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DYNAMIC ANALYSIS OF MOTHER-TO-CHILD TRANSMISSION OF HIV AND ANTIRETROVIRAL TREATMENT AS OPTIMAL CONTROL

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Abstract. Human immunodeficiency virus (HIV) is still an extremely dangerous pandemic and without a prominent cure. And one of the most vulnerable population prone to acquiring the virus can be newborn babies from their HIV positive mothers. It can even turn fatal when an individual gets acquired immunodeficiency syndrome (AIDS) and the disease is left untreated and uncontrolled. One such treatment for suppressing the infections is antiretroviral therapy (ART) treatment. To gain insight of the Indian scenario of the mother to child transmission (MTCT) and the present work of the ARTs strategy in India we shall study a model for HIV infected newborns. Hence, we have formulated a model consisting of newborns born to HIV infected mothers, infected newborns and newborns acquiring AIDS. We have found the equilibrium points and established the local stability of the system. We then considered ARTS as optimal control for the HIV infected newborns and thus, extended our model with the class of newborns going for ARTS. With the help of Pontryagin's Maximum Principle, we then obtain the optimal ART intensity as part of intervention to control infection among newborns for our optimal control problem. For the numerical simulations we took real time data of India for all parameters along with MTCT rate for the state of Maharashtra. One of our numerical results shows that ART's as strategy among newborns born to HIV infected

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mothers decreases the number of HIV infected babies. Thus, the paper highlights the necessary and crucial role of ART programs for babies born to HIV positive mothers in order to suppress the infection for their brighter futures in the epidemic dynamics of India.

Keywords: HIV; newborns; dynamic analysis; optimal control; antiretroviral treatment.

2010 AMS Subject Classification: 92D05, 92D25, 92D40, 49J15.

1. INTRODUCTION

Human immunodeficiency virus(HIV) is a variation of a virus that can lead to AIDS(Acquired immunodeficiency syndrome) where this particular variation of the virus is believed to have been transmitted from the African chimpanzees to humans by consumption of animal meat [1]. The emergence of the disease can be dated back to the 1900's and spreading from countries to continents. Even in recent times, millions of individuals have been infected with HIV. HIV has now become pandemic disease which has caused millions of deaths through the transmission of the virus which can take place through certain body fluids and is facilitated through unprotected sexual intercourse, use of infected needles/syringes, or even vertically i.e from infected mother to child. And there are also large instances of vertical transmissions to her new-born from pregnant woman which can happen during pregnancy in utero, during labour and delivery or even through breast feeding during postpartum. The transmission of infection to newborn babies is solely transmitted from infected mothers. Majorly about seventy five percent of transmission of infection occurs at the time of labour and delivery and about thirty percent of HIV transmission may occur in the late stage of pregnancy [2]. India has the third largest HIV infected population of about 2.39 million(approximately) living in India [3]. Of this estimate around 145,000 children in India of age less than fifteen years of are infected by HIV/AIDS [4]. Children too account for a proportion of HIV infection in India which is indicative of a troublesome future of our nation if correct actions are not taken.

In India during 2002 parent to child transmission interventions were initiated which included free admittance for each enrolled women with pregnancy for HIV diagnosis in nearby clinics, availability of Nevirapine for pregnant women who were infected with HIV at the time of labour and subsequently for their children as well instantly during birth. Later NACO for pregnant women adopted the WHO recommendations 'Option B' in India and changed the

strattefgy from the a dose of Nevirapine to multi-antiretroviral drug prophylaxis strategy. Then in 2013 NACO started to implement a more efficient "Option B+" with the intention to improve the health of pregnant women and simultaneously check vertical HIV transmission providing lifelong antiretroviral therapy (ART) treatment to each HIV infected woman and children.

ARTs as a strategy aims to avoid vertical HIV transmission and other added HIV prevention benefits for newborns and for enabling early infant diagnosis through retention of mother and baby in postpartum care of HIV [5]. With the prevalence of mother to child transmission (MTCT) to newborns in India there is a need to understand the dynamic of the HIV system. There is still poor knowledge of HIV/AIDS among the pregnant women for them and their newborns. This little knowledge on maternal care or HIV newborn care may be due to insufficient awareness campaigns or even it being a social taboo. ART's as a constant and efficient regime for HIV exposed newborns may be lagging due to lower acceptance among parents. More studies and research about ART's for HIV babies can hep understand the dynamic of the transmission and give positive results to motivate the HIV community and responsible stakeholders. Some help can be derived from available published evidence to comprehend the a system of newborns born to HIV infected mothers. Due to the emerging chronic nature of HIV, the course of illness is longer and may also show some stability. Thus, the primary healthcare settings within the chronic disease management model as part of HIV interventions should be re-conceptualised. As the infant will grow up, the duration and dosage of ART's will also alter with time depending on various factors.

Mathematical modelling is an application to formulate an interaction between mathematics and the physical real world system . Through this formulated expression, one can analyse the system and get a model behaviour. These models can help in understanding the system through the theoretic and numerical analysis. One can use certain value for the parameter in the model to get an insight on the future system behavior. The most recent development in mathematical modelling in the field of biology or epidemic can be seen in [6, 7, 8]. Models on HIV have been studied till now with various parameters to understand the dynamics of the disease [9, 10]. HIV models have been extended to add more parameters (biological and demographical) for

our varied and growing population. Studies go as far as 1990's on HIV with mathematical modelling. In 1997, Kirschner [11] gave a model of Combined Drug Therapy of HIV Infection. In regard to the MTCT cases, in [12] dynamic characteristics have been explored of the HIV MTCT epidemic in China. Mathematical analysis of a vertical transmission model consisting of a non-linear term which depends on the parents for children has been studied in [13]. An HIV-AIDS model has been formulated for vertical transmission with the incorporation of time delay of the period of adolescent maturity of infected newborns in [14]. In [15] a HIV/AIDS transmission epidemic model is proposed which is subjected to Pre-exposure prophylaxis (PrEP) as control consisting of antiretroviral medication and the systems dynamical analysis has also been shown. But analysis on prevention of transmission of infection in newborns born to HIV infected mother is scarce specifically in context of India. *Thus, we shall propose a model consisting of newborns/babies born to HIV infected mothers population along with ART's regime as early intervention and aim to discuss its local stability analysis as well as optimal control policy. For infants with in utero or intrapartum HIV infection, our study addresses the optimal intensity of initiation of antiretroviral therapy as a control for the Indian state of Maharashtra.*

1.1. Structure of our Study. We shall propose an HIV epidemic SIA(susceptible-infected-AIDS) model of newborn population exposed to HIV due to HIV positive mothers in Section 2. We have then in the same section extended our model by incorporating ART's as a control with the addition of another E(population going for ART's) compartment i.e SIAE model. Then we will proceed with the general analysis of our system though local stability analysis in Section 3. In Section 4 using Pontryagin's maximum principle [16], we will formulate an optimal control problem and discuss it. In Section 5 through numerical simulation using real time data of India we will aim to show the working of the system of the SIA model. Then we will perform numerical simulation of the optimal control to get proper understanding of mechanism of our SIAE system for India in the presence of the control and progression of infection among newborns.

2. Model Formulation

Two models have been proposed, Model 1 (SIA Model) without control and Model 2(SIAE) with control inspired from [13, 15, 12]. The assumptions for the model are as following:

- The recruitment rate is coming from newborns born to HIV positive mothers.
- As a newborn infected in AIDS stage do not have enough ability to meet other people in daily activity, they cannot transmit the disease.
- The infection process $\alpha\beta S$ in newborns is caused due to HIV infected mothers.
- The susceptible population are going for ART's due to exposure of HIV from their respective mothers and enter the treatment class E.

To define the model, the following notations are adopted throughout this paper:

Notations:

$S(t)$	:	Number of susceptible newborns at time t,
$I(t)$	:	Number of HIV infected newborns at time t but still have not been vaccinated,
$A(t)$	:	Number of infected individuals who have acquired AIDS,
$E(t)$	:	Number of newborns receiving treatment,
α	:	Proportion of HIV positive mothers,
μ	:	Death rate,
ξ	:	Growth rate,
p	:	fraction of individuals going for treatment,
γ	:	rate at which individuals acquire AIDS,
β	:	Mother to child transmission rate

2.1. Model 1: SIA model. We have formulated a model described by the following dynamical equations:

$$\frac{dS}{dt} = \xi - \alpha\beta S - \mu S \tag{1}$$

$$\frac{dI}{dt} = \alpha\beta S - \gamma I - \mu I \tag{2}$$

$$\frac{dA}{dt} = \gamma I - \mu A \tag{3}$$

Where, $\beta\alpha S$ term represents the transmission of infection in the newborns due to HIV positive mothers; γI indicates the HIV positive newborns acquiring AIDS; Note that $S(t)+I(t)+A(t) = M = \frac{\xi}{\mu}$.

2.2. Model 2: SIAE model(with control).

$$\frac{dS}{dt} = \xi - (1-p)\alpha\beta S - pu(t)S - \mu S \tag{4}$$

$$\frac{dI}{dt} = (1-p)\alpha\beta S - \gamma I - \mu I \tag{5}$$

$$\frac{dA}{dt} = \gamma I - \mu A \tag{6}$$

$$\frac{dE}{dt} = pu(t)S - \mu E \tag{7}$$

where E are the population of infected individuals going for ART.

3. General Analysis

We shall be discussing the stability analysis of the system in the upcoming subsections which would involve the existence of equilibrium points and local stability analysis for our SIA model, proceeded by the optimal control problem for SIAE model.

3.1. Equilibrium points. The disease free point for our system (1-3) is given by $E^0 = (\frac{\psi}{\alpha\beta+\mu}, 0, 0)$. The equilibrium for our system (1-3) is given by $E^* = (S^*, I^*, A^*)$ given by

$$S^* = \frac{\psi}{\alpha\beta+\mu}$$

$$I^* = \frac{\psi\alpha\beta}{(\alpha\beta+\mu)(\gamma+\mu)}$$

$$A^* = \frac{\gamma\psi\alpha\beta}{(\alpha\beta+\mu)(\gamma+\mu)\mu}$$

3.2. Local Stability Analysis. The jacobian corresponding to system with respect to E^* is as follows:

$$J = \begin{bmatrix} -(\alpha\beta+\mu) & 0 & 0 \\ \alpha\beta & -(\mu+\gamma) & 0 \\ 0 & \gamma & -\mu \end{bmatrix}$$

The characteristic equation at E^* is :

$$(\lambda+(\alpha\beta+\mu))(\lambda+(\mu+\gamma))(\lambda+\mu)=0$$

And we get $\lambda_1 = -(\alpha\beta+\mu)$, $\lambda_2 = -(\mu+\gamma)$ and $\lambda_3 = -\mu$. Since $\lambda_1, \lambda_2, \lambda_3 < 0$ then the system at E^* is locally asymptotically stable .

4. Optimal Control Antiretroviral Treatment Policy

We shall consider that a responsible stakeholders and parents need to provide for ART's for newborns as a efficient regime to decrease the number of infected individuals. The objective involves the minimising the number of infected individuals and also minimizing the total treatment costs. This type of treatments are costly specially in a developing country and we assume a quadratic promotional cost function [17, 18, 19, 20]:

$$C(u) = \frac{a}{2}u^2(t) \tag{8}$$

Suppose that the planning horizon is not very larges, we do not discount the future. The objective of the responsible stakeholders is :

- minimize the HIV infected newborn population
- minimize the costs incurred through antiretroviral treatment.

For our system of Eqns. (4)- (7), the objective function is :

$$maxJ = -\int_0^T \left(\dot{I}(t) + \frac{a}{2}u^2(t)\right)dt \tag{9}$$

where $a \geq 0$ is a constant value and denotes the magnitude of the treatment effort rates; $u(t) \geq 0$ is the promotional effort rate used by government. For our study, a simple and reasonable example of the treatment effort cost function is provided by quadratic form with the assumption that $C(u)$ is twice continuously differentiable function of u such that $C_u > 0, C_u u > 0, C(0) = 0$.

4.1. Maximum principle. The Hamiltonian is :

$$H = -\left(\dot{I}(t) + \frac{a}{2}u^2(t)\right) + \lambda_1\left(\xi - (1-p)\alpha\beta S - pu(t)S - \mu S\right) + \lambda_2\left((1-p)\alpha\beta S - \gamma I - \mu I\right) + \lambda_3\left(\gamma I - \mu A\right) + \lambda_4\left(pu(t)S - \mu E\right) \tag{10}$$

The optimal control

$$u^*(t) = \frac{1}{a}\big((\lambda_4 - \lambda_1)pS\big) \tag{11}$$

The adjoint variables $\lambda_1, \lambda_2, \lambda_3$ and λ_4 are described in the following differential equation:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S}, \quad \lambda_1(T) = 0 \tag{12}$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial I}, \quad \lambda_2(T) = 0 \tag{13}$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial A}, \quad \lambda_3(T) = 0 \tag{14}$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial E}, \quad \lambda_4(T) = 0 \tag{15}$$

The solution of 12- 15 are:
$\lambda_1 = -e^{(\alpha\beta(1-p)+\mu)t + \int_T^t \left\{\alpha\beta(1-p)(2-e^{-(\gamma\, mu)(T-\tau)})e^{-((\alpha\beta(1-p)+\mu)\tau - pU^*)}\right\}d\tau}$ where $U^*(t) = \int u^* dt$, $\lambda_2(t) = e^{(\gamma+\mu)(T-t)} - 1$, $\lambda_3(t) = 0$ and $\lambda_4(t) = 0$. Now, we get the optimal control:

$$u^*(t) = \frac{-\lambda_1}{a}pS = \frac{pS}{a}\left\{e^{(\alpha\beta(1-p)+\mu)t + pU^*}\int_T^t \left\{\alpha\beta(1-p)(2-e^{-(\gamma\, mu)(T-\tau)})e^{-((\alpha\beta(1-p)+\mu)\tau - pU^*)}\right\}\right\}.$$

5. Numerical Simulations

The section will deal with the numerical simulation of our epidemic model in order to examine the dynamics for newborns as well as the impact of ART's on transmission and controlling of HIV infection. We shall use MATLAB for our proposed models (SIA and SIAE) to numerically solve the system and the simulations are performed for a set of real data for India. We

have also chosen four states of India for our study and the parameters selection detail is given in the subsequent section.

5.1. Parameter Selection.

- $\alpha = 0.000733$: It is estimated that out of about thirty million annual pregnancies in India by National AIDS Control Organization (NACO), more than 22,000 pregnant women are infected by HIV [21].
- For β we have state wise rates:

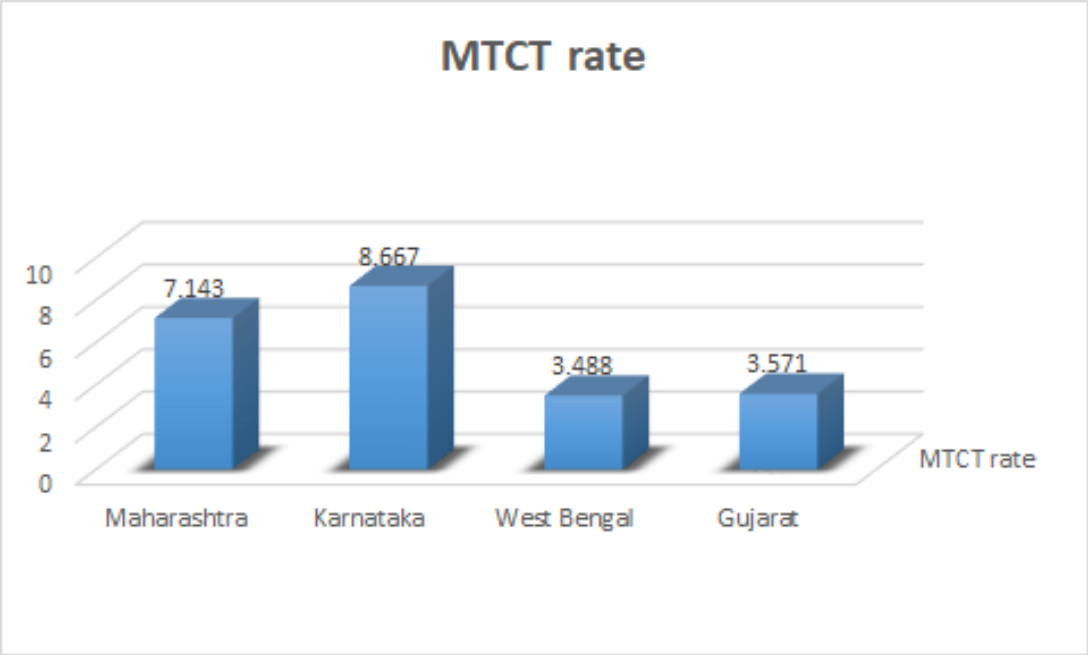


FIGURE 1. Statewise MTCT rate: Gujarat: $\beta = 3.571$ [22], Maharashtra: $\beta = 7.143$ [23], Karnataka: $\beta = 8.667$ [24] and West Bengal: $\beta = 3.488$ [25].

We shall be going forward with the rate of Maharashtra.

- $\mu = 0.006$ In [12] For age population of babies and young adolescents the natural mortality rate of children taken is six deaths per thousand per year in China. (rate for India was unavailable. As India is population wise and geographically closest to China hence we referred to rate of China)
- $\xi = 1537$: 1537 pairs of mothers and new births have been taken in [21] where the mothers are HIV positive. Thus, we shall assume the number of babies born to HIV positive mothers to be at least 1537.

- $\gamma = 0.17$: Among the HIV-infected children, the cumulative probabilities of developing AIDS is 0.17 [26].

Parameters	Values/Units	Source
ξ	1537	[21]
α	0.000733	[21]
μ	0.006	[12]
β	3.488-8.66	[21]
γ	0.17	[26]
p	0.1	assumed
a	1000	assumed

TABLE 1. Parameters and Values for the model

5.2. Results and Plots.

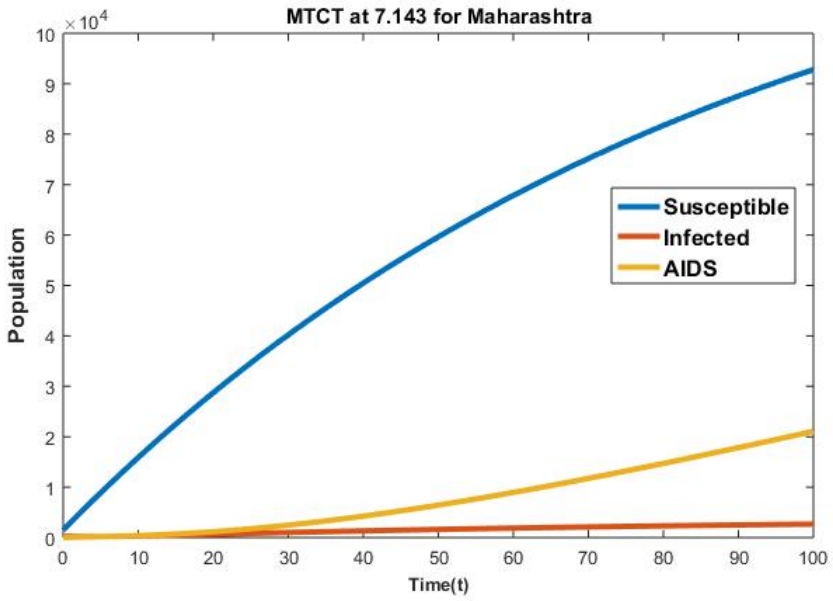
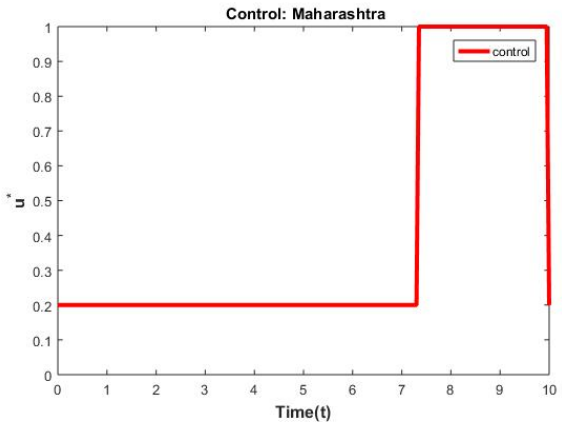


FIGURE 2. Behaviour of system w.r.t MCMT rate for Maharashtra

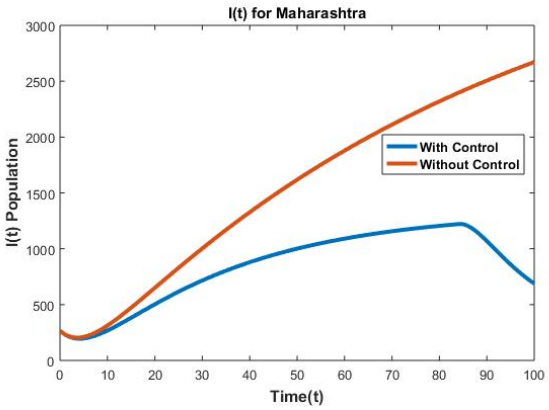
5.2.1. *Without control system.*

In Fig 2 we can see the behaviour of SIA individuals with a variation of MTCT rate for the state of Maharatshtra as seen in Fig 2. We get the following equilibrium point for our system using the parametric values in Table 1:

$E^*(92808.57, 2671.726, 21073.8)$ for Maharashtra.



(A) Maharashtra: Control Intensity



(B) Maharashtra: $I(t)$ infected population variations

5.2.2. *System with Control.* Efficiency of strategies using different type drugs and the durations of treatment for HIV newborn population is still being explored. There is very low-quality evidence of the use of antiretroviral regimens, its behaviour and its duration for HIV related babies [26]. Even the dosage of the antiretroviral drug is a matter for discussion for babies even as they grow up into toddlers or young adolescents. Thus, we proceed with the numerical simulation of the optimal control i.e SIAE model where we shall consider the values from Table 1 where $T = 100$ for the system dynamics as below: We have considered the MTCT rate of Maharashtra for the state's population behaviour when subjected to ART's system dynamics subject to the optimal control at $E^* = (19958.4, 688.7, 11263.9, 84783.9)$. The extremal behaviour of $u(t)$ for Maharashtra is shown in Fig 3a. The intensity of the control is initiated from 0.2 at the time of start of ART's program for the newborns in the system. Control is initially started from minimal effort with newborns. The intensity then approaches maximum efforts i.e towards 1. As mentioned before, as the infant grows up, the duration and dosage of ART's will also alter with time depending on various factors. The factors can be age, viral load or CD4 cells count.

The control then starts to dip back to minimal intensity which can be possible in case ART-associated immune reconstitution has occurred for a newborn and to minimise costs incurred for the treatments. In Fig 3b we can see that due to the control efforts, the infected individuals have reduced to 688.7 from 2671.726 of the non control system for the state of Maharashtra. Early intervention through ART's would be beneficial as it can delay the time of increased use of drugs on newborns, minimise use of ART's in the long run or even halt continuous use of antiretroviral therapy for some time. Early HIV diagnosis and subsequent early antiretroviral therapy reduces early infant mortality and HIV progression. This way AIDS class reduces and they start to advance into the treatment (E) class of newborns.

6. CONCLUSION

In this paper we have presented mathematical analysis of the role of early ART's intervention as control to decrease infection in the epidemic system of newborns. We found the equilibrium points of the SIA model and then proceeded to show local stability analysis. Later we extended our system to a SIAE model which considered an optimal control treatment strategy for minimising infected people and minimising treatment costs. Subject to this we have found a unique optimal value of ART's strategy rate. One of the differences in the prevalence of HIV among newborns through MTCT may be due to the differences in the sociodemographic and economic profiles of life among the states of India. Thus, we went forward with our numerical simulations using some real data of India and MTCT rate for the state of Maharashtra. We carried out the numerical simulations for SIA model to investigate how HIV is spreading among newborns born to HIV infected mothers. Then, we got the disease-behavior dynamics of the SIAE model and saw that the dynamics improved idealy with the impact of ART's. The numerical simulation of the optimal control showed that the ART's as a necessary regime can suppress the infection in the HIV system for newborns as infected individuals decreased phenomenally as seen in case Maharashtra. Prevention and treatment strategies, starting with availability of anti-retroviral drugs and coverage for health care system for all HIV positive pregnant and their children should be top priority for responsible stakeholders and parents. Thus, the public should also be motivated through positive awareness campaigns for HIV positive parents to inspire them to have health-seeking nature for a healthy lifestyle of their children. This way

parents will ardently follow the ART's regime for both the mother and newborns which will help keep a check of the viral load and suppress infection in the system.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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