# Effect of therapy on the dynamics of HIV model with adaptive immune response and two saturated rates

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# Plan

# Introduction

- Human Immunodeficiency virus (HIV) is a pathogen which causes the well known Acquired Immunodeficiency Syndrom (AIDS).
- The HIV dynamics involving the density uninfected cells, the density of the infected cells, the density of HIV virus and the amount of CTL cells have been widely studied starting from the work by Nowak and Bangham (1996)[1] and two years later by De Boer et al. (1998)[2].
- The dynamic of HIV including CTL cells and two saturated rates is studied by Tabit et al. (2014)[3]

[1] Nowak M.A.; Bangham C.R.M. Population dynamics of immune responses to persistent viruses. Science 173 1996, 272, 7479.

[2] De Boer, Rob J., Perelson. Alan S. Target cell limited and immune control models of HIV infection: a 200 comparison, Journal of theoretical Biology 190 (1998) 201214.

[3] Y. Tabit, K. Hattaf, N. Yousfi. Dynamics of an HIV pathogenesis model with CTL immune response and two saturated rates. World Journal of Modelling and Simulation, 2014, 10(3): 215–223 .

# The model

The dynamics of HIV infection with CTL, antibody responses and therapy that we consider is given by the following nonlinear system of differential equations

$$\begin{cases} \dfrac{dT}{dt} = s - dT - \dfrac{(1-\eta)\beta VT}{1+aV} + \rho I, \\ \dfrac{dI}{dt} = \dfrac{(1-\eta)\beta VT}{1+aV} - (\delta+\rho)I - pIZ, \\ \dfrac{dV}{dt} = (1-\epsilon)N\delta I - \mu V - qVW, \\ \dfrac{dW}{dt} = gVW - hW, \\ \dfrac{dZ}{dt} = \dfrac{cIZ}{1+\alpha I} - bZ. \end{cases} \tag{1}$$

With the initial conditions $T(0) = T_0$, $I(0) = I_0$, $V(0) = V_0$, $Z(0) = Z_0$ and $W(0) = W_0$.

**Theorem**

The solutions of the problem (1) exist. Moreover, they are bounded, nonnegative and verify:

**i)** $T_1(t) \leq T_1(0) + \frac{s}{\delta_1}$,

**ii)** $V(t) \leq V(0) + \frac{(1-\epsilon)N\delta}{\mu} \|I\|_\infty$,

**iii)** $W(t) \leq$
$W(0) + \frac{g}{q}[\max(1; 2 - \frac{\mu}{h})V(0) + (\frac{(1-\epsilon)N\delta}{\mu} + \frac{(1-\epsilon)N\delta}{h}) \|I\|_\infty]$,

**iv)** $Z(t) \leq Z(0) + \frac{c}{p}[\max(1; 2 - \frac{d}{b})T(0) + I(0) + \max(\frac{s}{b}; \frac{s}{d}) +$
$\max(0; 1 - \frac{\delta}{b}) \|I\|_\infty]$,

where $T_1(t) = T(t) + I(t)$ and $\delta_1 = \min(d; \delta)$.

# Elements of the Proof

**Proof (Elements)**

- We have $\dot{T}_1 = s - dT - \delta I - pIZ$, thus

$$T_1(t) \leq T_1(0)e^{-\delta_1 t} + \frac{s}{\delta_1}(1 - e^{-\delta_1 t})$$

- From $\dot{V} = (1-\epsilon)N\delta I - \mu V - qVW$, we have

$$V(t) \leq V(0)e^{-\mu t} + (1-\epsilon)N\delta \int_0^t I(\xi)e^{(\xi - t)\mu} d\xi$$

- See

$$\dot{W} + hW = gVW = \frac{g}{q}\left((1-\epsilon)N\delta I - (\dot{V} + \mu V)\right)$$

- From $\dot{Z} = \frac{cIZ}{1+\alpha I} - bZ$ we have

$$\dot{Z} + bZ \leq cIZ = \frac{c}{p}[s - (\dot{T} + dT) - (\dot{I} + \delta I)]$$

# Stability of the disease-free equilibrium

The basic reproduction number of the system is given by

$$R_0 = \frac{(1-\theta)N\delta s}{d\mu(\delta+\rho)}. \tag{2}$$

$$(1-\theta) = (1-\eta) \times (1-\epsilon)$$

# Stability of the disease-free equilibrium

There is an infection-free equilibrium

$$E_f = (\frac{s}{d}, 0, 0, 0, 0)$$

corresponding to the maximal level of healthy CD4+ T-cells.

# Stability of the disease-free equilibrium

**Theorem**

1. *The disease-free equilibrium, $E_f$, is locally asymptotically stable for $R_0 < 1$.*
2. *The disease-free equilibrium, $E_f$, is unstable for $R_0 > 1$.*

# Elements of the Proof

**Proof (Elements)** At the disease-free equilibrium, $E_f$, the Jacobian matrix is given as follows:

$$J_{E_f} = \begin{pmatrix} -d & \rho & -\frac{(1-\eta)\beta s}{d} & 0 & 0 \\ 0 & -(\delta+\rho) & \frac{(1-\eta)\beta s}{d} & 0 & 0 \\ 0 & (1-\epsilon)N\delta & -\mu & 0 & 0 \\ 0 & 0 & 0 & -h & 0 \\ 0 & 0 & 0 & 0 & -b \end{pmatrix} \tag{3}$$

The characteristic polynomial of $J_{E_f}$ is

$$P_{E_f}(\xi) = (\xi+d)(\xi+b)(\xi+h)[\xi^2+(\delta+\rho+\mu)\xi+(\delta+\rho)\mu(1-R_0)],$$

One of the eigenvalues is

$$\xi = \frac{-(\delta+\rho+\mu)+\sqrt{(\delta+\rho+\mu)^2-4(\delta+\rho)\mu(1-R_0)}}{2},$$

# Stability of the disease-free equilibrium

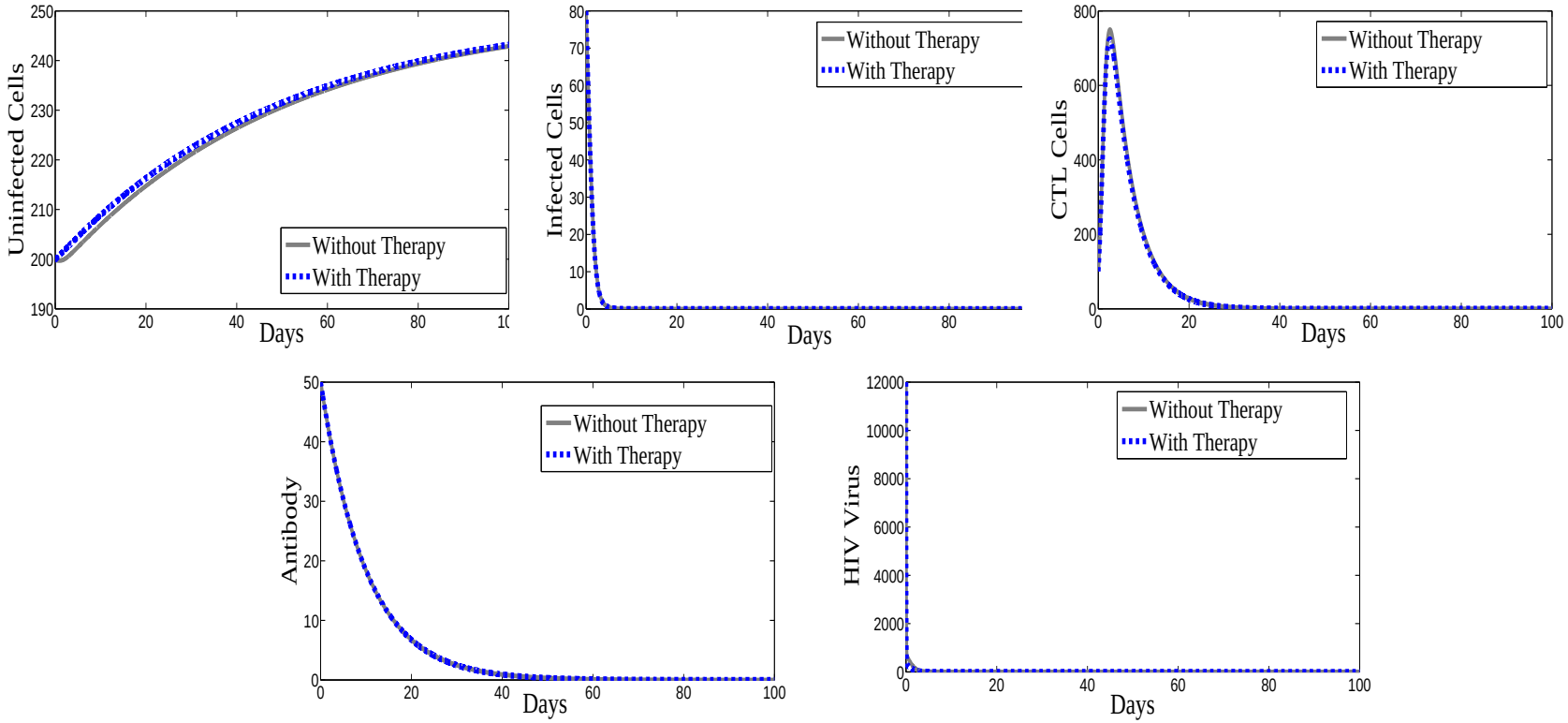


Figure 1: Behavior of the infection during the time which correspond to the stability of the free-equilibrium $E_f$. $s = 5$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 500$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.5$, $g = 10^{-11}$, $h = 0.1$, $\eta = 0.4$ and $\epsilon = 0.55$.

# Stabiliy of the infection steady states

The infection steady states:
$E_1 = (T_1, I_1, V_1, 0, 0)$, where

$$\begin{aligned} T_1 &= \frac{s}{d}[\frac{a(1-\epsilon)Ns + \mu}{a(1-\epsilon)Ns + \mu R_0}], \\ I_1 &= \frac{s}{\delta}[\frac{\mu(R_0 - 1)}{a(1-\epsilon)Ns + \mu R_0}], \\ V_1 &= \frac{(1-\epsilon)Ns(R_0 - 1)}{a(1-\epsilon)Ns + \mu R_0}, \end{aligned}$$

# Stabiliy of the infection steady states

$E_2 = (T_2, I_2, V_2, W_2, 0)$, where

$$
\begin{aligned}
T_2 &= \frac{(\rho+\delta)(g+ah)s}{d(\rho+\delta)(g+ah)+(1-\eta)\beta\delta h}, \\
I_2 &= \frac{(1-\eta)\beta hs}{d(\rho+\delta)(g+ah)+(1-\eta)\beta\delta h}, \\
V_2 &= \frac{h}{g}, \\
W_2 &= \frac{\mu}{q}\left[\frac{(1-\theta)N\delta\beta gs}{\mu[d(\rho+\delta)(g+ah)+(1-\eta)\beta\delta h]} - 1\right],
\end{aligned}
$$

# Stabiliy of the infection steady states

$E_3 = (T_3, I_3, V_3, 0, Z_3)$, where

$$
\begin{aligned}
I_3 &= \frac{b}{c - \alpha b}, \\
T_3 &= \frac{(a(1-\epsilon)N\delta\rho)I_3^2 + (a(1-\epsilon)Ns\delta + \mu\rho)I_3 + \mu s}{(1-\epsilon)N\delta(ad + (1-\eta)\beta)I_3 + \mu d}, \\
V_3 &= \frac{(1-\epsilon)N\delta I_3}{\mu}, \\
Z_3 &= \frac{-(1-\epsilon)N\delta[ad\rho + \delta(ad + (1-\eta)\beta)]I_3}{p((1-\epsilon)N\delta(ad + (1-\eta)\beta)I_3 + +\mu d)} \\
&\quad + \frac{((1-\theta)\beta Ns\delta - d\mu(\rho + \delta))}{p((1-\epsilon)N\delta(ad + (1-\eta)\beta)I_3 + \mu d)},
\end{aligned}
$$

and $E_4 = (T_4, I_4, V_4, W_4, Z_4)$, where

$$
\begin{aligned}
I_4 &= \frac{b}{c - \alpha b}, \\
V_4 &= \frac{h}{g}, \\
T_4 &= \frac{(s + \rho I_4)(1 + aV_4)}{d(1 + aV_4) + (1 - \eta)\beta V_4}, \\
W_4 &= \frac{1}{q}\left(\frac{(1 - \epsilon)N\delta I_4}{V_4} - 1\right), \\
Z_4 &= \frac{1}{p}\left(\frac{s}{I_4} - \frac{dT_4}{I_4} - \delta\right).
\end{aligned}
$$

# Stabiliy of the infection steady states

In order to study the local stability of the points $E_1$, $E_2$, $E_3$ and $E_4$, we first define the following numbers:

$$D_0^W = \frac{(1-\epsilon)gNs}{h\mu},\ \widetilde{D_0^W} = D_0^W \frac{\mu R_0}{(a(1-\epsilon)Ns + \mu R_0)},\ H_0^W = \frac{1}{\frac{1}{R_0} + \frac{1}{\widetilde{D_0^W}}},$$

$$D_0^Z = \frac{cs}{b\delta},\ \widetilde{D_0^Z} = D_0^Z \frac{\mu\delta R_0}{(a(1-\epsilon)Ns + \mu R_0) + \alpha\mu s(R_0 - 1)},\ H_0^Z = \frac{1}{\frac{1}{R_0} + \frac{1}{\widetilde{D_0^Z}}},$$

and

$$H_0^{W,Z} = \frac{D_0^Z R_0}{D_0^W(1 + \frac{ah}{g}) + R_0(1 + \frac{\alpha s^2}{\delta})}.$$

# Stability of $E_1$

**Theorem**

1. *If* $R_0 < 1$, *then the point* $E_1$ *does not exist.*
2. *If* $R_0 = 1$, *then* $E_1 = E_f$.
3. *If* $R_0 > 1$, *then* $E_1$ *is locally asymptotically stable for* $H_0^W < 1$, *and* $H_0^Z < 1$; *however it is unstable for* $H_0^W > 1$ *or* $H_0^Z > 1$.

**Proof (Elements)**

It easy to see that if $R_0 < 1$, then the point $E_1$ does not exist and if $R_0 = 1$ the two points $E_1$ and $E_f$ coincide. If $R_0 > 1$, the Jacobian matrix at $E_1$ is given by

$$J_{E_1} = \begin{pmatrix} -d - \frac{(1-\eta)\beta V_1}{1+aV_1} & \rho & -\frac{(1-\eta)\beta T_1}{(1+aV_1)^2} & 0 & 0 \\ \frac{(1-\eta)\beta V_1}{1+aV_1} & -(\delta+\rho) & \frac{(1-\eta)\beta T_1}{(1+aV_1)^2} & 0 & -pI_1 \\ 0 & (1-\epsilon)N\delta & -\mu & -qV_1 & 0 \\ 0 & 0 & 0 & gV_1 - h & 0 \\ 0 & 0 & 0 & 0 & \frac{cI_1}{1+\alpha I_1} - b \end{pmatrix}$$

then, its characteristic equation is

$$(\xi + h - gV_1)(\xi + b - \frac{cI_1}{1+\alpha I_1})(\xi^3 + a_1\xi^2 + a_2\xi + a_3) = 0,$$

where

$$a_1 = d + \delta + \mu + \rho + \frac{(1-\eta)\beta V_1}{1 + aV_1},$$

$$a_2 = (\delta + \mu + \rho)d + (\mu + \delta)\frac{(1-\eta)\beta V_1}{1 + aV_1} + \mu(\delta + \rho) - \frac{(1-\theta)N\delta\beta T_1}{(1 + aV_1)^2},$$

$$a_3 = \mu d(\delta + \rho) + \frac{\mu\delta(1-\eta)\beta V_1}{1 + aV_1} - \frac{(1-\theta)N\delta\beta T_1 d}{(1 + aV_1)^2},$$

We have $gV_1 - h = \dfrac{h\widetilde{D_0^W}(H_0^W - 1)}{H_0^W}$ and

$\dfrac{cI_1}{1 + \alpha I_1} - b = \dfrac{b\widetilde{D_0^Z}(H_0^Z - 1)}{H_0^Z}$. Checking the negativity by Routh-Hurwitz Theorem.

# Stability of $E_1$

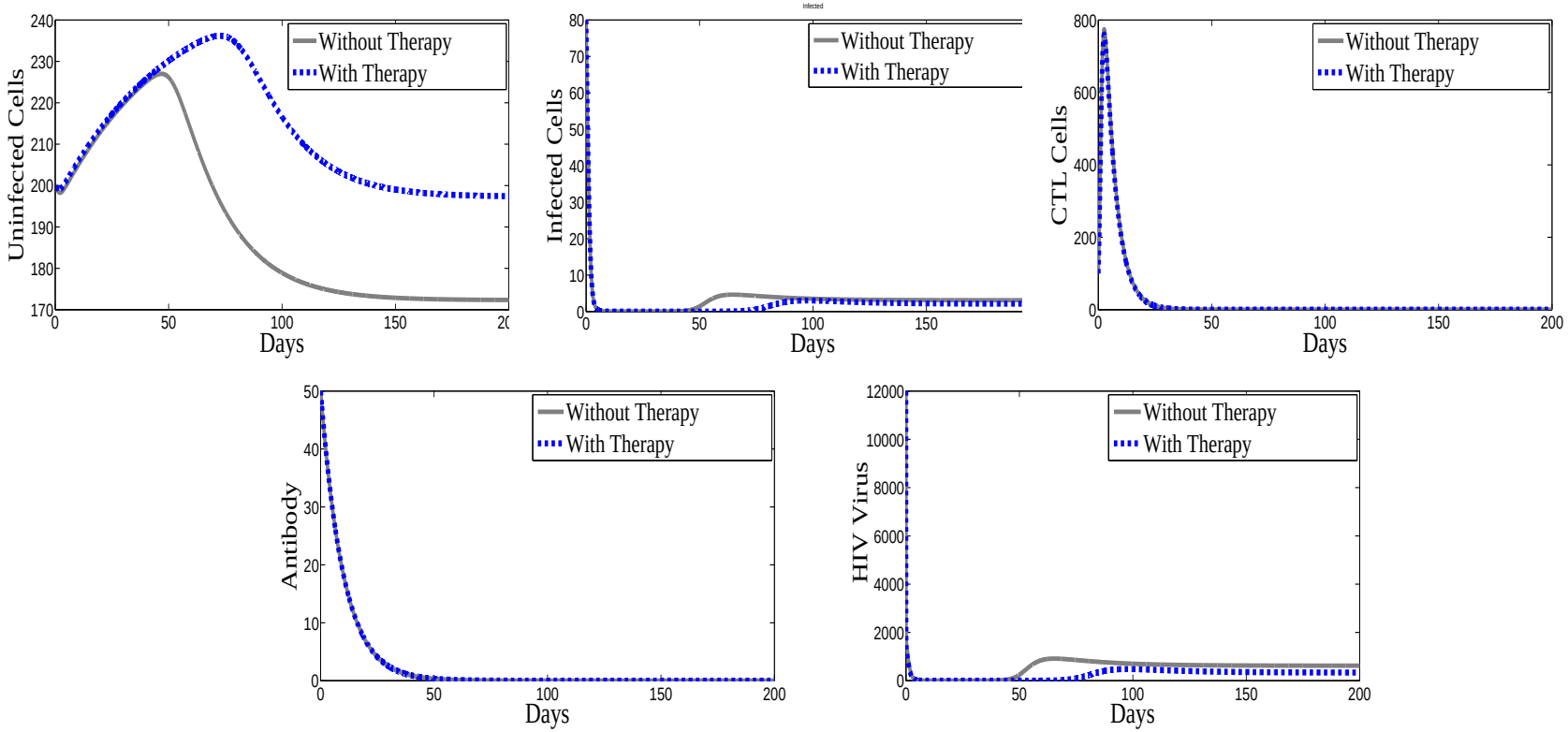


Figure 2: Behavior of the infection during the time which correspond to the stability of the endemic-equilibrium point $E_1$. $s = 5$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.5$, $g = 10^{-11}$, $h = 0.1$, $\eta = 0.1$ and $\epsilon = 0.2$.

# Stability of $E_2$

**Theorem**

1. *If* $H_0^W < 1$, *then the point* $E_2$ *does not exist.*
2. *If* $H_0^W = 1$ *then* $E_2 = E_1$.
3. *If* $H_0^W > 1$ *then* $E_2$ *is locally asymptotically stable for* $H_0^{W,Z} < 1$ *and unstable for* $H_0^{W,Z} > 1$.

# Stability of $E_2$

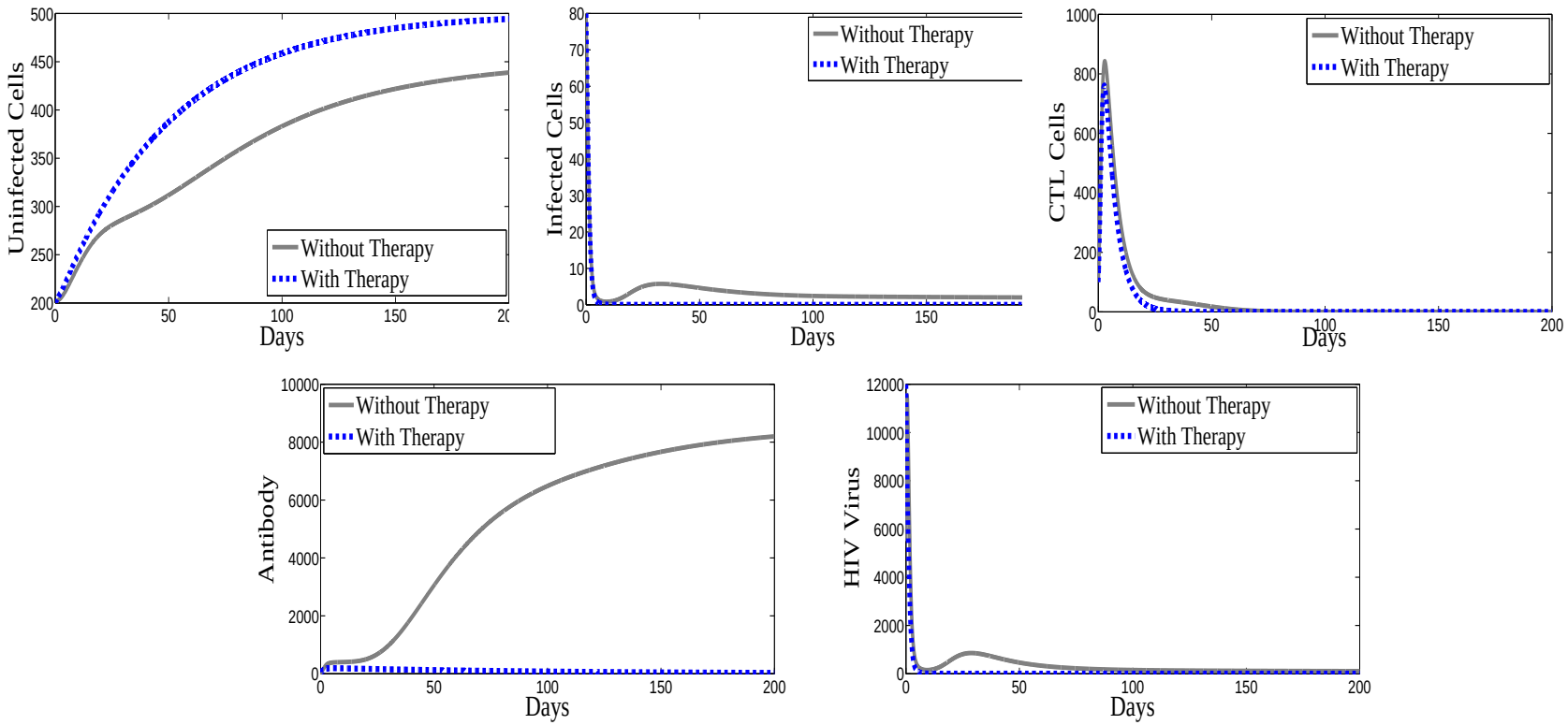


Figure 3: Behavior of the infection during the time which correspond to the stability of the endemic-equilibrium $E_2$, $s = 10$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.001$, $g = 10^{-4}$, $h = 0.01$, $\eta = 0.55$ and $\epsilon = 0.45$.

# Stability of $E_3$

**Theorem**

1. *If* $\alpha > \frac{c}{b}$ *or* $H_0^Z < 1$, *then the point* $E_3$ *does not exist and* $E_3 = E_2$ *when* $H_0^Z = 1$.
2. *If* $\alpha < \frac{c}{b}$, $H_0^Z > 1$ *and* $D_0^W < (1 - \frac{\alpha b}{c}) D_0^Z$ , *then* $E_3$ *is locally asymptotically stable.*
3. *If* $\alpha < \frac{c}{b}$, $H_0^Z > 1$ *and* $D_0^W > (1 - \frac{\alpha b}{c}) D_0^Z$, *then* $E_3$ *is unstable.*

# Stability of $E_3$

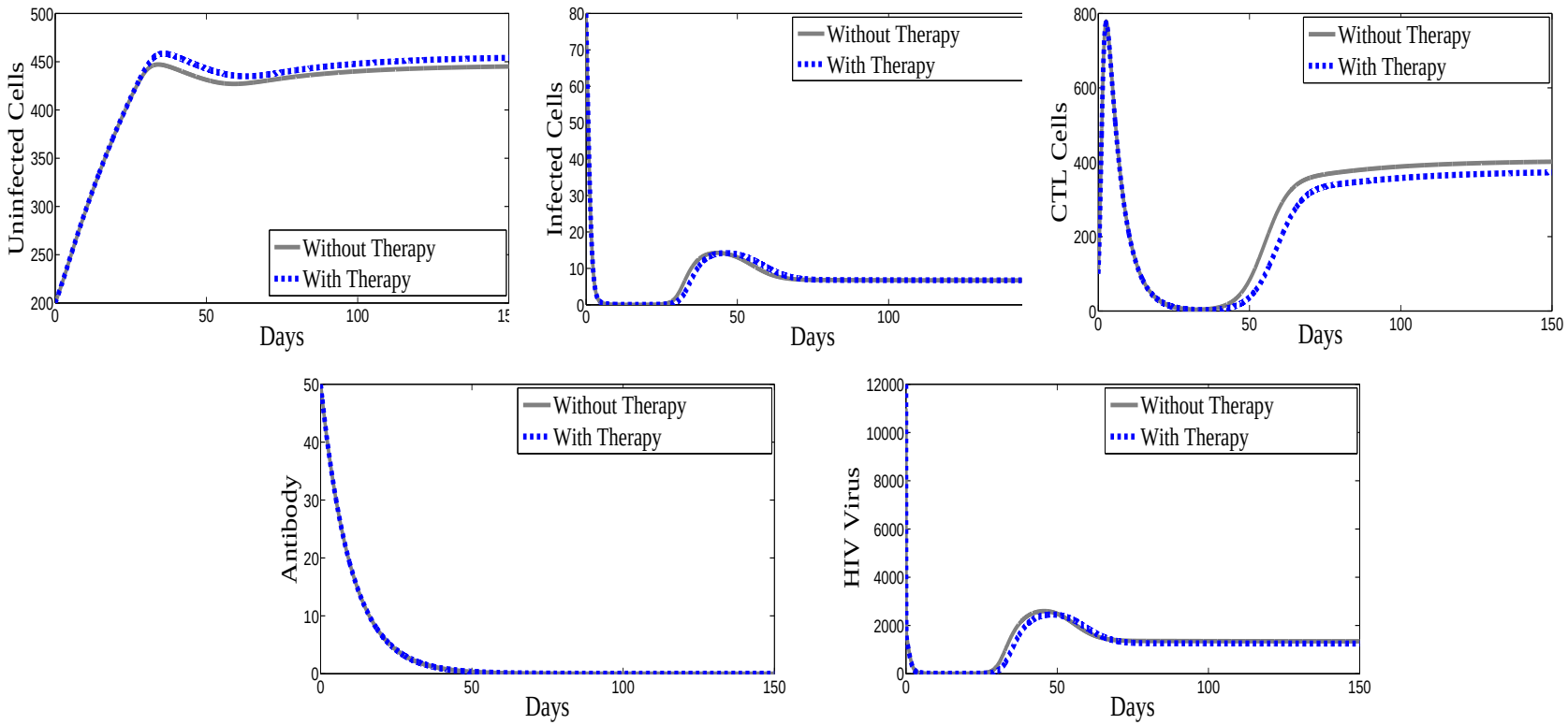


Figure 4: Behavior of the infection during the time which correspond to the stability of the endemic-equilibrium $E_3$, $s = 15$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.5$, $g = 10^{-11}$, $h = 0.1$, $\eta = 0.02$ and $\epsilon = 0.07$.

# Stability of $E_4$

**Theorem**

1. *If* $\alpha > \frac{c}{b}$ *or* $D_0^W < (1 - \frac{\alpha b}{c}) D_0^Z$ *or* $H_0^{W,Z} < 1$, *then the point* $E_4$ *does not exist. Moreover* $E_4 = E_2$ *when* $H_0^{W,Z} = 1$ *and* $E_4 = E_3$ *when* $D_0^W = D_0^Z$
2. *If* $\alpha < \frac{c}{b}$, $D_0^W > (1 - \frac{\alpha b}{c}) D_0^Z$ *and* $H_0^{W,Z} > 1$, *then* $E_4$ *is locally asymptotically stable.*

# Stability of $E_4$

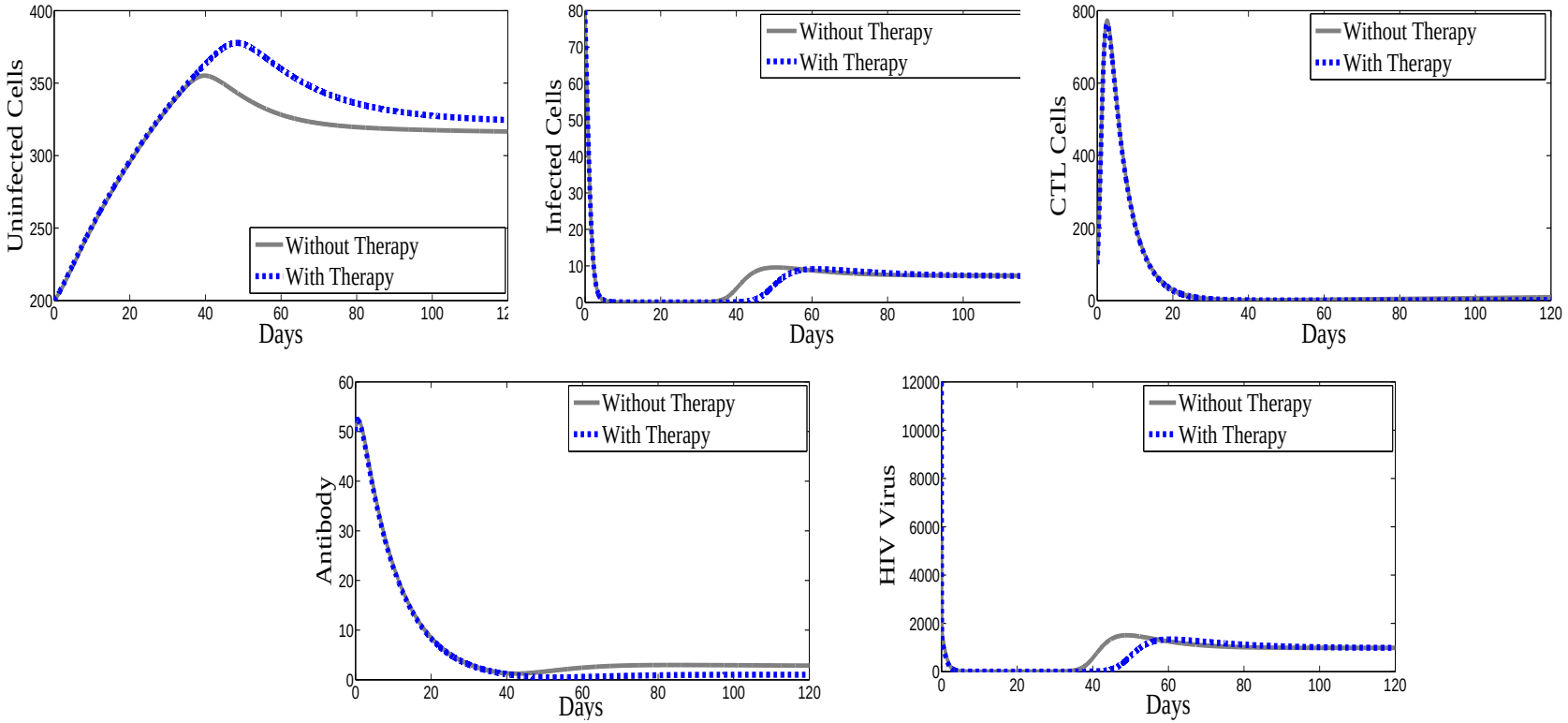


Figure 5: Behavior of the infection during the time which correspond to the stability of the endemic-equilibrium $E_4$, $s = 10$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.5$, $g = 10^{-4}$, $h = 0.1$, $\eta = 0.05$ and $\epsilon = 0.2$.

# Conclusion

- The local stability of the disease-free equilibrium depends on the basic reproduction number $R_0$.
- The local stability of the infection steady states depends on the basic reproduction number $R_0$, the CTL immune response reproduction number $D_0^Z$ and the antibody immune response reproduction number $D_0^W$.
- In the presence of therapy, an increases of the uninfected cells is observed.
- The results of this work confirm that the therapy may control the viral replication and reduce the infection.

# References I


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- Y. Tabit, A. Meskaf, K. Allali. Mathematical analysis of HIV model with two saturated rates, CTL and antibody responses. *World Journal of Modelling and Simulation*, 2016 **12**(2) : 137–146.
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Thank you for your attention