i(t), \\ \dot{\bar{X}}_p(t) &= d_i(t)r_1(t)\bar{X}_i(t) - d_p(t)\bar{X}_p(t) - f_2(\bar{X}_p(t))\bar{X}_c(t), \\ \dot{\bar{X}}_c(t) &= \varepsilon(t)\bar{X}_p(t) - d_c(t)\bar{X}_c(t) - \upsilon(t)f_2(\bar{X}_p(t))\bar{X}_c(t). \end{cases} \tag{4.11}$$

Applying Lemma 4.1 and using the standard comparison principle, we deduce that there exists a positive T-periodic function $y_1(t)$ satisfying $x(t) \le y_1(t)e^{k_1 t}$ where $x(t) = \begin{pmatrix} X_l(t) \\ X_i(t) \\ X_p(t) \\ X_c(t) \end{pmatrix}$ and $k_1 = \frac{1}{T}\ln\left(r(\varphi_{F-V+\delta_1 M_2}(T)\right) < 0$. Thus, $\lim_{t\to\infty} X_l(t) = \lim_{t\to\infty} X_i(t) = \lim_{t\to\infty} X_p(t) = \lim_{t\to\infty} X_c(t) = 0$. Furthermore, we have $\lim_{t\to\infty} X_u(t) - X_u^*(t) = 0$. Then, we deduce that the disease free periodic solution $\mathcal{E}_0(t)$ is globally attractive which complete the proof. □

For the following subsection, we consider only the case where $\mathcal{R}_0 > 1$.

4.2. **Endemic Periodic Solution .** From Lemma 4.2, system (4.1) admits a positively invariant compact set Ω^u. Let consider the case where $X_u^0 > 0, X_l^0 > 0, X_i^0 > 0, X_p^0 > 0$ and $X_c^0 > 0$.

Let us define the function $P : \mathbb{R}_+^5 \to \mathbb{R}_+^5$ to be the Poincaré map associated to system (4.1) such that $X_0 \mapsto u(T, X^0)$, where $u(t, X^0)$ is the unique solution of the system (4.1) with the initial condition $u(0, X^0) = X^0 \in \mathbb{R}_+^5$. Let us define

$$\Gamma = \left\{(X_u, X_l, X_i, X_p, X_c) \in \mathbb{R}_+^5\right\}, \ \Gamma_0 = Int(\mathbb{R}_+^5) \text{ and } \partial\Gamma_0 = \Gamma \setminus \Gamma_0.$$

Note that from Lemma 4.2, both Γ and Γ_0 are positively invariant. P is point dissipative. Define

$$M_\partial = \left\{(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in \partial\Gamma_0 : P^n(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in \partial\Gamma_0, \text{ for any } n \ge 0\right\}.$$

In order to apply the theory of uniform persistence detailed in Zhao [31] (also in [30, Theorem 2.3]), we prove that

$$M_\partial = \{(X_u, 0, 0, 0, 0), \ X_u \ge 0\}. \tag{4.12}$$

Note that $M_\partial \supseteq \{(X_u, 0, 0, 0, 0), \ X_u \ge 0\}$. To show that $M_\partial \setminus \{(X_u, 0, 0, 0, 0), \ X_u \ge 0\} = \emptyset$. Let consider $(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in M_\partial \setminus \{(X_u, 0, 0, 0, 0), \ X_u \ge 0\}$.

If $X_p^0 = 0$ and $0 < X_i^0$, thus $X_i(t) > 0$ for any $t > 0$. Then, it holds that $\dot{X}_p(t)_{|t=0} = d_i(0)r(0)X_i^0 > 0$. If $X_p^0 > 0$ and $X_i^0 = 0$, then $X_p(t) > 0$ and $X_u(t) > 0$ for any $t > 0$. Therefore, for any $t > 0$, we have

$$X_i(t) \geq \left[X_i^0 + \int_0^t p_2(\omega) f_1(X_p(\omega)) X_u(\omega) e^{\int_0^\omega d_i(u)du} d\omega \right] e^{-\int_0^t d_i(u)du} > 0,$$

for all $t > 0$. This means that $(X_u(t), X_l(t), X_i(t), X_p(t), X_c(t)) \notin \partial\Gamma_0$ for $0 < t \ll 1$. Therefore, Γ_0 is positively invariant from which we deduce (4.12). Using the previous discussion, we deduce that there exists one fixed point $(X_u^*(0), 0, 0, 0, 0)$ of P in M_∂. We deduce, therefore, the uniform persistence of the disease as follows.

Theorem 4.3. *Consider the case $\mathcal{R}_0 > 1$. (4.1) admits at least one positive periodic trajectory and $\exists\, \gamma > 0$ satisfying $\forall\, (X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in \mathbb{R}+ \times Int(\mathbb{R}_+^4)$,*

$$\liminf_{t\to\infty} X_p(t) \geq \gamma > 0.$$

Proof. Let start by proving that P is uniformly persistent respecting to $(\Gamma_0, \partial\Gamma_0)$, which will prove that the trajectory of the reduced system (4.1) is uniformly persistent respecting to $(\Gamma_0, \partial\Gamma_0)$ using [31, Theorem 3.1.1]. Recall that using Theorem 4.1, we obtain $r(\varphi_{F-V}(T)) > 1$. Therefore, $\exists\, \eta > 0$ small enough and satisfying $r(\varphi_{F-V-\eta M_2}(T)) > 1$. Let us consider the following perturbed equation

$$\dot{X}_{u_\alpha}(t) \;\; = \;\; \varrho(t) - (p_1(t) + p_2(t)) f_1(\alpha) X_{u_\alpha}(t) - d_u(t) X_{u_\alpha}(t). \tag{4.13}$$

The function P associated to the perturbed system (4.13) has a unique positive fixed point $\bar{X}_{u_\alpha}^0$ that it is globally attractive in $\mathbb{R}+$. Applying the implicit function theorem to deduce that $\bar{X}_{u_\alpha}^0$ is continuous respecting to α. Therefore, we can chose $\alpha > 0$ small enough and satisfying $\bar{X}_{u_\alpha}(t) > \bar{X}_u(t) - \eta$, $\forall\, t > 0$. Let $M_1 = (\bar{X}_u^0, 0, 0)$. Since the trajectory is continuous respecting to the initial condition, $\exists\, \alpha$ satisfying $(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in \Gamma_0$ with $\|(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) - u(t, M_1)\| \leq \alpha$, it holds that,

$$\|u(t, (X_u^0, X_l^0, X_i^0, X_p^0, X_c^0)) - u(t, M_1)\| < \alpha \text{ for } 0 \leq t \leq T.$$

We prove by contradiction that

$$\limsup_{n\to\infty}\; d(P^n(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0), M_1) \geq \alpha^* \text{ for any } (X_u^0, X_l^0, X_i^0) \in \Gamma_0. \tag{4.14}$$

Suppose that $\limsup_{n\to\infty} d(P^n(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0), M_1) < \alpha^*$ for some $(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in \Gamma_0$. Without loss of generality, we can assume that $d(P^n(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0), M_1) < \alpha^*$ for any $n > 0$. Then, from the above discussion, we have that

$$\|u(t, P^n(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0)) - u(t, M_1)\| < \alpha \text{ for any } n > 0 \text{ and } 0 \leq t \leq T.$$

For all $t \geq 0$, let $t = nT + t_1$, with $t_1 \in [0, T)$ and $n = [\frac{t}{T}]$ (greatest integer $\leq \frac{t}{T}$). Then, we get

$$\|u(t, (X_u^0, X_l^0, X_i^0, X_p^0, X_c^0)) - u(t, M_1)\| = \|u(t_1, P^n(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0)) - u(t_1, M_1)\| < \alpha \text{ for all } t \geq 0.$$

Set $(X_u(t), X_l(t), X_i(t), X_p(t), X_c(t)) = u(t, (X_u^0, X_l^0, X_i^0, X_p^0, X_c^0))$. Therefore $0 \le X_p(t) \le \alpha, t \ge 0$ and

$$\dot{X}_u(t) \ \ge \ \varrho(t) - (p_1(t) + p_2(t))f_1(\alpha)X_u(t) - d_u(t)X_u(t). \tag{4.15}$$

The fixed point $\bar{X}_{u\alpha 0}$ of the function P associated to the perturbed system (4.13) is globally attractive such that $\bar{X}_{u\alpha}(t) > \bar{X}_u(t) - \eta$, then $\exists\, T_2 > 0$ large enough and satisfying

$$X_u(t) > \bar{X}_u(t) - \eta \text{ for } t > T_2.$$

Therefore, for $t > T_2$

$$\begin{cases} \dot{X}_l(t) & \ge & p_1(t)f_1(X_p(t))(\bar{X}_u(t) - \eta) - (d_l(t) + \nu(t))X_l(t), \\ \dot{X}_i(t) & \ge & p_2(t)f_1(X_p(t))(\bar{X}_u(t) - \eta) + \nu(t)X_l(t) - d_i(t)X_i(t), \\ \dot{X}_p(t) & = & d_i(t)r_1(t)X_i(t) - d_p(t)X_p(t) - f_2(X_p(t))X_c(t), \\ \dot{X}_c(t) & = & \varepsilon(t)X_p(t) - d_c(t)X_c(t) - \upsilon(t)f_2(X_p(t))X_c(t). \end{cases} \tag{4.16}$$

Note that we have $r(\varphi_{F-V-\eta M_2}(T)) > 1$. Applying Lemma 4.1 and the comparison principle, there exists a positive T-periodic trajectory $y_2(t)$ satisfying $J(t) \ge e^{k_2 t}y_2(t)$ with $k_2 = \dfrac{1}{T}\ln \ r\left(\varphi_{F-V-\eta M_2}(T)\right) > 0$, which implies that $\lim\limits_{t\to\infty} X_p(t) = \infty$ which is impossible since the trajectories are bounded. Therefore, the inequality (4.14) is satisfied and P is weakly uniformly persistent respecting to $(\Gamma_0, \partial\Gamma_0)$. By applying Lemma 4.2, P has a global attractor. We deduce that $M_1 = (\bar{X}_u^0, 0, 0)$ is an isolated invariant set inside X and $W^s(M_1) \cap \Gamma_0 = \emptyset$. All trajectory inside M_∂ converges to M_1 which is acyclic in M_∂. Applying [31, Theorem 1.3.1 and Remark 1.3.1], we deduce that P is uniformly persistent respecting to $(\Gamma_0, \partial\Gamma_0)$. Furthermore, using [31, Theorem 1.3.6], P admits a fixed point $(\tilde{X}_u^0, \tilde{X}_l^0, \tilde{X}_i^0, \tilde{X}_p^0, \tilde{X}_c^0) \in \Gamma_0$. Note that $(\tilde{X}_u^0, \tilde{X}_l^0, \tilde{X}_i^0, \tilde{X}_p^0, \tilde{X}_c^0) \in R_+ \times Int(R_+^4)$.

We prove also by contradiction that $\tilde{X}_u^0 > 0$. Assume that $\tilde{X}_u^0 = 0$. Using the first equation of the reduced system (4.1), $\tilde{X}_u(t)$ verifies

$$\dot{\tilde{X}}_u(t) \ge \varrho(t) - (p_1(t) + p_2(t))f_1(\tilde{X}_p(t))\tilde{X}_u(t) - d_u(t)\tilde{X}_u(t), \tag{4.17}$$

with $\tilde{X}_u^0 = \tilde{X}_u(mT) = 0, m = 1, 2, 3, \cdots$. Applying Lemma 4.2, $\forall\, \delta_3 > 0$, there exists $T_3 > 0$ large enough and satisfying $\tilde{X}_p(t) \le \bar{S}_2 + \delta_3, t > T_3$. Then, we obtain

$$\dot{\tilde{X}}_u(t) \ge \varrho(t) - (p_1(t) + p_2(t))f_1(\bar{S}_2 + \delta_3)\tilde{X}_u(t) - d_u(t)\tilde{X}_u(t), \text{ for } t \ge T_3 \tag{4.18}$$

There exists $\bar{m}$ large enough and satisfying $mT > T_3$ for all $m > \bar{m}$. Applying the comparison principle, we deduce

$$\tilde{X}_u(mT) = \left[\tilde{X}_u^0 + \int_0^{mT} \varrho(\omega) e^{\int_0^{\omega}((p_1(u) + p_2(u))f_1(\bar{S}_2 + \delta_3) + d_u(u))du} d\omega\right] \times e^{-\int_0^{mT}((p_1(u) + p_2(u))f_1(\bar{S}_2 + \delta_3) + d_u(u))du} > 0$$

for any $m > \bar{m}$ which is impossible. Therefore, $\tilde{X}_u^0 > 0$ and $(\tilde{X}_u^0, \tilde{X}_l^0, \tilde{X}_i^0, \tilde{X}_p^0, \tilde{X}_c^0)$ is a positive T-periodic trajectory of the reduced system (4.1). □

5. Numerical Results and Conclusions

For the numerical simulations, we considered a nonlinear incidence rates of the form $f_1(X_p) = \frac{\bar{f}_1 X_p}{k_1 + X_p}$ and $f_2(X_p) = \frac{\bar{f}_2 X_p}{k_2 + X_p}$ named the Monod function (also Holling's type II). This form of function has been widely used to describe the transmission rate of diseases. $\bar{f}_i$ and $k_i, i = 1, 2$ are two constants. The parameters of the model are T-periodic functions having the following forms:

$$\begin{cases} \rho(t) &= \rho_0(1 + \rho_1 \cos(2\pi(t + \phi))), \\ p_1(t) &= p_1^0(1 + p_1^1 \cos(2\pi(t + \phi))), \\ p_2(t) &= p_2^0(1 + p_2^1 \cos(2\pi(t + \phi))), \\ d_u(t) &= d_u^0(1 + d_u^1 \cos(2\pi(t + \phi))), \\ d_l(t) &= d_l^0(1 + d_l^1 \cos(2\pi(t + \phi))), \\ d_i(t) &= d_i^0(1 + d_i^1 \cos(2\pi(t + \phi))), \\ d_p(t) &= d_p^0(1 + d_p^1 \cos(2\pi(t + \phi))), \\ d_c(t) &= d_c^0(1 + d_c^1 \cos(2\pi(t + \phi))), \\ \nu(t) &= \nu_0(1 + \nu_1 \cos(2\pi(t + \phi))), \\ \upsilon(t) &= \upsilon_0(1 + \upsilon_1 \cos(2\pi(t + \phi))), \\ r_1(t) &= r_1^0(1 + r_1^1 \cos(2\pi(t + \phi))), \\ \varepsilon(t) &= \varepsilon_0(1 + \varepsilon_1 \cos(2\pi(t + \phi))). \end{cases} \tag{5.1}$$

ρ_1, p_1^1, p_2^1, d_u^1, d_l^1, d_i^1, d_p^1, d_c^1, ν_1, υ_1, r_1^1 and ε_1 measure the amplitude(< 1) of the seasonal variation in each of the parameters. ϕ is the phase shift. Some fixed constants used for the numerical simulations are given in Table 2.

Parameter	ρ_0	p_1^0	p_2^0	d_u^0	d_l^0	d_i^0	d_p^0	d_c^0	ν_0	υ_0	r_1^0	ε_0	ϕ	$\bar{f}_2$	k_2
Value	6	0.8	0.8	2	2	2	2	2	0.5	0.5	0.7	0.2	4	2	2

Table 2. Some fixed parameters for numerical simulations.

We will consider three cases. The first case is dedicated for the case of constant parameters (autonomous system) to validate the obtained theoretical results concerning the local and global stability of the equilibrium points $\mathcal{E}_0$ and $\mathcal{E}^*$. The second case deals only with a seasonal contact (p_1 and p_2 are periodic functions) however the other parameters are constants (partially non-autonomous system). The third case considers all parameters as periodic functions (non-autonomous system).

5.1. **The case of the autonomous system.**

In a first step, we consider that all parameters of the system (2.1) are constants ($\rho_1 = p_1^1 = p_2^1 = d_u^1 = d_l^1 = d_i^1 = d_p^1 = d_c^1 = \nu_1 = \upsilon_1 = r_1^1 = \varepsilon_1 = 0$).

Thus, the model is given by

$$\begin{cases} \dot{X}_u(t) = \varrho_0 - (p_1^0 + p_2^0) f_1(X_p(t)) X_u(t) - d_u^0 X_u(t), \\ \dot{X}_l(t) = p_1^0 f_1(X_p(t)) X_u(t) - (d_l^0 + \nu_0) X_l(t), \\ \dot{X}_i(t) = p_2^0 f_1(X_p(t)) X_u(t) + \nu_0 X_l(t) - d_i^0 X_i(t), \\ \dot{X}_p(t) = d_i^0 r_1^0 X_i(t) - d_p^0 X_p(t) - f_2(X_p(t)) X_c(t), \\ \dot{X}_c(t) = \varepsilon_0 X_p(t) - d_c^0 X_c(t) - \upsilon_0 f_2(X_p(t)) X_c(t), \end{cases} \tag{5.2}$$

with positive initial condition $(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in \mathbb{R}_+^5$. We give some numerical results that confirm the stability of the equilibrium points of (5.2). In Fig. 1, we give the results for the case where $\mathcal{R}_0 > 1$. The approximated solution of the given model (5.2) approaches asymptotically to $\mathcal{E}^*$, which confirms that $\mathcal{E}^*$ is globally asymptotically stable once $\mathcal{R}_0 > 1$. In Fig. 2, we give the results for the case where $\mathcal{R}_0 < 1$. The approximated solution of the given model (5.2) approaches the equilibrium $\mathcal{E}_0$, which confirms that $\mathcal{E}_0$ is globally asymptotically stable once $\mathcal{R}_0 \leq 1$.

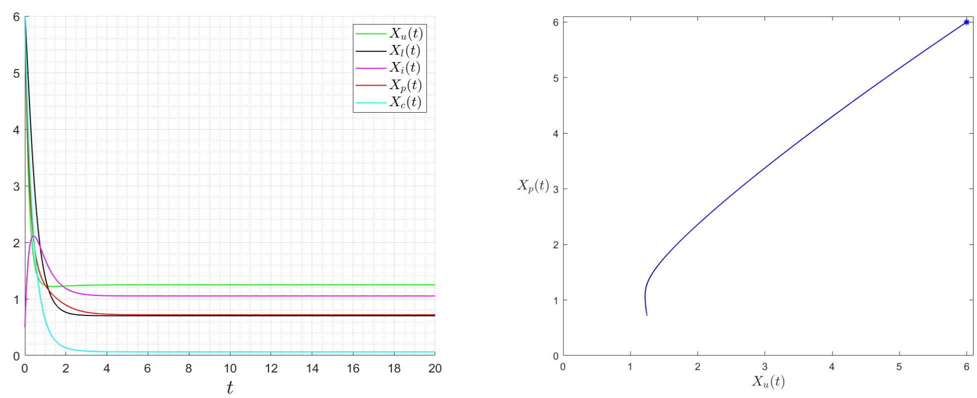

Figure 1. Behaviour of the solution of system (2.1) for $\bar{f}_1 = 2$ and $k_1 = 0.1$ then $\mathcal{R}_0 \approx 20.16 > 1$.

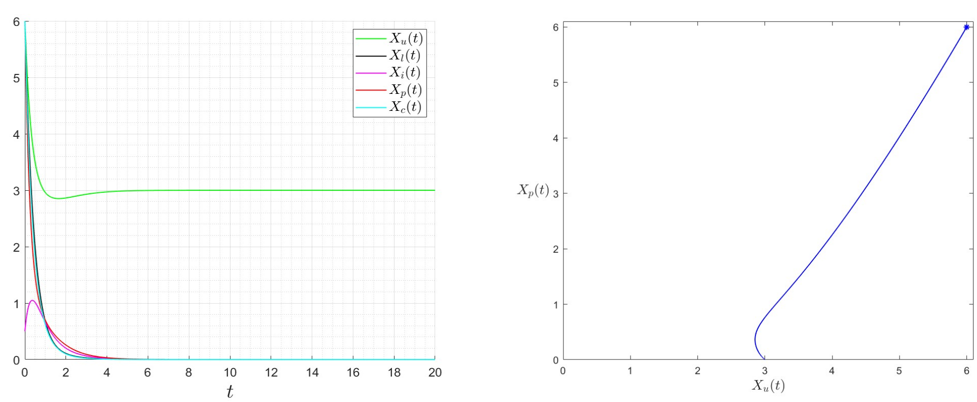

Figure 2. Behaviour of the solution of system (2.1) for $\bar{f}_1 = 0.6$ and $k_1 = 3$ then $\mathcal{R}_0 \approx 0.2 < 1$.

5.2. **The case of the partially non-autonomous system.** In a second step, we performed numerical simulations on the system (2.1) using linear function to express the transmission rate where only the seasonally forced T-periodic function $p_1(t)$ and $p_2(t)$ are depending on time, t. The other parameters are constants.

Thus the model is given by

$$\begin{cases} \dot{X}_u(t) = \varrho_0 - (p_1(t) + p_2(t))f_1(X_p(t))X_u(t) - d_u^0 X_u(t), \\ \dot{X}_l(t) = p_1^0 f_1(X_p(t))X_u(t) - (d_l^0 + \nu_0)X_l(t), \\ \dot{X}_i(t) = p_2^0 f_1(X_p(t))X_u(t) + \nu_0 X_l(t) - d_i^0 X_i(t), \\ \dot{X}_p(t) = d_i^0 r_1^0 X_i(t) - d_p^0 X_p(t) - f_2(X_p(t))X_c(t), \\ \dot{X}_c(t) = \varepsilon_0 X_p(t) - d_c^0 X_c(t) - \upsilon_0 f_2(X_p(t))X_c(t), \end{cases} \tag{5.3}$$

with positive initial condition $(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in \mathbb{R}_+^5$ where $\beta_1 = 0.8$. The basic reproduction number, $\mathcal{R}_0$, was approximated using the time-averaged system. We give some numerical results that confirm the asymptotic behaviour of the solution of (5.3). In Fig. 3, we give the results for the case where $\mathcal{R}_0 > 1$. The approximated solution of the given model (5.3) approaches asymptotically to a periodic solution with persistence of the disease. In Fig. 4, we give the results for the case where $\mathcal{R}_0 < 1$. The approximated solution of the given model (5.3) approaches the disease-free trajectory $\mathcal{E}_0 = \left(\frac{\rho_0}{d_u^0}, 0, 0, 0, 0\right)$ once $\mathcal{R}_0 \leq 1$.

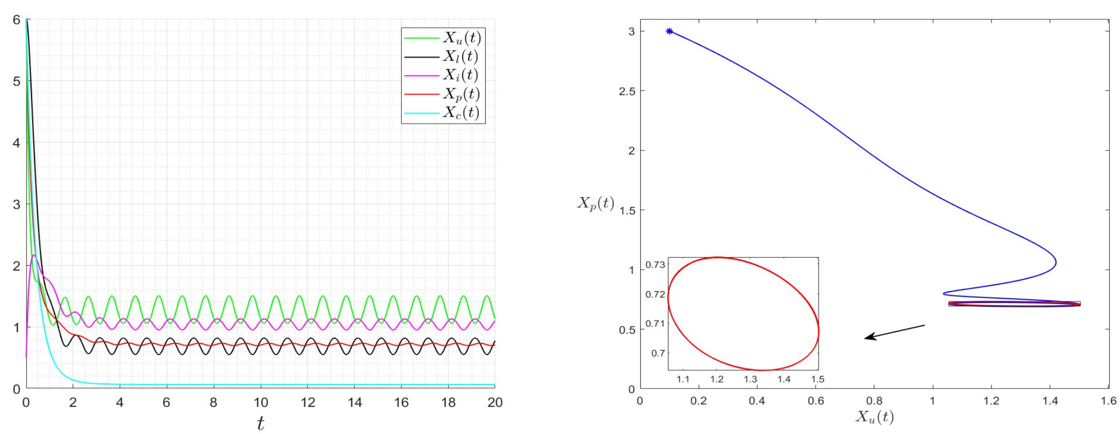

Figure 3. Behaviour of the solution of system (2.1) for $\bar{f}_1 = 2$ and $k_1 = 0.1$ then $\mathcal{R}_0 \approx 20.16 > 1$.

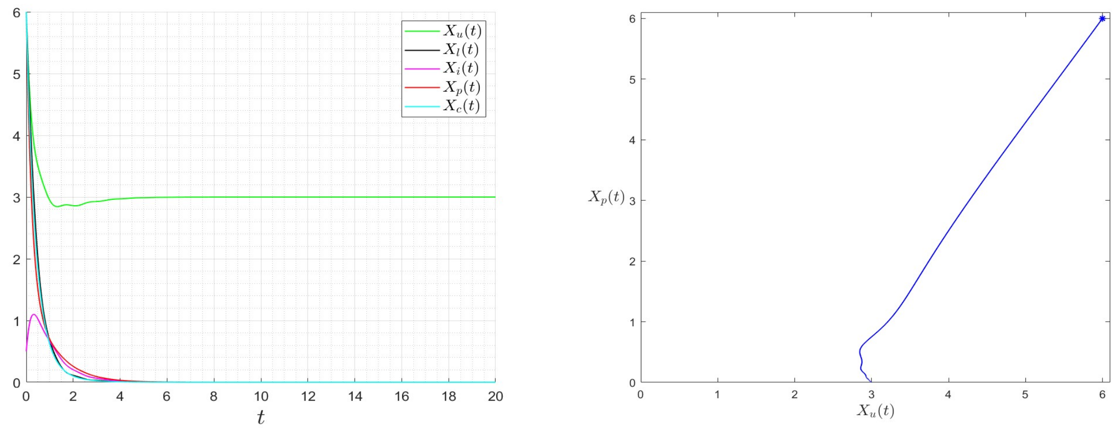

Figure 4. Behaviour of the solution of system (2.1) for $\bar{f}_1 = 0.6$ and $k_1 = 3$ then $\mathcal{R}_0 \approx 0.2 < 1$.

5.3. **The case of totally non-autonomous system.** In a third step, we performed numerical simulations on the system (2.1) using classical Monod function to express the transmission rate where all parameters are T-periodic functions. Thus the model is given by

$$\begin{cases} \dot{X}_u(t) = \varrho(t) - (p_1(t) + p_2(t))f_1(X_p(t))X_u(t) - d_u(t)X_u(t), \\ \dot{X}_l(t) = p_1(t)f_1(X_p(t))X_u(t) - (d_l(t) + \nu(t))X_l(t), \\ \dot{X}_i(t) = p_2(t)f_1(X_p(t))X_u(t) + \nu(t)X_l(t) - d_i(t)X_i(t), \\ \dot{X}_p(t) = d_i(t)r_1(t)X_i(t) - d_p(t)X_p(t) - f_2(X_p(t))X_c(t), \\ \dot{X}_c(t) = \varepsilon(t)X_p(t) - d_c(t)X_c(t) - \upsilon(t)f_2(X_p(t))X_c(t),, \end{cases} \tag{5.4}$$

with positive initial condition $(X_u^0, X_l^0, X_i^0, X_p^0, X_c^0) \in \mathbb{R}_+^5$. Additional constants used for the numerical simulations in this step are given in Table 3. The basic reproduction number, $\mathcal{R}_0$, was approximated using the time-averaged system.

Parameter	ρ_1	p_1^1	p_2^1	d_u^1	d_l^1	d_i^1	d_p^1	d_c^1	ν_1	υ_1	r_1^1	ε_1
Value	0.5	0.6	0.4	0.3	0.6	0.8	0.2	0.1	0.3	0.7	0.5	0.6

Table 3. Additional parameters for numerical simulations of the totally non-autonomous system.

We give some numerical results that confirm the asymptotic behaviour of the solution of (5.4). In Fig. 5, we give the results for the case where $\mathcal{R}_0 > 1$. The approximated solution of the given model (5.4) approaches asymptotically to a periodic solution with persistence of the disease.

In Fig. 6, we give the results for the case where $\mathcal{R}_0 < 1$. The approximated solution of the given model (5.4) approaches the disease-free periodic trajectory $\mathcal{E}_0(t) = (X_u^*(t), 0, 0, 0, 0)$ once $\mathcal{R}_0 \leq 1$.

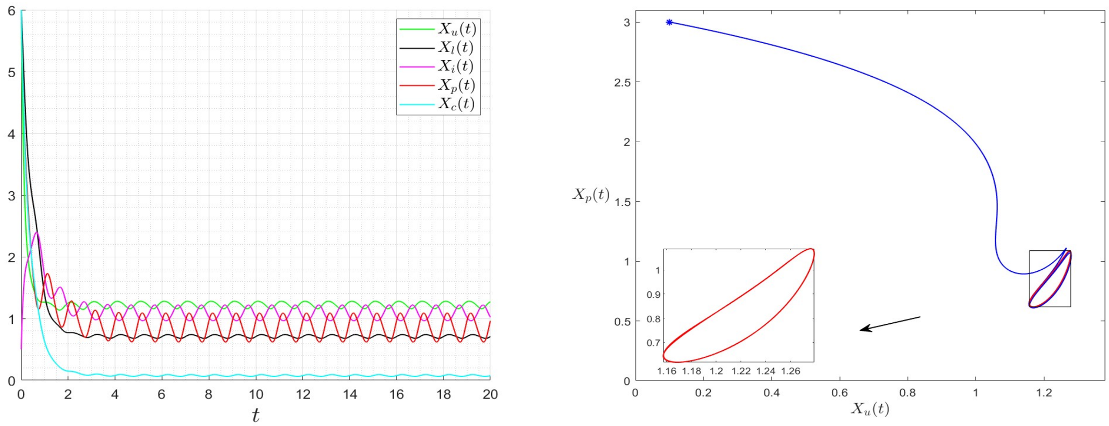

Figure 5. Behaviour of the solution of system (2.1) for $\bar{f}_1 = 2$ and $k_1 = 0.1$ then $\mathcal{R}_0 \approx 20.16 > 1$.

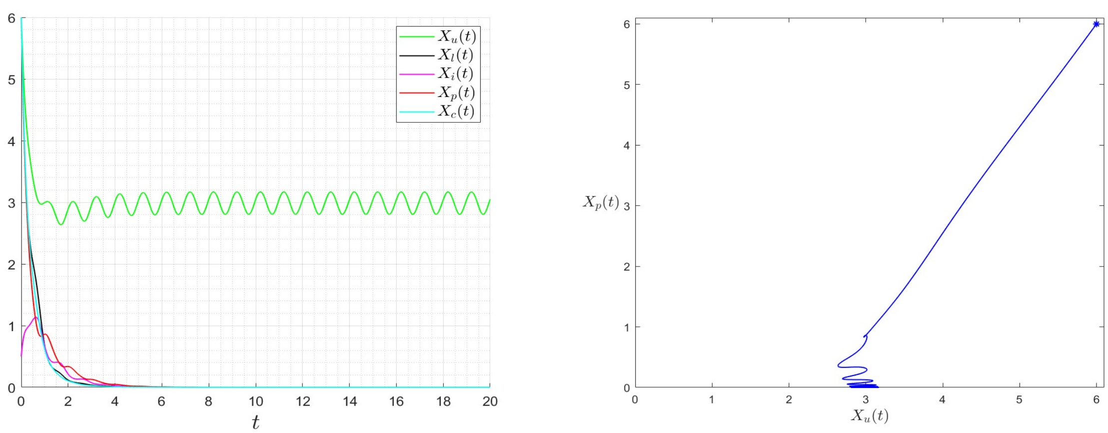

Figure 6. Behaviour of the solution of system (2.1) for $\bar{f}_1 = 0.6$ and $k_1 = 3$ then $\mathcal{R}_0 \approx 0.2 < 1$.

6. Conclusions

The human immunodeficiency virus (HIV) is the pathogen responsible for acquired immunodeficiency syndrome (AIDS). In this work, we proposed an extension of the HIV epidemic model given in [10, 11] in a seasonal environment. In the first step we studied the case of autonomous system where all parameters are supposed to be constants. In the second step, we considered the non-autonomous system and we give some basic results and we defined the basic reproduction number, $\mathcal{R}_0$. We show that $\mathcal{R}_0$-value compared to the unit is the threshold value between uniform persistence and extinction of the considered disease. More precisely, we showed that if $\mathcal{R}_0$ is less than 1, then the disease free periodic solution is globally asymptotically stable and if $\mathcal{R}_0$ is greater than 1, then the disease persists. Finally, we gave some numerical examples that supports the theoretical findings, including the autonomous system, the partially non-autonomous system and the full non-autonomous system. It is deduced that if the system is autonomous, the trajectories converge to one of the equilibrium of the system (2.1) according to theorems 3.3 and 3.4. However, if at least one of the model parameters is periodic, the trajectories converge to a limit cycle according to theorems 4.2 and 4.3.

Conflicts of Interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

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