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A model for drug therapy using integrase strand transfer inhibitor for acute and chronic infections of HIV

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Abstract: A Mathematical model for the effect of integrase stand transfer inhibitor on the HIV infected human immune system is proposed and analyzed. The model considers uninfected CD4+ T-cells, Pre-integrase inhibitor, Post- integrase inhibitor CD4+ T-cells and the virus populations described by a system of ordinary differential equations. The relation between the administered drug efficacy with the virus population has been discussed using numerical simulation. It is observed that the parameters p and q have a significant effect on the CD4+ T-cells and Virus population.

Keywords: CD4+ T cells, drug therapy, non-linear incidence rate, cytotoxic T lymphocytes.

1 Introduction

Human immunodeficiency virus HIV has infected 78 million and out of this 39 million people have died of AIDS related illnesses since the case of the virus reported in 1981 [1,2]. In 2015 about 36.7 million people were living with HIV and it resulted in 1.1 million deaths. Most of those infected live in sub-Saharan Africa. Through this time it becomes the most intensely studied viral pathogens but many characteristics of HIV infection dynamics and disease pathogenesis within a host are still not understood. Besides, the only effective way for clinical treatment of HIV infection so far is highly active antiretroviral therapy (HAART)consisting multiple anti-HIV drugs, including reverse transcriptase inhibitors (RTIs), protease inhibitors (PIs), fusion inhibitor, co-receptor antagonists and integrase inhibitors (INIs) [3]. Integrase inhibitors are relatively new class of agents with two generation of three drugs registered by U.S Food and Drug Administration (FDA). The first generation drugs are raltegravir (RAL, Isentress, formerly MK-0518) and elvitegravir (EVG, GS-9137, JTK-303) approved on 2007 and 2012 respectively, by FDA for AIDS treatment [4,5]. The second generation of drug is Dolutegravir (DTG, TIVICAY, S/GSK1349572) approved by FDA for treatment-naive and treatment experienced persons with HIV infection in August 2013. DTG appears to have a higher genetic barrier to resistance than RAL or EVG [6].

A single HIV particle contains approximately $40-100$ integrase molecules [7,8]. The primary role of these integrase molecules is to catalyze the insertion of the proviral DNA into the genome of infected cells. Integration, following fusion and reverse transcription, is required to replicate viral particles inside the host cells. The insertion of HIV-1 viral genomic DNA into the host chromosome is a process often referred to as strand transfer, and this will be catalyzed by the enzyme called integrase. Integrase inhibitors inhibit this step, and as a result are often referred to as Integrase strand-transfer inhibitors (INSTIs) [9]. Reviews shown that the latest INSTIs have demonstrated activity against isolates resistant to both RTIs and PIs [9,10]. And also the drugs can be administered once per day without the need for a pharmacokinetic booster and may be co-formulated with other antiretrovirals in a single-tablet regimen hence they offer

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advantages in safety, efficacy, and simplicity of dosing [11,12,13,14,15].

Mathematical modeling has helped to improve our understanding of the infection as well as the dynamics of the immune response. Fitting models to clinical data has provided estimates for the turnover rate of target cells [16,17,18] the lifetime of infected cells and viral particles [19,20], as well as for the rate of viral production by infected cells [21,22]. Most mathematical models applied to experimental data on viral infections have been formulated as systems of ordinary differential equations [23,19,20]. The cytotoxic T Lymphocytes (CTLs) contribute a role to kill infected cells due to a cell-mediated immune response, this will lead to decline in Viraemia for the primary infections of HIV [24,25,15].

In this model both the infections, the acute and chronic infections, are considered and as a result the cytotoxic T Lymphocytes (CTLs), which will lead to decline in Viremia for the acute infections of HIV. [26,24] And the interaction of T-cells and the virus population is not linear as it may be less than linear due to saturation at high virus concentration and may be greater than linear if infectious fraction was very small or if multiple exposures were necessary for infection [24]. Further, due to failure of entry of the virus in to the host cells [25], there is a fraction of pre-INSTI T-cells revert back to uninfected class.

2 The model

We develop a mathematical model for primary infection with INSTI inhibitor under the above mentioned assumptions. We consider three populations of CD4+ T cells and the virus population.

(1) T represents density of susceptible CD4+ T cells,
(2) T_1^* represents density of infected CD4+ T cells which are in pre-INSTI class,
(3) T^* represents density of infected CD4+ T cells in which integration is completed (post-INSTI class) and they are capable of producing virus and
(4) V is virus density.

Here we discuss the dynamics of the above populations: CD4+ T cells will be produced from bone marrow and thymus with constant rate s and dies with natural death rate μ so that the population decreases by μT. We considered the interactions of T-cells and Virus populations are non linear as it is less than linear when the saturation of the virus population is high and greater than linear when the infection fraction is very small so we represent this situation with incidence rate q and having the interaction-infection rate k, kVT^q population will leave the population of T-cells and progress to pre-INSTI T-cells, T_1^*. These pre-INSTI T-cells will leave to Post-INSTI T-cells, T^* with translation rate α but due to the presence of INSTI drug of efficacy η where $0 < \eta < 1$, $\eta\alpha T_1^*$ amount of cells will reverts back to uninfected class of T, and the remaining $(1-\eta)\alpha T_1^*$ progress to class of T^*. Besides, due to incomplete process of integration of the virus bT_1^* amount revert back to uninfected T-cells[27]. Moreover the immune response of the CTLa will kill productively infected cells, T^* with rate of p, so pT^*V amount of cells will be cleared from the population. Hence we have the following model.

$$\frac{dT}{dt} = s - kVT^q - \mu T + (\eta\alpha + b)T_1^* \tag{1}$$

$$\frac{dT_1^*}{dt} = kVT^q - (\mu_1 + \alpha + b)T_1^* \tag{2}$$

$$\frac{dT^*}{dt} = (1-\eta)\alpha T_1^* - \delta T^* - pT^*V \tag{3}$$

$$\frac{dV}{dt} = N\delta T^* - cV \tag{4}$$

with $T(0) = T_0, T_1^*(0) = 0, T^*(0) = 0, V(0) = V_0$. Here μ_1 is death rate of infected cells, δ represents death rate of actively infected cells and includes the possibility of death by bursting of infected T cells, c is the clearance rate of virus and N is the total number of viral particles produced by an infected cell. p is the efficacy of the immune response in killing infected cells by CTLs.

The above system has the following two steady states.

(1) The non-infected steady state $E_1 = (\widehat{T} = \frac{s}{\mu}, 0, 0, 0)$ and
(2) The infected steady state $E_2 = (\overline{T}, \overline{T_1^*}, \overline{T^*}, \overline{V})$ with components.

$$\overline{T} = \left(\frac{(\mu_1+\alpha+b)c}{N\alpha k(1-\eta)}\right)^{\frac{1}{q}},$$
$$\overline{T_1^*} = \frac{k^2\alpha N\delta(1-\eta)}{p(\mu_1+\alpha+b)^2}\overline{T}^{2q} - \frac{k\delta}{P(\mu_1+\alpha+b)}T^q,$$
$$\overline{T^*} = -\frac{c}{2Np} + \sqrt{\frac{c^2}{4N^2P^2} + \frac{\alpha c(1-\eta)}{pN\delta}\overline{T_1^*}}$$
$$\overline{V} = \frac{N\delta}{c}\overline{T^*}.$$

Feasible existence of E_2 is ensured whenever basic reproduction number

$$R_0 = \left(\frac{s}{\mu}\right)\left[\frac{k\alpha N(1-\eta)}{c(\mu_1+\alpha+b)}\right]^{\frac{1}{q}} > 1.$$

So we find the critical value for the drug efficacy.

$$\eta_{crit} = 1 - \frac{\mu c(\mu_1+\alpha+b)}{N\alpha ks}.$$

Whenever $\eta < \eta_{crit}$ both E_1 and E_2 coexist and when $\eta > \eta_{crit}$, the infection is cleared and only uninfected steady state E_1 will exist.

Boundedness of solution: Equations (1) and (2) of the system give

$$\frac{d}{dt}(T+T_1^*) = s - \mu T - \mu_1 T_1^* - (1-\eta)\alpha T_1^* \leq s - \mu_m(T+T_1^*),$$

where $\mu_m = min(\mu, \mu_1)$. Hence $\limsup(T+T_1^*) \leq \frac{s}{\mu_m}$. Without loss of generality, we can assume that $\limsup T \leq \frac{s}{\mu_m}$ and $\limsup T_1^* \leq \frac{s}{\mu_m}$. Now using the bound for T_1^* in Eq. (3), we get the bound for T^* and using this in (4), we get the following positively invariant set

$$\Gamma = \{(T, T_1^*, T^*, V) \in \mathbb{R}^4 : 0 \leq T, T_1^* \leq \frac{s}{\mu_m}, 0 \leq T^* \leq M, 0 \leq V \leq S\}$$

with respect to the system (1) - (4), where

$$M = \frac{\alpha s(1-\eta)}{\mu_m\delta} \text{ and } S = \frac{N\alpha s(1-\eta)}{\mu_m c}.$$

3 Stability analysis

Theorem 1. *The non-infected steady state E_1 is locally stable if and only if $R_0 < 1$.*

Proof. The linearized matrix evaluated at E_1 is given as

$$\begin{bmatrix} -\mu & \eta\alpha+b & 0 & -k(\frac{s}{\mu})^q \\ 0 & -(\mu_1+\alpha+b) & 0 & k(\frac{s}{\mu})^q \\ 0 & (1-\eta)\alpha & -\delta & 0 \\ 0 & 0 & N\delta & -c \end{bmatrix}$$

and its characteristic equation is $(\lambda+\mu)(\lambda^3+A_1\lambda^2+A_2\lambda+A_3)=0$, where

$$\begin{aligned} A_1 &= \mu_1+\alpha+b+\delta+c>0, \\ A_2 &= (\mu_1+\alpha+b)(\delta+c)+c\delta>0 \text{ and} \\ A_3 &= c\delta(\mu_1+\alpha+b)-kN\delta\alpha(1-\eta)(\frac{s}{\mu})^q. \end{aligned}$$

One eigenvalue is negative, $\lambda=-\mu$, the local stability of E_1 demands all roots of $\lambda^3+A_1\lambda^2+A_2\lambda+A_3=0$ to have negative real parts. It can easily be see that $A_1A_2-A_3>0$. Moreover, $R_0<1$ gives that $A_3>0$, hence, Routh-Hurwitz criterion is satisfied. If $R_0<1$, the characteristic equation of the linearized matrix has a zero root which is simple and all other roots have negative real parts. Hence, E_1 will be locally stable for $R_0<1$.

Theorem 2. *The infected steady state E_2 whenever it exists (i.e., for $R_0>1$), is locally asymptotically stable.*

Proof. The Jacobian matrix evaluated at E_2 is given as

$$\begin{bmatrix} -qk\overline{V}\,\overline{T}^{q-1}-\mu & \eta\alpha+b & 0 & -k\overline{T}^q \\ qk\overline{V}\,\overline{T}^{q-1} & -(\mu_1+\alpha+b) & 0 & k\overline{T}^q \\ 0 & (1-\eta)\alpha & -\delta-p\overline{V} & -p\overline{T^*} \\ 0 & 0 & N\delta & -c \end{bmatrix}$$

and its characteristic equation is $\lambda^4+B_1\lambda^3+B_2\lambda^2+B_3\lambda+B_4=0$ where

$$\begin{aligned} B_1 &= \alpha+b+c+\delta+\mu+\mu_1+p\overline{V}+qk\overline{V}\overline{T}^{q-1}, \\ B_2 &= c(\delta+p\overline{V})+N\delta p\overline{T^*}+\mu_1qk\overline{V}\overline{T}^{q-1}+\alpha kq(1-\eta)\overline{V}\overline{T}^{q-1}+\mu(\mu_1+\alpha+b)+(\delta+p\overline{V}+c)(qk\overline{V}\overline{T}^{q-1}+\mu+\mu_1+\alpha+b) \\ B_3 &= (c+\delta+p\overline{V})[(\mu_1+\alpha(1-\eta))qk\overline{V}\overline{T}^{q-1}+\mu(\mu_1+\alpha+b)] \\ &\quad +c\delta(\mu+qk\overline{V}\overline{T}^{q-1})+(cp\overline{V}+N\delta P\overline{T^*})(\mu+\mu_1+\alpha+b+qk\overline{V}\overline{T}^{q-1})+c\delta(\mu_1+\alpha+b)-N\alpha k\delta(1-\eta)\overline{T}^q \\ B_4 &= (cp\overline{V}+N\delta p\overline{T^*})[\mu(\mu_1+\alpha+b)+\mu_1qk\overline{V}\overline{T}^{q-1}+\alpha k(1-\eta)q\overline{V}\overline{T}^{q-1}] \\ &\quad +(\mu+\alpha(1-\eta))c\delta qk\overline{V}\overline{T}^{q-1}+c\delta\mu(\mu_1+\alpha+b)-\mu N\alpha\delta k(1-\eta)\overline{T}^q. \end{aligned}$$

Since $R_0<1$ and $\overline{T}^q<(\frac{s}{\mu})^q$ the last two terms of B_3 and B_4

$$\begin{aligned} &c\delta(\mu_1+\alpha+b)-N\alpha k\delta(1-\eta)\overline{T}^q>0 \text{ and} \\ &c\delta\mu(\mu_1+\alpha+b)-\mu N\alpha\delta k(1-\eta)\overline{T}^q>0. \end{aligned}$$

Hence, each $B_i > 0$, for $i = 1,2,3$, and 4 as each of all the other terms are positive. Moreover, with the help of MAPLE it is easy to show

$$\Delta_1 = B_1B_2 - B_3 > 0, \Delta_2 = \Delta_1B_3 - B_1^2B_4 > 0 \text{ and } \Delta_3 = B_4\Delta_2 > 0,$$

Therefore, by the Routh Hurwitz criterion all the roots of the characteristic equation of have negative real parts.

Theorem 3. *The non-infected steady state E_1 is globally asymptotically stable if $R_0 \leq 1$.*

Proof. Define a Lyapunov function L of system (1) - (4) as follows:

$$L = \frac{\alpha(1-\eta)p}{(\mu_1+\alpha+b)}T_1^* + pT^* + \frac{p}{N}V.$$

Its derivative along a solution of system (1) - (4),

$$\frac{dL}{dt} = \left[\frac{(\alpha(1-\eta)kT^q}{(\mu_1+\alpha+b)} - pT^* - \frac{c}{N}\right]pV.$$

Then for $R_0 \leq 1$, we have

$$\left(\frac{s}{\mu}\right)\left[\frac{N\alpha k(1-\eta)}{(\mu_1+\alpha+b)c}\right]^{\frac{1}{q}} \leq 1$$

which gives

$$\left[\frac{(\alpha(1-\eta)k(\frac{s}{\mu})^q}{(\mu_1+\alpha+b)} - pT^* - \frac{c}{N}\right]pV \leq 0,$$

at E_1 we have have $T = \frac{s}{\mu}$ hence $\frac{dL}{dt} \leq 0$. Then by Lyapunov-LaSalle Theorem The non infected steady E_1 is globally asymptotically stable.

4 Numerical simulations and results

To check the validity of the model (1) - (4)and to provide an illustration for analytical results, we solve the system numerically in MATLAB using the selected parametric values shown in Table 1.

Parameter	Value	Reference
s=inflow rate of CD4+ T cells	10 mm^3day^{-1}	[28]
k=Interaction - infection Rate of T-cells	0.000024 mm^3day^{-1}	[28]
δ=Death rate of infected cells	0.26 day^{-1}	[28]
c=Clearance rate of Virus	2.4 day^{-1}	[28]
μ=Natural death rate of T cells	0.01 day^{-1}	[16]
μ_1=death Rate of Latent cells (T_1^*)	0.015 day^{-1}	[29]
η=INSTI Drug efficacy	Varying 0.6,0.7,0.8,0.9	–

Table 1: Parametric values for numerical simulation

Based on literature [19,**?**,**?**,**?**,**?**,**?**,**?**] the other parameters vary,

(1) the translation rate α of T cells to T_1^* varies between 0.3 and 0.5 and $\alpha = 0.4$ is taken for simulation
(2) the burst size of virus N varies between 100 and some thousands, we took $N = 1000$

(3) the reverting rate b of infected T_1^* cells to T-cells has different values and we took $b = 0.05$.
(4) We also consider the two infection stages: the acute infection with p varies from 0.01 to 0.04 and the chronic infection with p varies from 0.00025 to 0.001.
(5) we assumed the drug efficacy η to vary from 0.6 to 0.9.
(6) incidence rate q of Virus V and T cells to vary from 0.92 to 1.02.

For all of the simulations the initial conditions are taken to be the same as $T(0) = 300mm^{-3}, T_1^*(0) = 10mm^{-3}, T^*(0) = 10mm^{-3}$ and $V(0) = 10mm^{-3}$.

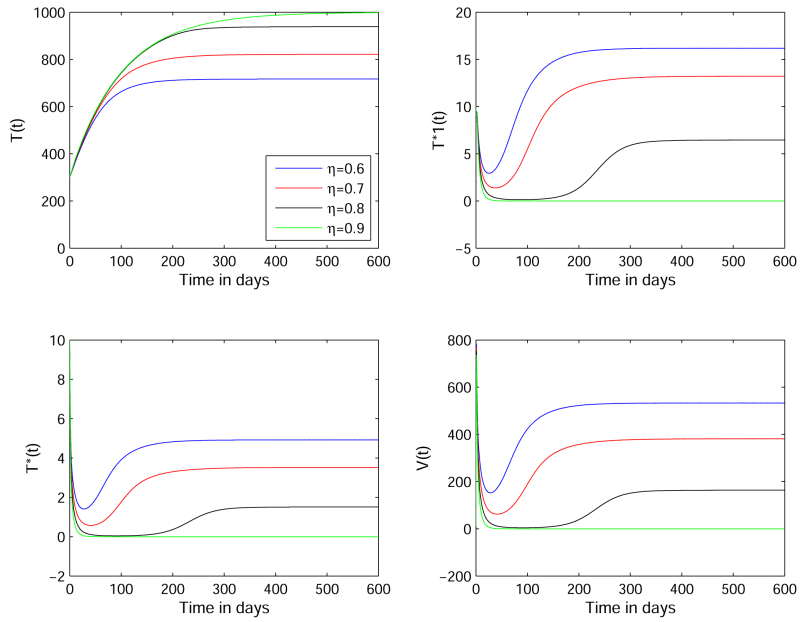

Fig. 1: Solution Trajectories of system (1) - (4) for different values of η keeping p=0.0005 and q=0.97

In Fig. 1 the numerical simulation done for INSTI inhibitor drug efficacy η varying from 0.6 to 0.9, p=0.0005, q=0.97 and the other parameters as described above. In the left top piece of Fig. 1 it is shown that the level of CD4+ T cells increases with increase in η.
The right top piece show also for η close to 0.9 the latent T_1^* cells populations drops down towards 0. It can also be seen that for $\eta = 0.6, 0.7$ and 0.8 the density of T_1^* decreases for the first few weeks and increases back in few months. The initial value $T_1^*(0) = 10mm^{-3}$ will increase to around 16, 13 and 7 resp.
In left bottom piece the infected cells density T^* will be below half mark of the initial value $T^*(0) = 10mm^{-3}$ specially for η close to 0.9 T^* closes down to 0.
In right bottom piece shows when the drug efficacy η increases towards 0.9 the system approaches to the infection free steady state and as η increases from 0.6 to 0.9 the viral level decreases and in case when $\eta = 0.9$ it approaches to zero.

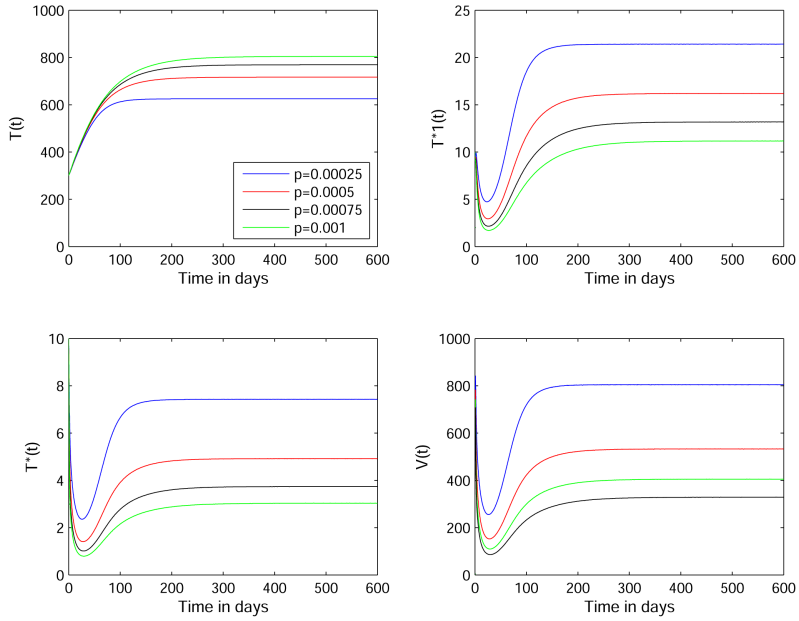

Fig. 2: Solution Trajectories of system (1) - (4) for different values of p keeping η = 0.6 and q=0.97

In Fig. 2 we simulated numerically for p = 0.00025 to 0.001 again for same set of parameters as above keeping $\eta = 0.6$ and q=0.97. It can be easily seen that increase in p results increasing in CD4+ T cells and decreasing in viral level.

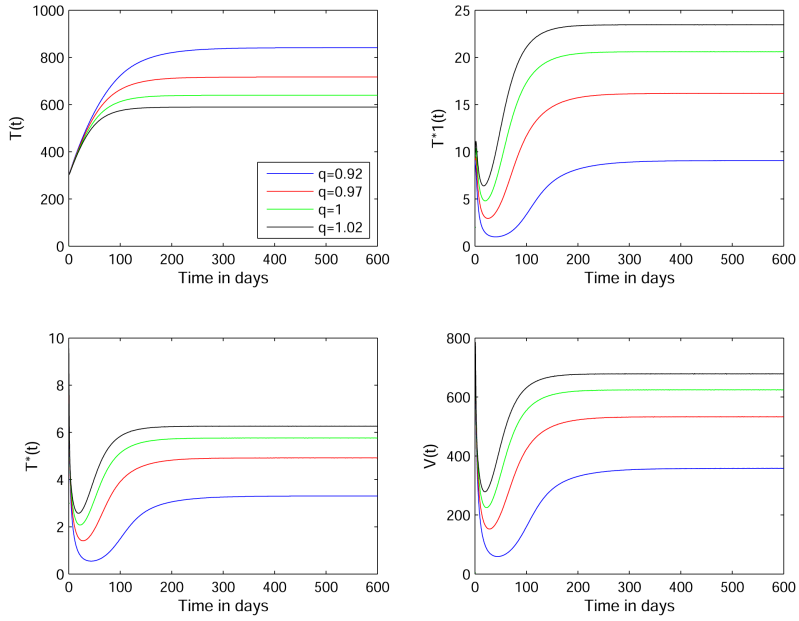

Fig. 3: Solution Trajectories of system (1) - (4) for different values of q keeping η=0.6, and p=0.0005

In Fig. 3 the simulation is done for q=0.92 to 1.02, η=0.6, and p=0.0005 with remaining parameters in 1. The figure shows that whenever q increases the CD4+ T cells decreases and the Virus density increases.

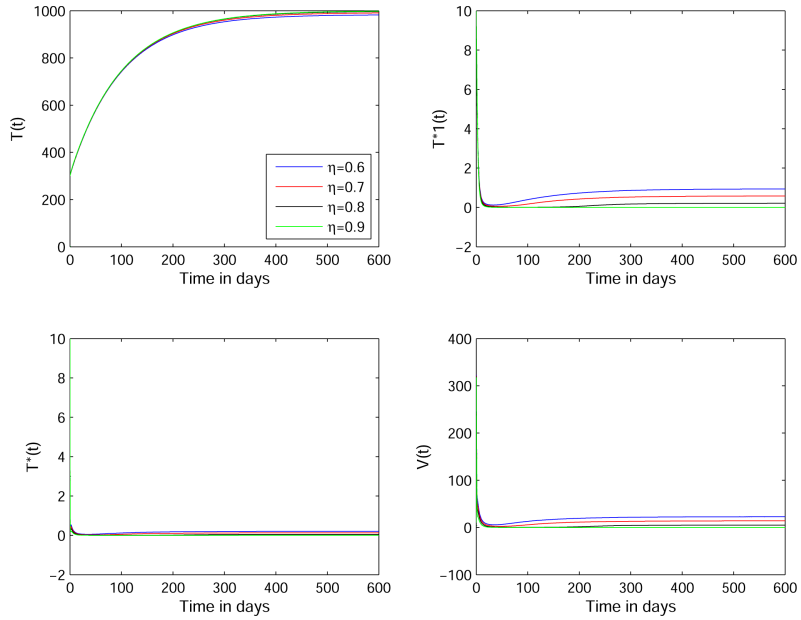

Fig. 4: Solution Trajectories of system (1) - (4) for acute infection taking different values of η keeping p=0.02 and q=0.97

In Fig. 4 the simulation of the system (1) - (4) has been done for acute infection stage taking η to vary from 0.6 to 0.9 keeping p=0.02 and q=0.97. It shows that the change in drug efficacy doesn't produce much difference.
In Fig. 5 the simulation is done for p=0.01 to 0.04 and the result indicate there is no such a big difference in both T-celss and the viral loads.

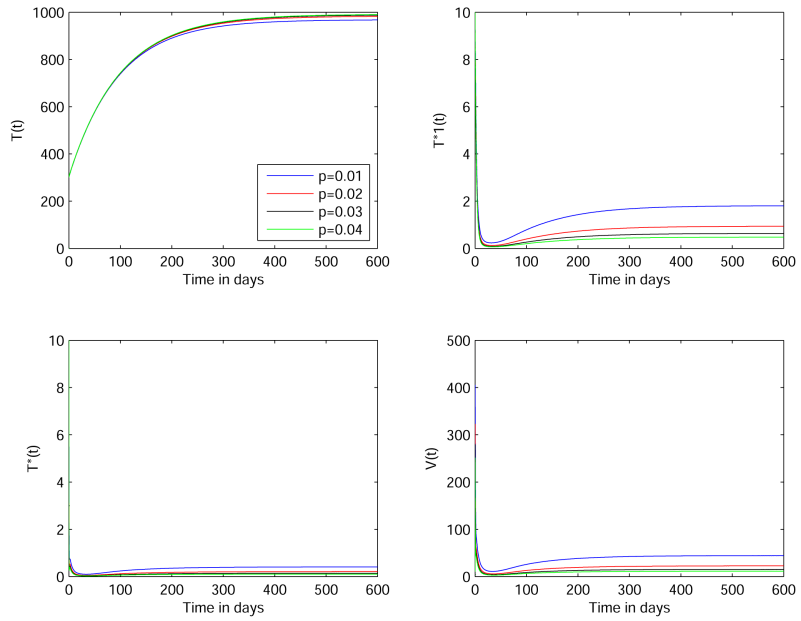

Fig. 5: Solution Trajectories of system (1) - (4) for acute infection taking different values of p keeping η=0.6 and q=0.97

5 Conclusion

In this paper we proposed a mathematical model for HIV infection in the presence of INSTI inhibitor drug. It was considered that only INST inhibitor was given. This model is different from others in literature since it considers the possibility of incidence rate of V and T, i.e q, being non-linear; the killing rate of virus producing cells by CTL; and the reverting rate of infected cells back into healthy T-cells with INSTI inhibitor administered whenever the drug efficacy is not 100%. We analyzed the stability of the equilibrium points. If the basic reproduction number $R_0 \leq 1$ is satisfied then the infection will be cleared and the non-infected steady state E_1 will be globally stable and The infected steady state E_2 is locally asymptotically stable if $R_0 > 1$. It was shown using numerical simulations that when the efficacy was increased to 90% the infection was cleared. Whenever the incidence rate q is getting lower below linear the Viral load increases and getting grater than linear the viral load decreases. It is also shown that whenever CTL killing rate increased the viral load decreases.

References

[1] UNAIDS, *Fact sheet 2014*, (2014).

[2] J. A. Gayle, R. M. Selik, S. Y. Chu, *Surveillance for aids and hiv infection among black and hispanic children and women of childbearing age, 1981-1989., MMWR. CDC surveillance summaries: Morbidity and mortality weekly report. CDC surveillance summaries*, Centers for Disease Control 39 (3) (1990) 23 - 30.

[3] R. Heaton, J. Currier, P. L. Williams, J. A. McCutchan, J. W. Wu, Robertson, et al., *Hiv suppression by haart preserves cognitive function in advanced, immune-reconstituted aids patients*, Aids 21 (9) (2007) 1109 - 1117.

[4] W.-G. Gu, *Newly approved integrase inhibitors for clinical treatment of aids* , Biomedicine and Pharmacotherapy 68 (8) (2014) 917 - 921.

[5] J.-L. Blanco, V. Varghese, S.-Y. Rhee, J. M. Gatell, R. W. Shafer, *Hiv-1 integrase inhibitor resistance and its clinical implications*, Journal of Infectious Diseases 203 (9) (2011) 1204 - 1214.

[6] Food and drug administration, *https://en.wikipedia.org/wiki/Food and Drug Administration*.

[7] E. De Clercq, *Hiv life cycle: targets for anti-hiv agents, HIV-1 Integrase*: Mechanism and Inhibitor Design (2011) 1 - 14

[8] T. Evering, M. Markowitz, *Hiv-1 integrase inhibitors*, The PRN Note book 13 (2008) 1 - 9.

[9] Y. Matsuzaki, W. Watanabe, K. Yamataka, M. Sato, S. Enya, Kano et al., *JTK-303/GS 9137, a novel small-molecule inhibitor of HIV-1 integrase: anti-HIV activity profile and pharmacokinetics in animals*, (2006).

[10] B. M. Shah, J. J. Schafer, J. A. DeSimone, *Dolutegravir: a new integrase strand transfer inhibitor for the treatment of HIV*, Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 34 (5), 506 - 520, (2014)

[11] D. Daelemans, R. Lu, E. De Clercq, A. Engelman, *Characterization of a replication-competent, integrase-defective human immunodeficiency virus (HIV)/simian virus 40 chimera as a powerful tool for the discovery and validation of HIV integrase inhibitors*, Journal of virology, 81(8), 4381 - 4385, (2007)

[12] M. Markowitz, J. O. Morales-Ramirez, B. Y. Nguyen, C. M. Kovacs, R. T. Steigbigel, Cooper, et al., *Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals*, JAIDS Journal of Acquired Immune Deficiency Syndromes, 43(5), 509 - 515, (2006).

[13] E. DeJesus, D. Berger, M. Markowitz, C. Cohen, T. Hawkins, Ruane, et al., *Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-naive and treatment-experienced patients*, JAIDS Journal of Acquired Immune Deficiency Syndromes, 43(1), 1 - 5, (2006).

[14] B. Grinsztejn, B.-Y Nguyen, C. Katlama, J. M. Gatell, A. Lazzarin, Vittecoq, et al., *Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial*, The Lancet, 369(9569), 1261 - 1269, (2007).

[15] L. Rong, M. A. Gilchrist, Z. Feng, A. S. Perelson, *Modeling within-host HIV-1 dynamics and the evolution of drug resistance: trade-offs between viral enzyme function and drug susceptibility*, Journal of Theoretical biology, 247(4), 804 - 818, (2007).

[16] H. Mohri, S. Bonhoeffer, S. Monard, A. S. Perelson, D. D. Ho, *Rapid turnover of T lymphocytes in SIV-infected rhesus macaques*, Science, 279(5354), 1223 - 1227, (1998).

[17] H. Mohri, A. S. Perelson, K. Tung, R. M. Ribeiro, B. Ramratnam, Markowitz, et al., *Increased turnover of T lymphocytes in HIV-1 infection and its reduction by antiretroviral therapy*, The Journal of experimental medicine, 194(9), 1277 - 1288, (2001).

[18] R. M. Ribeiro, H. Mohri, D. D. Ho, A. S. Perelson, *In vivo dynamics of T cell activation, proliferation, and death in HIV-1 infection: why are CD4+ but not CD8+ T cells depleted?*, Proceedings of the National Academy of Sciences, 99(24), 15572 - 15577, (2002).

[19] A. S. Perelson, A. U. Neumann, M. Markowitz, J. M. Leonard, D. D. Ho, *HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time*, Science, 271(5255), 1582 - 1586, (1996).

[20] B. Ramratnam, S. Bonhoeffer, J. Binley, A. Hurley, L. Zhang, Mittler, et al., *Rapid production and clearance of HIV-1 and hepatitis C virus assessed by large volume plasma apheresis*, The Lancet, 354(9192), 1782 - 1785, (1999).

[21] H. Y. Chen, M. Di Mascio, A. S. Perelson, D. D. Ho, L. Zhang, *Determination of virus burst size in vivo using a single-cycle SIV in rhesus macaques*, Proceedings of the National Academy of Sciences, 104(48), 19079 - 19084, (2007).

[22] A. T. Haase, K. Henry, M. Zupancic, G. Sedgewick, R. A. Faust, Melroe, et al., *Quantitative image analysis of HIV-1 infection in lymphoid tissue*, Science, 274(5289), 985 - 989, (1996).

[23] M. Nowak, R. M. May, *Virus dynamics: mathematical principles of immunology and virology: mathematical principles of immunology and virology*, Oxford university press, (2000).

[24] X. Wang, X. Song, *Global stability and periodic solution of a model for HIV infection of CD4¡ sup¿+¡/sup¿ T cells*, Applied Mathematics and Computation, 189(2), 1331 - 1340, (2007).

[25] A. S. Perelson, *Modelling viral and immune system dynamics*, Nature Reviews Immunology, 2(1), 28 - 36, (2002).

[26] Y. Wang, D. Huang, S. Zhang, H. Liu, *Dynamic behavior in a HIV infection model for the delayed immune response*, Biomedical Engineering and Informatics (BMEI), 2011 4th International Conference on, 4, 1834 - 1838, (2011).

[27] J. A. Zack, S. J. Arrigo, S. R. Weitsman, A. S. Go, A. Haislip, I. S. Chen, *HIV-1 entry into quiescent primary lymphocytes: molecular analysis reveals a labile, latent viral structure*, Cell, 61(2), 213 - 222, (1990).

[28] A. S. Perelson, D. E. Kirschner, R. De Boer, *Dynamics of HIV infection of CD4+ T cells*, Mathematical biosciences, 114(1), 81 - 125, (1993).

[29] P. Srivastava, M. Banerjee, P. Chandra, *Modeling the drug therapy for HIV infection*, Journal of Biological Systems, 17(02), 213 - 223, (2009).

[30] P. Essunger, A. S. Perelson, *Modeling HIV infection of CD4+ T-cell subpopulations*, Journal of theoretical biology, 170(4), 367 - 391, (1994).

[31] M. Elemans, A. Florins, L. Willems, B. Asquith, *Rates of ctl killing in persistent viral infection in vivo*, PLoS computational biology, 10(4), (2014)