Section A-Research paper
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HIV-CM (cryptococcal meningitis) co-infection and control in immunocompromised individuals

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Abstract

Immunological deficiency syndromes are illnesses or disorders where one or more immune system components have been lost or are defective. Specific infections and cancers are more prone to develop in patients with certain syndromes. Infection with the human immunodeficiency virus (HIV) most frequently increases the risk of developing Cryptococcal Meningitis (CM), which raises the mortality rate. Globally, there are thought to be 1,52,000 instances of Cryptococcal Meningitis among HIV/AIDS patients each year, which results in roughly 1,12,000 fatalities. The prevalence of cryptococcal infection has mainly remained constant in low- and middle-income countries despite the widespread use of antiretroviral therapy (ART), according to the Centres for Disease Control and Prevention (CDC). In this article, a nonlinear SIR mathematical model for co-infection of HIV and cryptococcal meningitis in immunocompromised individuals is formulated. The basic reproduction number ($\mathcal{R}_0$) is calculated at disease free equilibrium point (E_0) by next gen matrix method. Disease-free and disease exist co-infection of HIV and cryptococcal meningitis model equilibria are found. Stability of co-infection of HIV and cryptococcal meningitis is discussed. The optimal control parameters u_1 represent the anti-fungal medicine treatment, u_2 represent CD4 testing (patients who have low CD4 levels) in HIV infected individuals, u_3 represent the screening for cryptococcal meningitis in HIV infected individuals, The control on treatment of cryptococcal meningitis infected individuals is u_4 and the control on treatment of cryptococcal meningitis in co-infected individuals is u_5. The HIV-CM model data is validated with Numerical simulation and ends with the conclusion.

Keywords: *Mathematical modeling, HIV, Cryptococcal meningitis (CM), Optimal Control*

1. Introduction

The human immunodeficiency virus (HIV) is a sexually transmitted virus that attacks the immune system of the body, causing acquired immunodeficiency syndrome (AIDS), which was first exposed in 1981[1]. Around the globe, there were over 38.4 million individuals living with HIV as of 2021, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS). In 2021, 1.5 million new HIV infections and 650,000 deaths related to HIV were predicted to have occurred globally [2,3].

Especially, HIV attracts on CD4+T cells. When HIV kills these cells, the body is less able to fight off other infections, and people are more likely to get infectious diseases like TB, HCV, and Covid-19 [1,4-6,19,20]. Cryptococcal infections are a dangerous opportunistic infection and a leading source of morbidity and mortality in persons with advanced HIV illness [2,7].

On every part of the planet, there is the fungus Cryptococcus neoformans. In most cases, people can breathe this fungus a few times in their lives without getting sick. However, if the immune system is compromised, as it is in individuals with HIV, the fungus can remain dormant in the body and later develop a severe brain illness known as cryptococcal meningitis. Each year, there are over 152,000 new cases of cryptococcal meningitis worldwide, which leads to an estimated 112,000 fatalities [8-10].

The majority of HIV-related diseases and fatalities occur in nations with low resources. Many HIV patients' immune systems have been boosted by access to antiretroviral therapy (ART), reducing their chance of developing cryptococcal meningitis. Cryptococcal meningitis persists as a serious threat in areas with a high HIV incidence and poor availability of medical care [8,9].

Cryptococcal antigen is a biological marker which indicates a person has cryptococcal infection, can be detected in the body weeks before symptoms of meningitis appear. It is important to conduct a cryptococcal antigen test on people with advanced HIV infection [11]. Antifungal medications are available for patients who test positive for cryptococcal antigen to aid the body in fighting the early stages of the infection. According to research, patient's risk of contracting cryptococcal meningitis is lower when this combination of strategies is used. Meningitis can be treated with antifungal medication, and it can also be avoided in healthy people [8].

The shortage of a licensed vaccine for cryptococcal meningitis underlines its risk, and mathematical models are essential for explaining the spread of infectious illness like HIV and meningitis. [12-16,25]. In this paper a new model with optimal control on prevention, screening, testing and treatment of cryptococcal meningitis disease is investigated [17,18,21,22]. To choose the best control, we use Pontryagin's maximum principle [23,24]. Results show that effective control significantly reduces cryptococcal meningitis infection.

The document is structured as follows: section 2 describes a formulation of mathematical model with system of ordinary differential equations, schematic diagram with control measures, and the population flow between the compartments. In section 3, equilibrium

solution, basic reproduction number, and stability analysis at disease free equilibrium point is carried out. In Section 4, the concept of optimal control theory for maximize the treatment for each phase is discussed and applied to the model. To see how control strategies affect the model, the model is numerically simulated in section 5.

2. Formulation of mathematical model

Mathematical modelling is used in this proposed work to create a dynamical system of non-linear differential equations that describes the behavior of the transmission of various infectious diseases both independently and collectively. Our co-infected model will be based on HIV-infected and uninfected individuals with cryptococcal meningitis (CM). There are five distinct subpopulations within the entire population (N(t)) at time t are susceptible population(S), Individuals with advanced HIV infection (HIV-infected individuals in an advanced stage) (I_H), those who have contracted cryptococcal meningitis (I_C), An individual who is affected by both HIV and cryptococcal meningitis (I_{HC}), Individual recovered from CM infection from co-infected or CM infected community (R). In this model, the susceptible class is characterized as immunocompromised.

New individuals enter susceptible class with β rate. Susceptible individuals who have contracted HIV and are transitioning toward class (I_H) by β_1 rate. Individuals with impaired immune systems are more susceptible to develop cryptococcal meningitis (CM). So, susceptible individuals are supposed to infected with CM and join the class (I_C) by β_2 rate. It is assumed that, the HIV infected individuals can also be infected with CM and join the class (I_{HC}) with β_3 rate and CM infected individual can also be infected with HIV by β_4 rate and join the class (I_{HC}). Co-infected individuals (I_{HC}) can recovered from CM infection and join the recovered class (R) by β_5 rate. Similarly, Individuals from class I_C can recovered from CM infection and join the recovered class (R) by β_6 rate. By losing the temporary immunity, recovered individuals (R) can move to again susceptible class (S) by β_7 rate. μ is considered as a natural death rate for all five classes. The death rate μ_H, μ_C and μ_{HC} are considered as a death rate due to HIV/AIDS, CM and HIV/AIDS-CM, respectively.

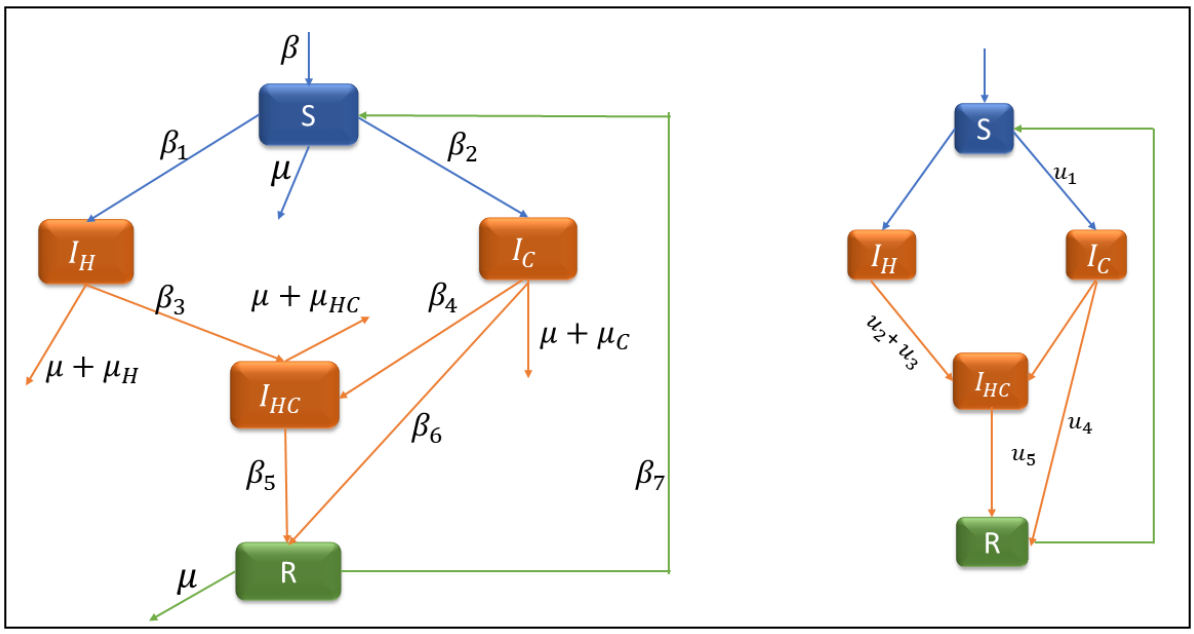


Figure 1. Schematic diagram of HIV-CM model with control measures

With the above information, we derive the system of five ordinary differential equations for HIV-CM coinfection with control measures.

$$\frac{dS}{dt} = \beta - \beta_1 S I_H - \beta_2 S I_C + \beta_7 R - (u_1 + \mu)S$$

$$\frac{dI_H}{dt} = \beta_1 S I_H - \beta_3 I_{HC} - (\mu + \mu_H + u_2 - u_3) I_H$$

$$\frac{dI_C}{dt} = \beta_2 S I_C - \beta_4 I_{HC} - (\beta_6 + \mu + \mu_C + u_4) I_C + u_1 S \qquad (1)$$

$$\frac{dI_{HC}}{dt} = (\beta_3 + \beta_4 - \beta_5 - u_5 - \mu - \mu_{HC}) I_{HC} + (u_2 - u_3) I_H$$

$$\frac{dR}{dt} = (\beta_5 + u_5) I_{HC} + (\beta_6 + u_4) I_C - (\beta_7 + \mu) R$$

where $N(t) = S(t) + I_H(t) + I_C(t) + I_{HC}(t) + R(t)$.

The above system satisfies the conditions $S(t) \geq 0, I_H(t) \geq 0, I_C(t) \geq 0, I_{HC}(t) \geq 0, R(t) \geq 0$

Combining the sets of differential equations, we get,

$$\frac{d(N(t))}{dt} \leq \beta - \mu N \Rightarrow \lim_{t \to \infty} Sup\ N \leq \frac{\beta}{\mu}$$

The Feasible region of the system is $A = \left\{(S + I_H + I_C + I_{HC} + R): 0 \leq S + I_H + I_C + I_{HC} + R \leq \frac{\beta}{\mu}\right\}$

3. Equilibrium solutions:

Equating $\frac{dS}{dt} = \frac{dI_H}{dt} = \frac{dI_C}{dt} = \frac{dI_{HC}}{dt} = \frac{dR}{dt} = 0$, following are the equilibrium solutions for the compartments.

Disease free equilibrium point (DFE)

By setting equation (1) equal to 0 and putting $I_H = I_C = I_{HC} = R = 0$ we obtain the disease-free equilibrium point

$$E_0 = \left(\frac{\beta}{\mu}, 0, 0, 0, 0\right)$$

$$S_0 = \frac{\beta}{\mu}$$

$$I_{H_0} = 0$$

$$I_{C_0} = 0$$

$$I_{HC_0} = 0$$

$$R_0 = 0$$

Disease Exist equilibrium (DEE) E_*

By solving all the ordinary differential equations from (1), we get the following disease exist equilibrium points:

1. $EC_1\left(S_1, I_{H_1}, I_{C_1}, I_{HC_1}, R_1\right)$

$$S_1 = \frac{\beta}{\mu} + \frac{0.5(\mu u_4+\mu^2+\beta_6\mu+\beta_7\mu+\beta_7\mu_C+\mu\mu_C)(\beta_6\mu^3+\mu^3u_4+(\beta_6+u_4)\sqrt{p_1}+\beta_6^2\mu^2+p_2)}{\mu(u_4+\beta_6)(p_3)}$$

$$I_{H_1} = 0$$

$$I_{C_1} = \frac{-0.5(\beta_7+\mu)(\beta_6\mu^3+\mu^3u_4+(\beta_6+u_4)\sqrt{p_1}+\beta_6^2\mu^2+p_2)}{(\beta_6+u_4)(p_3)}$$

$$I_{HC_1} = 0$$

$$R_1 = \frac{-0.5(\beta_6\mu^3+\mu^3u_4+(\beta_6+u_4)\sqrt{p_1}+\beta_6^2\mu^2+p_2)}{(p_3)}$$

2. $EC_2\left(S_2, I_{H_2}, I_{C_2}, I_{HC_2}, R_2\right)$

$$S_2 = \frac{\beta}{\mu} + \frac{0.5(\mu u_4+\mu^2+\beta_6\mu+\beta_7\mu+\beta_7\mu_C+\mu\mu_C)(\beta_6\mu^3+\mu^3u_4-(\beta_6+u_4)\sqrt{p_1}+\beta_6^2\mu^2+p_2)}{\mu(\beta_6+u_4)(p_3)}$$

$$I_{H_2} = 0$$

$$I_{C_2} = \frac{-0.5(\beta_7+\mu)(\beta_6\mu^3+\mu^3u_4-(\beta_6+u_4)\sqrt{p_1}+\beta_6^2\mu^2+p_2)}{(\beta_6+u_4)(p_3)}$$

$I_{HC_2} = 0$

$R_2 = \frac{-0.5\left(\beta_6\mu^3+\mu^3u_4-(\beta_6+u_4)\sqrt{p_1}+\beta_6^2\mu^2+p_2\right)}{(p_3)}$

where, $p_1 = \beta^2\beta_2^2\beta_7^2 + 2\beta^2\beta_2^2\beta_7\mu + \beta^2\beta_2^2\mu^2 - 2\beta\beta_2\beta_6\beta_7^2\mu - 4\beta\beta_2\beta_6\beta_7\mu^2 + 2\beta\beta_2\beta_6\beta_7\mu u_1 - 2\beta\beta_2\beta_6\mu^3 + 2\beta\beta_2\beta_6\mu^2u_1 - 2\beta\beta_2\beta_7^2\mu^2 - 2\beta\beta_2\beta_7^2\mu\mu_C + 2\beta\beta_2\beta_7^2\mu u_1 - 2\beta\beta_2\beta_7^2\mu u_4 + 2\beta\beta_2\beta_7^2\mu_C u_1 - 4\beta\beta_2\beta_7\mu^3 - 4\beta\beta_2\beta_7\mu^2\mu_C + 4\beta\beta_2\beta_7\mu^2u_1 - 4\beta\beta_2\beta_7\mu^2u_4 + 4\beta\beta_2\beta_7\mu\mu_C u_1 + 2\beta\beta_2\beta_7\mu u_1u_4 - 2\beta\beta_2\mu^4 - 2\beta\beta_2\mu^3\mu_C + 2\beta\beta_2\mu^3u_1 - 2\beta\beta_2\mu^3u_4 + 2\beta\beta_2\mu^2\mu_C u_1 + 2\beta\beta_2\mu^2u_1u_4 + \beta_6^2\beta_7^2\mu^2 + 2\beta_6^2\beta_7\mu^3 + 2\beta_6^2\beta_7\mu^2u_1 + \beta_6^2\mu^4 + 2\beta_6^2\mu^3u_1 + \beta_6^2\mu^2u_1^2 + 2\beta_6\beta_7^2\mu^3 + 2\beta_6\beta_7^2\mu^2\mu_C + 2\beta_6\beta_7^2\mu^2u_1 + 2\beta_6\beta_7^2\mu^2u_4 + 2\beta_6\beta_7^2\mu\mu_C u_1 + 4\beta_6\beta_7\mu^4 + 4\beta_6\beta_7\mu^3\mu_C + 6\beta_6\beta_7\mu^3u_1 + 4\beta_6\beta_7\mu^3u_4 + 6\beta_6\beta_7\mu^2\mu_C u_1 + 2\beta_6\beta_7\mu^2u_1^2 + 4\beta_6\beta_7\mu^2u_1u_4 + 2\beta_6\beta_7\mu\mu_C u_1^2 + 2\beta_6\mu^5 + 2\beta_6\mu^4\mu_C + 4\beta_6\mu^4u_1 + 2\beta_6\mu^4u_4 + 4\beta_6\mu^3\mu_C u_1 + 2\beta_6\mu^3u_1^2 + 4\beta_6\mu^3u_1u_4 + 2\beta_6\mu^2\mu_C u_1^2 + 2\beta_6\mu^2u_1^2u_4 + \beta_7^2\mu^4 + 2\beta_7^2\mu^3\mu_C + 2\beta_7^2\mu^3u_1 + 2\beta_7^2\mu^3u_4 + \beta_7^2\mu^2\mu_C^2 + 4\beta_7^2\mu^2\mu_C u_1 + 2\beta_7^2\mu^2\mu_C u_4 + \beta_7^2\mu^2u_1^2 + 2\beta_7^2\mu^2u_1u_4 + \beta_7^2\mu^2u_4^2 + 2\beta_7^2\mu\mu_C^2u_1 + 2\beta_7^2\mu\mu_C u_1^2 + 2\beta_7^2\mu\mu_C u_1u_4 + \beta_7^2\mu_C^2u_1^2 + 2\beta_7\mu^5 + 4\beta_7\mu^4\mu_C + 4\beta_7\mu^4u_1 + 4\beta_7\mu^4u_4 + 2\beta_7\mu^3\mu_C^2 + 8\beta_7\mu^3\mu_C u_1 + 4\beta_7\mu^3\mu_C u_4 + 2\beta_7\mu^3u_1^2 + 6\beta_7\mu^3u_1u_4 + 2\beta_7\mu^3u_4^2 + 4\beta_7\mu^2\mu_C^2u_1 + 4\beta_7\mu^2\mu_C u_1^2 + 6\beta_7\mu^2\mu_C u_1u_4 + 2\beta_7\mu^2u_1^2u_4 + 2\beta_7\mu^2u_1u_4^2 + 2\beta_7\mu\mu_C^2u_1^2 + 2\beta_7\mu\mu_C u_1^2u_4 + \mu^6 + 2\mu^5\mu_C + 2\mu^5u_1 + 2\mu^5u_4 + \mu^4\mu_C^2 + 4\mu^4\mu_C u_1 + 2\mu^4\mu_C u_4 + \mu^4u_1^2 + 4\mu^4u_1u_4 + \mu^4u_4^2 + 2\mu^3\mu_C^2u_1 + 2\mu^3\mu_C u_1^2 + 4\mu^3\mu_C u_1u_4 + 2\mu^3u_1^2u_4 + 2\mu^3u_1u_4^2 + \mu^2\mu_C^2u_1^2 + 2\mu^2\mu_C u_1^2u_4 + \mu^2u_1^2u_4^2$

$p_2 = \mu^2u_4^2 + \beta_6\beta_7\mu^2 + \beta_6^2\beta_7\mu + \beta_6\mu^2\mu_C + \beta_6\mu^2u_1 + \beta_6^2\mu u_1 + 2\beta_6\mu^2u_4 + \beta_7\mu u_4^2 + \beta_7\mu^2u_4 + \mu^2\mu_C u_4 + \mu u_1u_4^2 + \mu^2u_1u_4 - \beta\beta_2\beta_6\beta_7 - \beta\beta_2\beta_6\mu + \beta_6\beta_7\mu\mu_C - \beta\beta_2\beta_7u_4 - \beta\beta_2\mu u_4 + \beta_6\beta_7\mu u_1 + 2\beta_6\beta_7\mu u_4 + \beta_6\beta_7\mu_C u_1 + \beta_6\mu\mu_C u_1 + \beta_7\mu\mu_C u_4 + 2\beta_6\mu u_1u_4 + \beta_7\mu u_1u_4 + \beta_7\mu_C u_1u_4 + \mu\mu_C u_1u_4$

$p_3 = \beta_2\mu^3 + \beta_2\beta_6\mu^2 + 2\beta_2\beta_7\mu^2 + \beta_2\beta_7^2\mu + \beta_2\beta_7^2\mu_C + \beta_2\mu^2\mu_C + \beta_2\mu^2u_4 + \beta_2\beta_6\beta_7\mu + 2\beta_2\beta_7\mu\mu_C + \beta_2\beta_7\mu u_4$

3.1 Basic reproduction number

The basic reproduction number ($\mathcal{R}_0$) is obtained using the next-generation matrix approach [22]. We have,

$$\boldsymbol{F} = \begin{bmatrix} -\beta_1 I_H - \beta_2 I_C & -\beta_1 S & -\beta_2 S & 0 & 0 \\ \beta_1 I_H & \beta_1 S & 0 & 0 & 0 \\ \beta_2 I_C & 0 & \beta_2 S & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\boldsymbol{V} = \begin{bmatrix} \mu + u_1 & 0 & 0 & 0 & -\beta_7 \\ 0 & (u_2 - u_3 + \mu + \mu_H) & 0 & \beta_3 & 0 \\ 0 & 0 & (u_4 + \beta_6 + \mu + \mu_C) & \beta_4 & 0 \\ 0 & -(u_2 - u_3) & 0 & -\beta_3 - \beta_4 + \beta_5 + u_5 + \mu + \mu_{HC} & 0 \\ 0 & 0 & -(\beta_6 + u_4) & -(\beta_5 + u_5) & (\beta_7 + \mu) \end{bmatrix}$$

$$\boldsymbol{FV^{-1}}(E_0) =$$

$$\begin{bmatrix} \frac{-\beta\beta_2 u_1(\beta_7+\mu)}{\mu d_1} & \frac{\beta\beta_2 n_1}{d_2} - \frac{\beta\beta_1 n_2}{\mu d_3} & \frac{-\beta\beta_2(u_1+\mu)(\beta_7+\mu)}{\mu d_1} & \frac{\beta\beta_2 n_3}{d_2} + \frac{\beta\beta_1\beta_3}{\mu d_3} & \frac{-\beta\beta_2\beta_7 u_1}{\mu d_1} \\ 0 & \frac{\beta\beta_1 n_2}{\mu d_3} & 0 & \frac{-\beta\beta_1\beta_3}{\mu d_3} & 0 \\ \frac{\beta\beta_2 u_1(\beta_7+\mu)}{\mu d_1} & \frac{-\beta\beta_2 n_1}{d_2} & \frac{\beta\beta_2(u_1+\mu)(\beta_7+\mu)}{\mu d_1} & \frac{-\beta\beta_2 n_3}{d_2} & \frac{\beta\beta_2\beta_7 u_1}{\mu d_1} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

where, $p = (-\beta_4 + \beta_5 + u_5 + \mu + \mu_{HC})[(u_2 - u_3) + (\mu + \mu_H)] - \beta_3(\mu + \mu_H)$

$n_1 = (u_2 - u_3)\big(\beta_4(\mu + \beta_7)(\mu + u_1) - \beta_7 u_1(\beta_5 + u_5)\big)$

$n_2 = (-\beta_3 - \beta_4 + \beta_5 + \mu + \mu_{HC} + u_5)$

$n_3 = n_1 + \beta_4\mu^2(u_1 + \beta_7 + \mu + \mu_H) + \beta_4\mu\mu_H(u_1 + \beta_7) + u_1\beta_7(\mu + \mu_H)(\beta_4 - \beta_5 - u_5)$

$d_1 = \mu^2(\beta_6 + \beta_7 + \mu + \mu_C + u_1 + u_4) + \mu\big((\beta_7 + u_1)(\beta_6 + \mu_C + u_4) + \beta_7 u_1\big) + \beta_7\mu_C u_1$

$d_2 = \mu\{\mu^4[(\beta_5 - \beta_3 - \beta_4) + (\beta_6 + \beta_7 + \mu_H + \mu_C + u_4) + (u_2 - u_3) + \mu_{HC} + u_1 + u_5 + \mu] + \mu^3[(\beta_5 - \beta_3 - \beta_4)(\beta_6 + \beta_7 + \mu_H + \mu_C + u_4 + u_1) + (u_2 - u_3)(-\beta_4 + \beta_5 + \beta_6 + \beta_7 + \mu_C + \mu_{HC} + u_1 + u_4 + u_5) + (\beta_6 + \beta_7 + \mu_C)(\mu_H + \mu_{HC} + u_1 + u_5) + (\beta_6 + \mu_C)\beta_7 + (\mu_H + u_1)\mu_{HC} + (u_1 + u_4 + u_5)\mu_H + (\beta_7 + \mu_{HC} + u_5)u_4] + \mu^2\big[u_1\big((\beta_5 - \beta_3 - \beta_4 + u_5)(\beta_6 + \beta_7 + \mu_C + \mu_H + u_4) + (u_2 - u_3)(-\beta_4 + \beta_5 + \beta_6 + \beta_7 + \mu_C + \mu_{HC} + u_4 + u_5) + (\mu_H + \mu_{HC})(\beta_6 + \beta_7 + \mu_C + u_4) + \beta_7\mu_C + \mu_H\mu_{HC}\big) + (\beta_5 - \beta_3 - \beta_4)\big((\beta_6 + \mu_C)\beta_7 + (\beta_6 + \beta_7 + \mu_C)\mu_H\big) + (u_2 - u_3)\big((\beta_6 + \beta_7 + \mu_C + u_4)u_5 + (-\beta_4 + \beta_5 + \beta_7 + \mu_{HC})u_4\big) + \beta_7(\beta_6 + \mu_C)(\mu_H + \mu_{HC}) + \mu_H\mu_{HC}(\beta_6 + \beta_7 + \mu_C) + u_4u_5(\beta_7 + \mu_H)\big] + \mu\big[(u_2 - u_3)\big((u_1(\beta_6 + \beta_7) + \beta_7(\beta_6 + \mu_C) + \beta_7u_4 + (\mu_C + u_4)u_1\big)(-\beta_4 + \beta_5 + \mu_{HC} + u_5) + \mu_C\beta_7u_1\big) + (\beta_5 - \beta_3 - \beta_4)\big(\mu_H(\beta_7 + u_1)(\beta_6 + \mu_C + u_4) + \beta_7u_1(\mu_C + \mu_H)\big) + \mu_H(\mu_{HC} + u_5)\big(u_1(\beta_6 + \beta_7) + \beta_7(\beta_6 + \mu_C)\big) + \beta_7\mu_Cu_1(\mu_H + \mu_{HC}) + 2\mu_Hu_4u_5(\beta_7 + u_1)\big] + \big[\beta_7\mu_Cu_1(u_2 - u_3)(-\beta_4 + \beta_5 + \mu_{HC} + u_5) + \mu_C\mu_Hu_1\big(u_5(\beta_7 + \mu) + \beta_7(\beta_5 - \beta_3 - \beta_4)\big) + \beta_7\mu_H\mu_{HC}(\mu u_4 + \mu_Cu_1)\big]\}$

$d_3 = n_2(u_2 - u_3 + \mu + \mu_H) + (u_2 - u_3)\beta_3$

The spectral radius of $\boldsymbol{FV^{-1}}$ at E_0 is $\mathcal{R}_0 = \frac{\beta\beta_1(-\beta_3-\beta_4+\beta_5+u_5+\mu+\mu_{HC})}{\mu n_2(u_2-u_3+\mu+\mu_H)+(u_2-u_3)\beta_3}$

where, n_2 is as above.

3.2 Stability at disease free equilibrium point E_0

Jacobian matrix of the system at disease free equilibrium point (E_0) is given below.

$$\boldsymbol{J}(E_0) =$$

$$\begin{bmatrix} -(\mu+u_1) & \frac{-\beta\beta_1}{\mu} & -\frac{\beta\beta_2}{\mu} & 0 & \beta_7 \\ 0 & -\left(\mu+\mu_H+u_2-u_3-\frac{\beta\beta_1}{\mu}\right) & 0 & -\beta_3 & 0 \\ u_1 & 0 & -\left(\beta_6+u_4+\mu+\mu_{HC}-\frac{\beta\beta_2}{\mu}\right) & -\beta_4 & 0 \\ 0 & (u_2-u_3) & 0 & -n_2 & 0 \\ 0 & 0 & \beta_6+u_4 & \beta_5+u_5 & -(\beta_7+\mu) \end{bmatrix}$$

With the parametric values given in the Tables 1, $\text{trace}(\mathbf{J}) < 0$ and $\det(\mathbf{J}) > 0$, if $\mathcal{R}_0 < 1$.

Hence the disease-free equilibrium point is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

4. Optimal Control

For HIV- Cryptococcal Meningitis (CM) co-infection, optimal control model is formulated. In this section, we apply Pontryagin's Maximum Principle [21] to determine the necessary conditions for the optimal control of the HIV- Cryptococcal Meningitis (CM) co-infection.

The control u_1 represent the efforts on preventing cryptococcal meningitis by giving antifungal medicine. The control u_2 represent CD4 testing (patients who have low CD4 levels and are most at risk for developing cryptococcal meningitis must also be identified using CD4 testing) in HIV infected individuals and u_3 represent the screening for cryptococcal meningitis in HIV infected individuals. The control on treatment of cryptococcal meningitis in cryptococcal meningitis infected community is u_4 and the control on treatment of cryptococcal meningitis infected individuals in co-infected community is u_5.

By implementing control or therapy in each phase, the goal of this research of control theory is to shield people from the co-infection. For the necessary condition, the objective functional is,

$$\Im(u_1,u_2,u_3,u_4,u_5)$$

$$= \int_0^T \left(\alpha_1 S^2 + \alpha_2 (I_H)^2 + \alpha_3 (I_C)^2 + \alpha_4 (I_{HC})^2 + \alpha_5 R^2 + \sigma_1 u_1^2 + \sigma_2 u_2^2 + \sigma_3 u_3^2 + \sigma_4 u_4^2 + \sigma_5 u_5^2\right) dt$$

The control functions considering the functional as, $u_1, u_2, u_3, u_4,$ and u_5 are bounded, Lebesgue integrable functions. In order, to minimize disease spread using weights constants $\alpha_i > 0$, for $i = 1,2 \ldots 5$. Also, to minimize the prevention, treatment and screening in a way that spread of infection can be controlled by choosing weights $\sigma_i > 0$ for $i = 1, 2 \ldots 5$.

We look for the best optimal control $u_1^*, u_2^*, u_3^*, u_4^*,$ and u_5^* such that

$$\Im(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*) = \min\{\Im(u_1, u_2, u_3, u_4, u_5 | u_1, u_2, u_3, u_4, u_5 \epsilon \mathcal{T})\}$$

where, $\mathcal{T} = \{u_1, u_2, u_3, u_4, u_5 / u_i(t) \text{is piecevise continuous on} [0, T]\}$ is the control set with $0 < a_i \leq u_i \leq b_i < 1, i = 1,2 \ldots 5.$

It is necessary to generate the ad-joint variable for the optimal control problem offered by using Lagrangian methods for a problem along with Hamiltonian.

Introducing the Lagrangian to derive the optimality conditions,

$$\mathcal{L}(x(t), u(t), \rho) = \alpha_1 S^2 + \alpha_2 (I_H)^2 + \alpha_3 (I_C)^2 + \alpha_4 (I_{HC})^2 + \alpha_5 R^2 + \sigma_1 u_1^2 + \sigma_2 u_2^2 + \sigma_3 u_3^2 + \sigma_4 u_4^2 + \sigma_5 u_5^2$$

To obtain the minimal value of the Lagrangian, defining the Hamiltonian H for the control problem as,

$$\mathrm{H}(x(t), u(t), \rho) =$$

$$\alpha_1 S^2 + \alpha_2 (I_H)^2 + \alpha_3 (I_C)^2 + \alpha_4 (I_{HC})^2 + \alpha_5 R^2 + \sigma_1 u_1^2 + \sigma_2 u_2^2 + \sigma_3 u_3^2 + \sigma_4 u_4^2 + \sigma_5 u_5^2$$

$$+\rho_S[\beta - \beta_1 S I_H - \beta_2 S I_C + \beta_7 R - (u_1 + \mu) S]$$

$$+\rho_{I_H}[\beta_1 S I_H - \beta_3 I_{HC} - (\mu + \mu_H + u_2 - u_3) I_H]$$

$$+\rho_{I_C}[\beta_2 S I_C - \beta_4 I_{HC} - (\beta_6 + \mu + \mu_C + u_4) I_C + u_1 S]$$

$$+\rho_{I_{HC}}[(\beta_3 + \beta_4 - \beta_5 - u_5 - \mu - \mu_{HC}) I_{HC} + (u_2 - u_3) I_H]$$

$$+\rho_R[(\beta_5 + u_5) I_{HC} + (\beta_6 + u_4) I_C - (\beta_7 + \mu) R]$$

where, $\rho_S, \rho_{I_H}, \rho_{I_C}, \rho_{I_{HC}}, \rho_R$ are the adjoint variables or co-state variables and $x = (S, I_H, I_C, I_{HC}, R)$. By considering the proper partial derivatives of the Hamiltonian with respect to the related state variable, the system of equations is discovered.

Theorem: The necessary condition for $\Im(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$ to be optimal control with associated state $x = (S, I_H, I_C, I_{HC}, R)$ variables is that there exist adjoint variables $\rho_S, \rho_{I_H}, \rho_{I_C}, \rho_{I_{HC}}, \rho_R$ satisfies $\frac{d\rho_i}{dt} = -\frac{\partial \mathrm{H}}{\partial i}$ where, $i = S, I_H, I_C, I_{HC}, R$ and with transversality conditions

$$\rho_S(T) = \rho_{I_H}(T) = \rho_{I_C}(T) = \rho_{I_{HC}}(T) = \rho_R(T) = 0$$

And the optimal controls can be given by

$$u_1^*(t) = \min\left\{1, max\left(0, \frac{(\rho_S - \rho_{I_C}) S}{2\sigma_1}\right)\right\}$$

$$u_2^*(t) = \min\left\{1, max\left(0, \frac{(\rho_{I_H} - \rho_{I_{HC}}) I_H}{2\sigma_2}\right)\right\}$$

$$u_3^*(t) = \min\left\{1, max\left(0, \frac{(\rho_{I_{HC}} - \rho_{I_H})I_H}{2\sigma_3}\right)\right\}$$

$$u_4^*(t) = \min\left\{1, max\left(0, \frac{(\rho_{I_C} - \rho_R)I_C}{2\sigma_4}\right)\right\}$$

$$u_5^*(t) = \min\left\{1, max\left(0, \frac{(\rho_{I_{HC}} - \rho_R)I_{HC}}{2\sigma_5}\right)\right\}$$

Proof: The adjoint equations can be written as

$$\dot{\rho_S} = -\frac{\partial \mathrm{H}}{\partial S} = -2\alpha_1 S + (\rho_S - \rho_{I_H})\beta_1 I_H + (\rho_S - \rho_{I_C})(\beta_2 I_C + u_1) + \mu\rho_S$$

$$\dot{\rho_{I_H}} = -\frac{\partial \mathrm{H}}{\partial I_H} = -2\alpha_2 I_H + (\rho_S - \rho_{I_H})\beta_1 S + (\rho_{I_H} - \rho_{I_{HC}})(u_2 - u_3) + (\mu + \mu_H)\rho_{I_H}$$

$$\dot{\rho_{I_C}} = -\frac{\partial \mathrm{H}}{\partial I_C} = -2\alpha_3 I_C + (\rho_S - \rho_{I_C})\beta_2 S + (\rho_{I_C} - \rho_R)(u_4 + \beta_6) + (\mu + \mu_C)\rho_{I_C}$$

$$\dot{\rho_{I_{HC}}} = -\frac{\partial \mathrm{H}}{\partial I_{HC}} = -2\alpha_4 I_{HC} + (\rho_{I_H} - \rho_{I_{HC}})\beta_3 + (\rho_{I_C} - \rho_{I_{HC}})\beta_4 + (\rho_{I_{HC}} - \rho_R)(u_5 + \beta_5) + (\mu + \mu_{HC})\rho_{I_{HC}}$$

$$\dot{\rho_R} = -\frac{\partial \mathrm{H}}{\partial R} = -2\alpha_5 R + (\rho_R - \rho_S)\beta_7 + \mu\rho_R$$

Solving for $u_1^*, u_2^*, u_3^*, u_4^*,$ and u_5^* subject to the constraints, the optimality conditions can be derived as

$$0 = \frac{\partial H}{\partial u_1} = 2\sigma_1 u_1 + \left(\rho_{I_C} - \rho_S\right) S$$

$$0 = \frac{\partial H}{\partial u_2} = 2\sigma_2 u_2 + \left(\rho_{I_{HC}} - \rho_{I_H}\right) I_H$$

$$0 = \frac{\partial H}{\partial u_3} = 2\sigma_3 u_3 + \left(\rho_{I_H} - \rho_{I_{HC}}\right) I_H$$

$$0 = \frac{\partial H}{\partial u_4} = 2\sigma_4 u_4 + \left(\rho_R - \rho_{I_C}\right) I_C$$

$$0 = \frac{\partial H}{\partial u_5} = 2\sigma_5 u_5 + \left(\rho_R - \rho_{I_{HC}}\right) I_{HC}$$

By solving optimality conditions for optimal control gives,

$$u_1^*(t) = \frac{(\rho_S - \rho_{I_C})S}{2\sigma_1}$$

$$u_2^*(t) = \frac{(\rho_{I_H} - \rho_{I_{HC}})I_H}{2\sigma_2}$$

$$u_3^*(t) = \frac{(\rho_{I_{HC}} - \rho_{I_H})I_H}{2\sigma_3}$$

$$u_4^*(t) = \frac{(\rho_{I_C} - \rho_R)I_C}{2\sigma_4}$$

$$u_5^*(t) = \frac{(\rho_{I_{HC}} - \rho_R)I_{HC}}{2\sigma_5}$$

By standard control arguments involving the bounds on the controls, we conclude

$$u_i^* = \begin{cases} 0, & \text{if } \gamma_i^* \le 0 \\ \gamma_i^*, & \text{if } 0 < \gamma_i^* < 1 \\ 1, & \text{if } \gamma_i^* \ge 1 \end{cases} \quad \text{for , } i = 1,2 \ldots 5 \text{ and where,}$$

$$\gamma_1^* = \frac{(\rho_S - \rho_{I_C})S}{2\sigma_1}$$

$$\gamma_2^* = \frac{(\rho_{I_H} - \rho_{I_{HC}})I_H}{2\sigma_2}$$

$$\gamma_3^* = \frac{(\rho_{I_{HC}} - \rho_{I_H})I_H}{2\sigma_3}$$

$$\gamma_4^* = \frac{(\rho_{I_C} - \rho_R)I_C}{2\sigma_4}$$

$$\gamma_5^* = \frac{(\rho_{I_{HC}} - \rho_R)I_{HC}}{2\sigma_5}$$

Table1. Description of the parametric values used in the model

Parameters	Description	Value	Reference
$N(t)$	Number of individuals at any instant of times	100	Assumed
β	Birth rate	1	Assumed
β_1	Rate at which individuals infected with HIV	0.76	Assumed
β_2	Rate at which individuals infected with CM	0.071	Assumed
β_3	CM progression rate in HIV infected community	0.1466	Calculated
β_4	HIV progression rate in CM infected community	0.05	Assumed
β_5	Recovery rate of CM from co-infection community	0.089	Assumed
β_6	Recovery rate of CM from CM infected community	0.72	Assumed
β_7	Rate at which recovered individuals become susceptible by losing temporary immunity.	0.10	Assumed
μ	Natural death rate	0.0136	Calculated

			[4]
μ_H	Death rate due to HIV	0.15	[1]
μ_C	Death rate due to CM	0.12	Assumed
μ_{HC}	Death rate due to co-infection	0.8227	Calculated

The next section simulates a numerical interpretation of optimal control theory.

5. Numerical Simulation

The co-infection model for HIV-cryptococcal meningitis (CM) is numerically simulated in this section. We have used the MATLAB R2021a for examined the impact of various parameters on the spread as well as prevent the cryptococcal meningitis and co-infection of HIV and cryptococcal meningitis. For simulation, parametric data from Table 1. are utilized. To replicate over problem, we use ode45 in MATLAB, it is a Runge-Kutta (4,5) nonstiff one step solver.

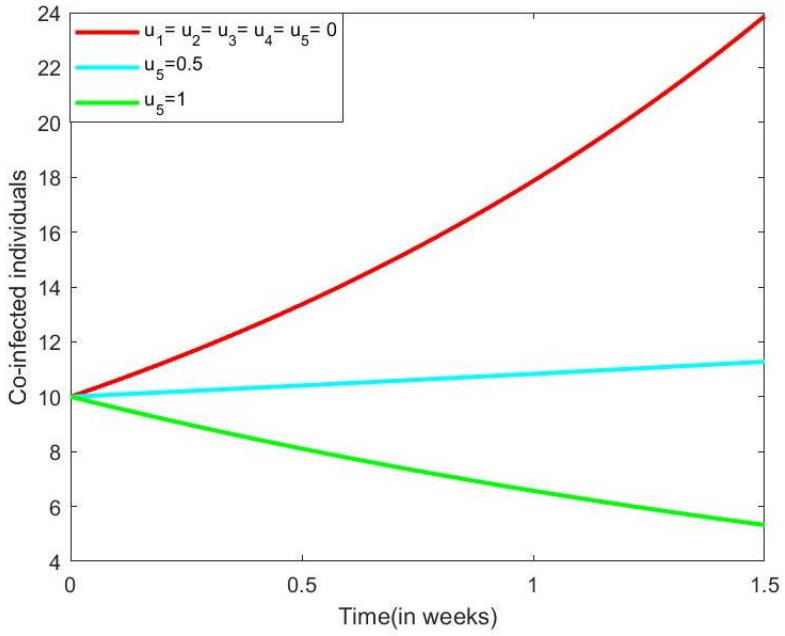


Figure 2(a): Simulation of the HIV-CM model showing the effect of treatment only on I_{HC} compartment

It is observed that the spread of co-infection can be controlled up to a certain level by applying 50% treatment control strategi for cryptococcal meningitis infection in a co-infection community. Furthermore, by increasing the treatment to 100%, the infection can be further reduced in the co-infection community.

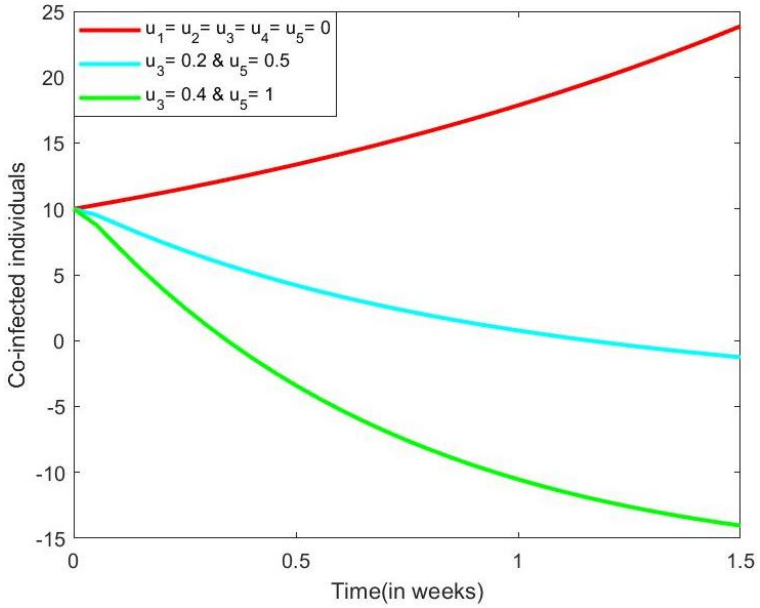


Figure 2(b): Simulation of the HIV-CM model showing the effect of CM screening and treatment only on I_{HC} compartment

It can be seen from the plot that by applying screening and treatment measures simultaneously for CM infection, co-infection can be decreasing, and individuals can be recovered from cryptococcal meningitis infection. It has been deduced that by strategically increasing both the amount of treatment and the implementation of screening measures, co-infection can be controlled up to a certain level.

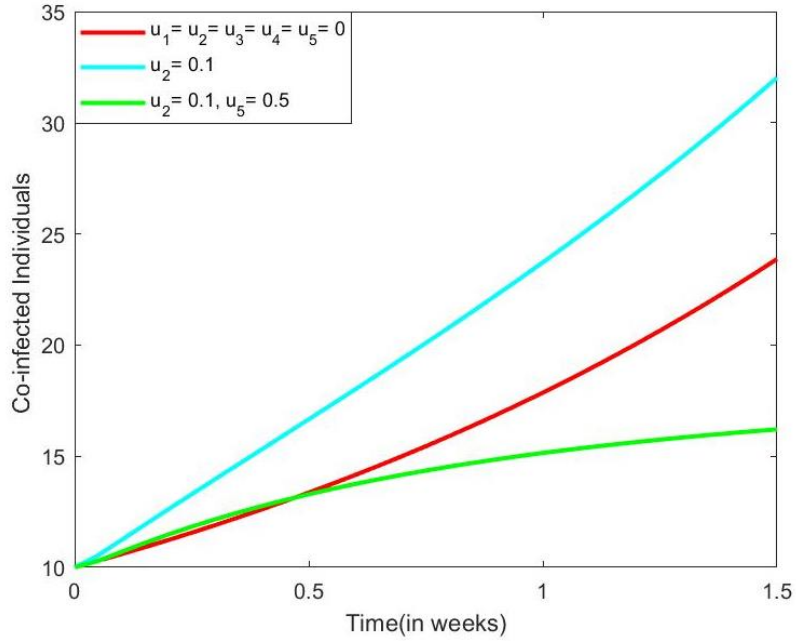


Figure 2(c): Simulation of the HIV-CM model showing the effect of CM testing and treatment only on I_{HC} compartment

Figure 2(c) shows that, initially, as testing for cryptococcal meningitis is increases up to 10% in the HIV-infected community, co-infection is expected to increase due to the identification of CM infection in HIV-infected individuals. However, promptly initiating treatment up to 50% for cryptococcal meningitis can subsequently lead to a reduction in co-infection.

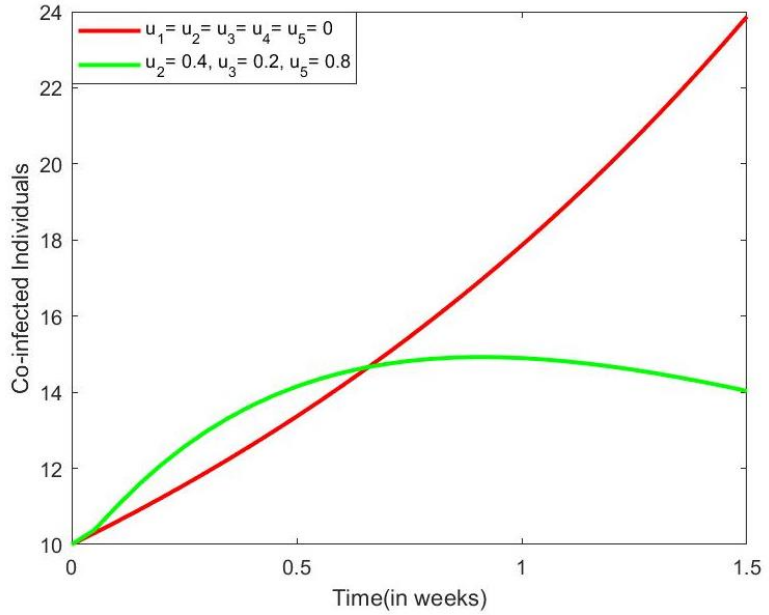


Figure 2(d): Simulation of the HIV-CM model showing the effect of CM screening, testing and treatment only on I_{HC} compartment

It can be observed from the plot that upon implementing screening and testing measures at 20% and 40% levels respectively, the initial trend shows an increase in the rate of co-infection. However, as treatment is gradually administered up to 80%, the infection rate starts to decrease over time. This strategy suggests that treatment against CM infection in a co-infected community would be very effective approach to effectively control CM infection.

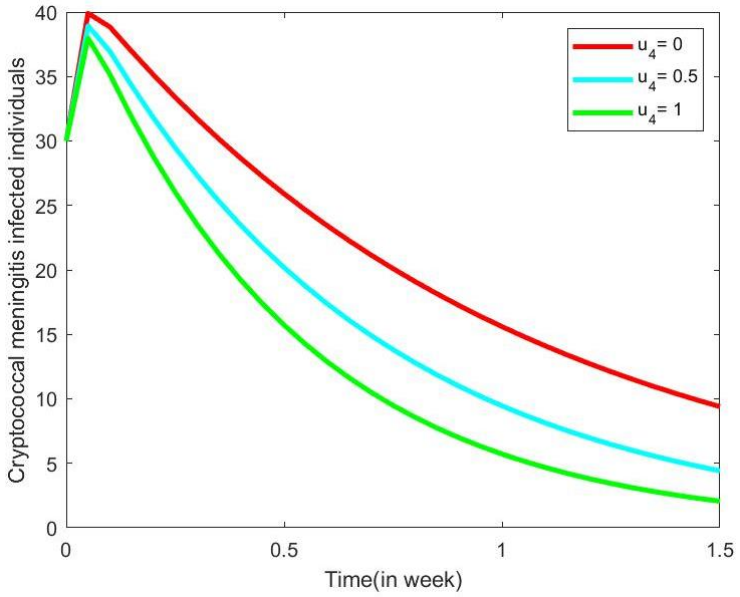


Figure 3(a): Simulation of the HIV-CM model showing the effect of prevention and treatment only on I_C compartment

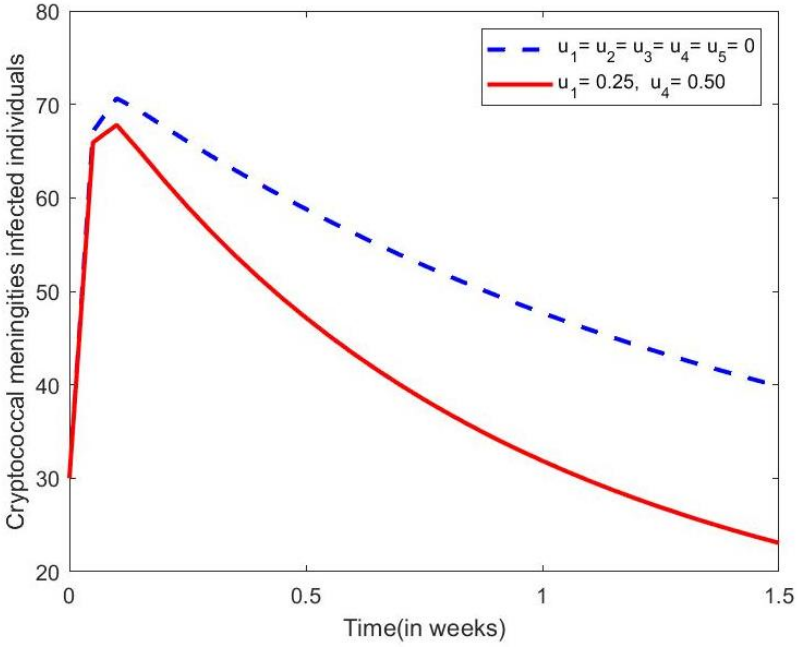


Figure 3(b): Simulation of the HIV-CM model showing the effect of prevention and treatment only on I_C compartment

This strategy suggests that optimal prevention & treatment against CM infection in CM infected community would not better than treatment only against CM infection from Figure 3(a) and 3(b).

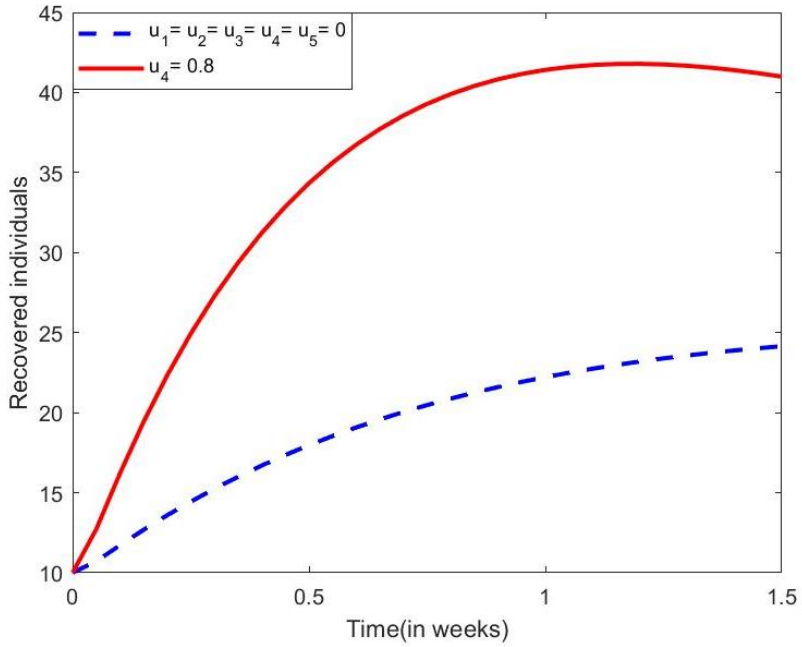


Figure 4(a): Simulation of the HIV-CM model showing the effect of treatment on recovered compartment

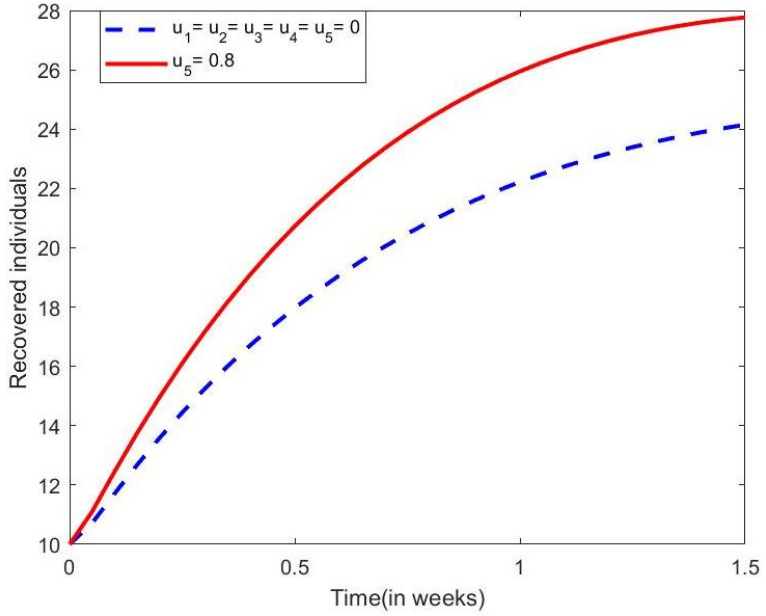


Figure 4(b): Simulation of the HIV-CM model showing the effect of treatment on recovered compartment

Figure 4(a) and 4(b) shows that the recovery rate is significantly higher in a community with CM infection when patients are administered therapy up to 80%, compared to the increased recovery rate observed when administering 80% of treatment for CM infection in a co-infected community.

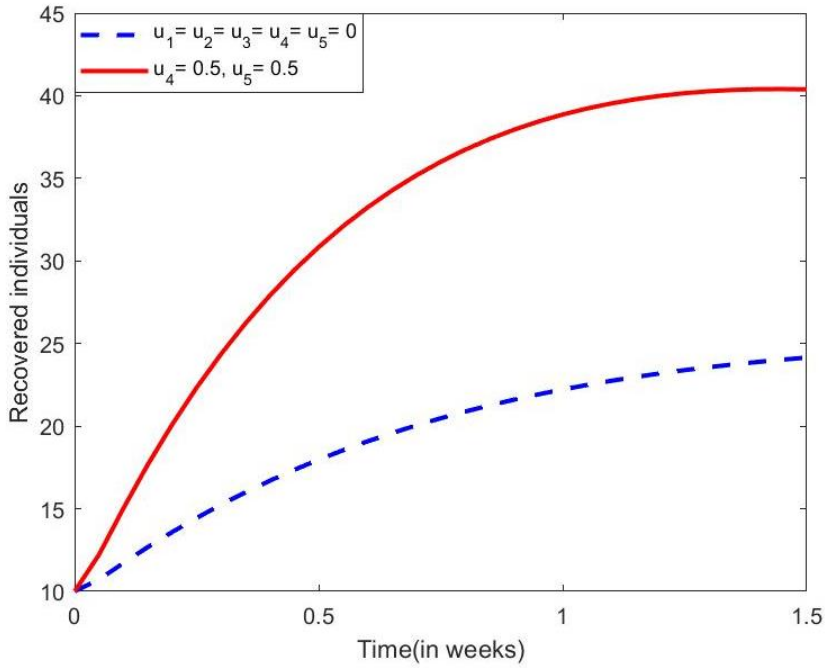
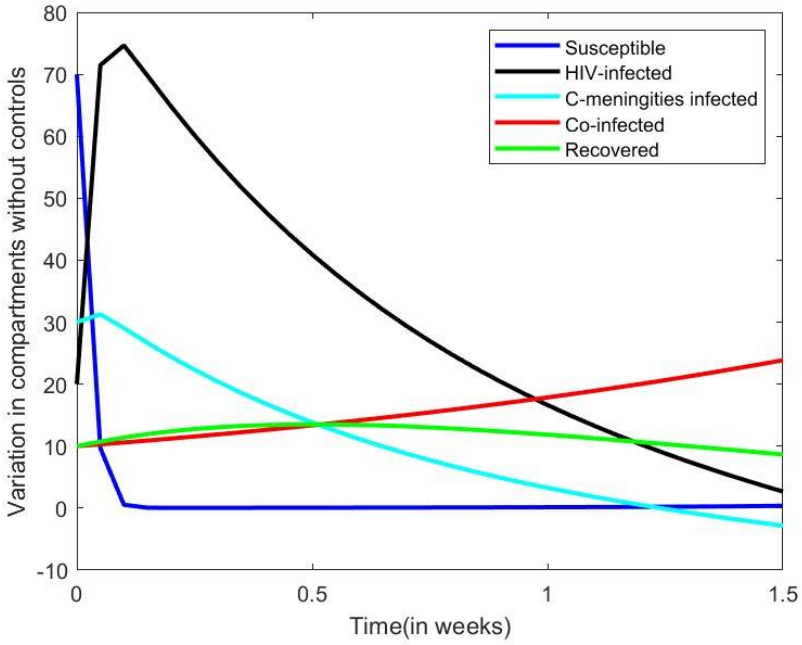
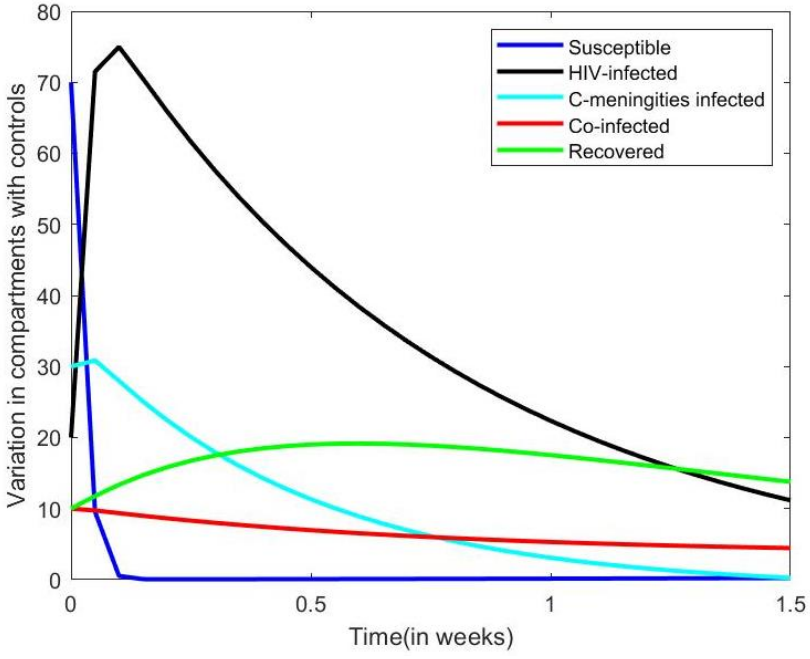


Figure 4(c): Simulation of the HIV-CM model showing the effect of treatment only on recovered compartment

The figure clearly demonstrates that the implementation of treatment control strategies for CM infection leads to a significant increase in the survival rate and decrease in the mortality rate.



Figures 5(a): Displays the changes in all the compartment of the model with and without controls.



Figures 5(b): Displays the changes in all the compartment of the model with and without controls.

From figures 5(a) & 5(b), it is evident that a large population of susceptible individuals become infected over time in the absence of any control measures. However, after

implementing all the necessary controls, the rate of infection starts to decline, and the recovery rate begins to increase.

6. Conclusion

In this paper, we formulated and analyzed a deterministic model for the transmission of HIV-cryptococcal meningitis co-infection in immunocompromised individuals that includes use of preventions, treatments of infectives and also performed optimal control analysis of the model. The model includes five control variables in the form of control strategies. These strategies include prevention by medication (antifungal) from CM infection, screening and CD4 cells testing for CM infection in HIV infected community, and treatment by medication (antifungal) for CM infection in an infected community. Local stability is carried out for disease free equilibrium point (E_0). By simulating the model, distinct and combined effects of these control variables on different compartments are observed and examined graphically. The observations lead us to the conclusion that by applying treatment strategy to CM infected individuals in a community, the number of CM infected individuals can be decrease and recovered individuals can be increased.

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