PENDEKATAN DUA TERAPI UNTUK PENGOBATAN INFEKSI HIV PADA TAHAP AIDS

PEMODELAN MATEMATIKA DAN SIMULASI

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KATA PENGANTAR

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Dalam makalah ini, penulis mengangkat masalah menyelesaikan persoalan Pengobatan Infeksi HIV Pada Tahap AIDS dengan menggunakan Pendekatan Dua Terapi yaitu Highly Active Antiretroviral Therapy (HAART) dan Immunotherapy dengan Interleukin-2. Dalam hal ini akan dianalisa tingkat infeksi pada tubuh manusia yang terjangkit virus HIV dengan cara melihat perilaku grafik dari suatu sistem persamaan, titik kestabilan, dan sistem optimal (Prinsip maksimum Pontryagin) yang diselesaikan secara numerik menggunakan metode iterasi skema order 4 Runge-Kutta.

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ABSTRAK

Dalam jurnal ini, dikemukakan suatu pendekatan kontrol optimal untuk strategi terapi yang tepat dari infeksi HIV. Berawal dari suatu sistem pemodelan persamaan diferensial biasa infeksi HIV (Human Immunodeficiency Virus) dan interaksinya dengan sistem imun. Pada mulanya, keberadaan suatu kontrol yang merupakan suatu pengobatan menggunakan HAART (Highly Active Antiretrovial Therapy) diperkenalkan, kemudian kombinasi antara HAART dan Immunotherapy menggunakan Interleukin-2. Suatu perbandingan dari hasil tersebut, maka dipilih suatu strategi pengobatan yang mampu mengurangi viral load dan efek samping, memaksimalkan tingkat imun dan jumlah sel-$T\ CD4^{+}$ yang sehat, namun meminimalkan harga pengobatan. Prinsip Pontryagin maksimum digunakan untuk mengkarektarisasi kontrol optimal. Sistem optimalisasi diturunkan dan diselesaikan secara numerik menggunakan metode iterasi skema Runge-Kutta orde empat.

Kata kunci: Infeksi HIV, Kontrol Optimal, Interleukin-2, HAART (Highly Active Antiretroviral Therapy, Skema Runge-Kutta orde empat.

ABSTRACT

In this paper was introduced an optimal control for adequate therapeutic strategy for HIV infection. Starting from a system of ordinary differential equations modeling the human immunodeficiency virus (HIV) infection and its interaction with the immune system. Firstly, it was introduced a treatment using Highly Active Antiretroviral Therapy (HAART), then it was introduced a combination treatment between HAART and Immunotherapy using the Interleukin-2. A comparison of the results was a strategy to reduce the viral load and the side effects, maximize the immune response level, the number of healthy $CD4^+$ T-cells while minimizing the cost treatment. The Pontryagin's maximum principle was used to characterize the optimal controls. The optimality system was derived and solved numerically using an iterative method with Runge-Kutta fourth order scheme.

Keywords: HIV infection, Optimal control, Interleukin-2, Highly Active Antiretroviral Therapy (HAART), Runge-Kutta fourth order scheme.

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BAB I
PENDAHULUAN

1.1. Latar Belakang

HIV (*Human Immunodeficiency Virus*) adalah virus penyebab AIDS. Secara fisiologis, virus HIV merupakan virus yang menyerang sistem kekebalan tubuh manusia dengan menyerang salah satu sel darah putih yaitu sel-$T\ CD4^+$, yang menyebabkan sekumpulan gejala penyakit yang menyerang tubuh manusia, sehingga terjadi kerusakan sistem kekebalan tubuh yang disebut AIDS. AIDS (*Acquired Immune Deficiency Syndrome*) adalah sindrom menurunnya sistem kekebalan tubuh manusia yang disebabkan oleh HIV.

Modulasi respon imun penderita HIV/AIDS akan menurun secara signifikan, seperti aktivitas APC (makrofag), IL-2, Imunoglobin (A, G, E) dan anti-HIV. Saat HIV telah membunuh sel-$T\ CD4^+$ hingga jumlahnya menyusut kurang dari 20 per microliter darah, maka kekebalan di tingkat sel akan hilang. Penurunan tersebut mencapai 18 sel tiap tahun berdampak terhadap penurunan jumlah CD4 yang merupakan jenis sel darah putih atau limfosit yang penting dari sistem kekebalan tubuh manusia.

Secara umum pemodelan matematika yang terkait dengan masalah HIV ada dua macam yaitu model epidemik HIV/AIDS dan model sistem imun HIV. Model matematika yang telah digunakan secara ekstensif dalam penelitian epidemiologi dari HIV/AIDS untuk mengetahui faktor utama yang mempengaruhi pandemik.

Pada makalah ini dikemukakan model HIV/AIDS dengan suatu pendekatan kontrol optimal untuk strategi terapi yang tepat dari infeksi HIV. Berawal dari suatu sistem pemodelan persamaan diferensial biasa infeksi HIV dan interaksinya dengan sistem imun, HAART merupakan metode terapi yang pada mulanya digunakan, kemudian kombinasi antara HAART dan Immunotherapy menggunakan Interleukin-2. Perbandingan hasil dari dua metode terapi tersebut dapat dipilih suatu strategi yang mampu mengurangi viral load untuk mengkarakterisasi kontrol optimal.

1.2. Rumusan Masalah

Berdasarkan latar belakang diatas, maka permasalahn yang dibahas dalam makalah ini adalah sebagai berikut.

1. Bagaimana konstruksi model infeksi virus dasar (*Basic Virus Infection Model* atau BVIM) pada epidemik HIV/AIDS, model matematika dengan pengobatan menggunakan HAART (*Highly Active Antiretroviral Therapy*), kombinasi pengobatan HAART dan Immunotherapy menggunakan Interleukin-2 (IL-2)?
2. Bagaimana fungsi objektif pada kontrol optimal yang digunakan untuk meningkatkan konsentrasi sel?
3. Bagaimana interpretasi hasil analisis model dengan strategi terapi HAART (*Highly Active Antiretroviral Therapy*) kemudian kombinasi antara HAART dan Immunotherapy menggunakan Interleukin-2 (IL-2)?

3.1. Batasan Masalah

Pembahasan pada makalah ini dibatasi oleh beberapa hal sebagai berikut.

1. Populasi bersifat tertutup sehingga tidak ada migrasi.
2. Penyebaran virus terjadi karena adanya interaksi antar individu.
3. Kontrol optimal $u_1(t)$ pada HAART (*Highly Active Antiretroviral Therapy*) adalah $0 \leq u(t) \leq 1$, sedangkan kontrol optimal pada Immunotherapy menggunakan Interleukin-2 (IL-2) adalah $0.0001 \leq u_2(t) \leq 0.003$.

3.2. Tujuan

Tujuan penulisan makalah ini adalah sebagai berikut.

1. Mengkonstruksi model infeksi virus dasar (*Basic Virus Infection Model* atau BVIM) pada epidemik HIV/AIDS, model matematika dengan pengobatan menggunakan HAART (*Highly Active Antiretroviral Therapy*), kombinasi pengobatan HAART dan Immunotherapy menggunakan Interleukin-2 (IL-2).
2. Menginterpretasikan hasil analisis model dengan pengobatan menggunakan HAART (*Highly Active Antiretroviral Therapy*), kombinasi pengobatan HAART dan Immunotherapy menggunakan Interleukin-2 (IL-2).

BAB II
TINJAUAN PUSTAKA

2.1. Sistem Kekebalan Tubuh

Sistem kekebalan atau sistem imun adalah sistem perlindungan tubuh dari pengaruh luar (bakteri atau virus) yang dilakukan oleh sel dan organ khusus pada suatu organisme khususnya makrofag dan sel-$T\ CD4^+$. Makrofag merupakan sel yang menelan dan mencerna patogen. Selain itu makrofag juga menstimulasi sel kekebalan tubuh lain seperti sel-$T\ CD4^+$ untuk memberikan reaksi pada patogen. Sel-$T\ CD4^+$ tidak langsung menyerbu patogen akan tetapi membantu aktivasi sel-T Cytotoxic. Sel-T Cytotoxic berperan sebagai penghancur sel – sel yang telah terinfeksi virus ataupun tumor (Carr, 2007).

2.2. HIV dan AIDS

HIV (*Human Immunodeficiency Virus*) merupakan salah satu jenis virus yang hanya menginfeksi manusia dan menyebabkan menurunnya system kekebalan tibuh penderita HIV. HIV juga disebut sebagai *lentivirus*. Lenti berarti lambat sehingga *lentivirus* adalah virus yang memiliki jangka waktu yang lama antara waktu pertama kali menginfeksi manusia dengan waktu dimana seseorang menunjukkan gejala – gejala infeksi yang serius. HIV menghancurkan system kekebalan tubuh manusia dengan cara merusak sel yang dibutuhkan oleh sel-T Cytotoxic untuk menjadi aktif. Infeksi HIV pada akhirnya menyebabkan penderita mengalami AIDS (*Acquired Immune Deficiency Syndrome*) yaitu suatu kondisi dimana penderita HIV mengalami penurunan tingkat kekebalan tubuh. Tanpa adanya sel kekebalan yang cukup, tubuh tidak mampu mempertahankan diri dari berbagai macam infeksi yang ada di lingkungan sekitarnya. Berbagai macam infeksi yang dialami oleh penderita HIV karena melemahnya sistem kekebalan tubuh disebut sebagai infeksi oportunistik. Tahap infeksi virus HIV yang lebih lanjut (AIDS) diindikasi oleh dua hal. Pertama dideteksi dari jumlah sel-$T\ CD4^+$ yang kurang dari $200\ sel/mm^3$ dan dilihat dari munculnya infeksi oportunistik (Judy, 2013).

2.3. Teori Kontrol Optimal

Dalam teori kontrol, permasalahan pada kontrol optimal adalah untuk mendapatkan kendali pada sistem dinamik yang sesuai dengan target atau variabel keadaan dan pada waktu yang sama juga dapat dilakukan optimasi (maksimum/minimum) pada fungsi tujuan (*performance index*). Secara matematika dapat ditulis sebagai berikut.

$$J = x'(t_f)F_x(t_f) + \int_{t_0}^{t_f} [x'(t)Q_x(t) + u'(t)Ru(t)]\,dt$$

dimana R merupakan matriks definit positif, Q, F merupakan matriks semidefinit positif, dan $u^*(t)$ merupakan kontrol optimal yang menyebabkan sistem linier yaitu $\dot{x}(t) = Ax(t) + Bu(t)$ menghasilkan lintasan $x^*(t)$ yang mengoptimalkan (minimum atau maksimum) suatu *performance index J* (Desineni, 2003).

2.4. Prinsip Maksimum Pontryagin

Misal (x^*, u^*) merupakan lintasan kontrol yang didefinisikan atas interval $[t_0, T]$ dengan kontrol u^* yang kontinu. Jika (x^*, u^*) optimal, maka terdapat suatu kostanta $\lambda_0 \geq 0$ dan $\lambda: [t_0, T] \longrightarrow (\mathbb{R}^n)^*$ adalah *adjoint variable* yang memenuhi kondisi berikut:

a). $(\lambda_0, (t)) \neq 0$ untuk setiap $t \in [t_0, T]$

b). $\dot{\lambda}(t) = -\lambda_0 L_x\big(t, x^*(t), u^*(t)\big) - \lambda(t) f_x\big(t, x^*(t), u^*(t)\big)$

c). $H\big(t, \lambda_0, \lambda(t), x^*(t), u^*(t)\big) = \min_{v \in U} H(t, \lambda_0, \lambda(t), x^*(t), v)$ adalah kondisi minimum pada interval $[t_0, T]$

Jika Lagrangian L dan f adalah turunan yang kontinu pada waktu t, maka fungsi

$$h: t \longrightarrow H\big(t, \lambda_0, \lambda(t), x^*(t), u^*(t)\big)$$

adalah turunan kontinu dengan turunan sebagai berikut.

$$\dot{h}(t) = \frac{dh(t)}{dt} = \frac{\partial H}{\partial t}\big(t, \lambda_0, \lambda(t), x^*(t), u^*(t)\big)$$

d). Kondisi transversal pada titik akhir lintasan control $(H + \lambda_0\varphi_t, -\lambda + \lambda_0\varphi_x)$ adalah ortogonal pada kendala N karena terdapat $v \in (\mathbb{R}^{n+1-k})^*$ sedemikian sehingga

$H + \lambda_0\varphi_t + vD_t\Psi = 0, \qquad \lambda = \lambda_0\varphi_x + vD_x\Psi$ pada $(T, x^*(T))$ (Schättler, 2012).

2.5. Runge-Kutta Order 4

Metode Runge-Kutta merupakan metode langkah tunggal yang lebih teliti dibandingkan metode Euler. Semua metode Runge-Kutta dapatr ditulis sebagai

$$y_{i+1} = y_i + h\Phi(x_i, y_i, h)$$

dimana $\Phi(x_i, y_i, h)$ disebut fungsi penambah. Metode Runge-Kutta order empat terdiri dari tiga jenis metode, yaitu

a). Metode Pertama

$$y_{i+1} = y_i + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

$$k_1 = f(x_i, y_i)$$

$$k_2 = f\left(x_i + \frac{h}{2}, y_i + \frac{hk_1}{2}\right)$$

$$k_3 = f\left(x_i + \frac{h}{2}, y_i + \frac{hk_2}{2}\right)$$

$$k_4 = f(x_i + h, y_i + hk_3)$$

b). Metode Kedua

$$y_{i+1} = y_i + \frac{h}{8}(k_1 + 3k_2 + 3k_3 + k_4)$$

$$k_1 = f(x_i, y_i)$$

$$k_2 = f\left(x_i + \frac{h}{3}, y_i + \frac{hk_1}{3}\right)$$

$$k_3 = f\left(x_i + \frac{2h}{3}, y_i - \frac{hk_1}{3} + hk_2\right)$$

$$k_4 = f(x_i + h, y_i + hk_1 - hk_2 + hk_3)$$

c). Metode Ketiga

$$y_{i+1} = y_i + \frac{h}{6}\left[k_1 + \left(2 - \sqrt{2}\right)k_2 + \left(2 - \sqrt{2}\right)k_3 + k_4\right]$$

$$k_1 = f(x_i, y_i)$$

$$k_2 = f\left(x_i + \frac{h}{2}, y_i + hk_1\right)$$

$$k_3 = f\left(x_i + \frac{h}{2}, y_i + \frac{\left(-1 + \sqrt{2}\right)hk_1}{2} + \left(1 - \frac{1}{\sqrt{2}}\right)hk_2\right)$$

$$k_4 = f\left(x_i + h, y_i - \frac{hk_2}{\sqrt{2}} + \left(1 + \frac{1}{\sqrt{2}}\right)hk_3\right)$$

(Djoko, 2001)

2.6. Metode Maju-Mundur Sweep (FBSM)

Metode Maju-Mundur Sweep (Forward-Backward Sweep Method atau FBSM) merupakan metode yang digunakan untuk menyelesaikan sistem diferensial dengan Prinsip Maximum yang mengkarakterisasi solusi. Metode Maju-Mundur Sweep (FBSM) juga disebut sebagai metode tak langsung untuk menyelesaikan masalah kontrol optimal, karena metode ini mengaproksimasi solusi secara numerik dengan menyelesaikan masalah nilai batas untuk sistem diferensial dengan Prinsip Maksimum. Berikut beberapa langkah untuk mencari solusi optimal dengan menggunakan Metode Maju-Mundur Sweep (FBSM).

1. Mencari solusi persamaan $x' = g(t, x, u)$ dengan Metode Runge-Kutta.
2. Mencari solusi persamaan *co-state* $\frac{d\lambda}{dt} = -\frac{\partial H}{\partial x}, \lambda(t_1) = 0,$ mundur terhadap waktu, dengan Metode Runge-Kutta, kemudian meng-update kontrol. Langkah ini menghasilkan aproksimasi baru pada *state*, *co-state*, dan kontrol (x, λ, u).
3. Proses berlangsung dengan menggunakan *updates* yang baru, menghitung aproksimasi Runge-Kutta yang baru, dan kontrol *updates* hingga mendapatkan nilai optimal di titik (x, λ, u). Proses berakhir saat nilai kesalahan (*error*) dari *state*, *co-state*, dan control cukup kecil (Mitter, 1966).

BAB III
MODEL MATEMATIKA

3.1. Deskripsi Model

Pada bagian ini akan dibahas dinamika penyebaran virus HIV pada tubuh manusia yang terdiri dari populasi populasi sel-$T\ CD4^+$ yang sehat (*uninfected*) dengan ukuran x, populasi sel-$T\ CD4^+$ yang tidak sehat (*infected*) dengan ukuran y, dan populasi sel imun CTL dengan ukuran z. Model Infeksi Virus Dasar (*Basic Virus Infection Model*/ BVIM) dalam dinamika penyebaran virus HIV ini diberikan sebagai berikut.

$$\frac{dx}{dt} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - \beta xy$$

$$\frac{dy}{dt} = \beta xy - ay - lyz \tag{3.1}$$

$$\frac{dz}{dt} = sy - bz$$

dengan

x : populasi sel-$T\ CD4^+$ sehat (*Uninfected*)

y : populasi sel-$T\ CD4^+$ tidak sehat (*Infected*)

z : populasi sel imun CTL

λ : laju produksi sel-$T\ CD4^+$ yang sehat

β : laju infeksi dan laju replikasi virus

d : laju kematian alami sel-$T\ CD4^+$ yang sehat

p : laju proliferasi maksimum sel-$T\ CD4^+$ yang sehat

a : laju kematian alami sel-$T\ CD4^+$ yang terinfeksi

l : laju kematian sel yang memproduksi virus oleh sel CTL

s : laju produksi sel CTL

b : laju kematian alami sel CTL

T_m : jumlah sel-$T\ CD4^+$ setelah prolifersi maksimum

3.1.1. Laju Perubahan Populasi Sel-$T\ CD4^+$ Sehat (Uninfected)

Laju perubahan populasi sel-$T\ CD4^+$ sehat terhadap waktu dipengaruhi oleh parameter $\lambda, p, T_m, d,$ dan β. Dalam populasi sel-$T\ CD4^+$ sehat, λ menyatakan laju produksi sel-$T\ CD4^+$ yang sehat, p menyatakan laju proliferasi maksimum sel-$T\ CD4^+$ yang sehat, dan T_m menyatakan jumlah sel-$T\ CD4^+$ setelah prolifersi maksimum. Namun, dalam populasi sel-$T\ CD4^+$ sehat ini ada kemungkinan terinfeksi. Laju perubahan populasi sel-$T\ CD4^+$ sehat berbanding lurus dengan laju produksi sel-$T\ CD4^+$ yang sehat, laju proliferasi maksimum sel-$T\ CD4^+$ yang sehat, dan jumlah sel-$T\ CD4^+$ setelah prolifersi maksimum pada waktu t, yaitu

$$\frac{dx}{dt} = \lambda + px\left(1 - \frac{x}{T_m}\right)$$

Populasi sel-$T\ CD4^+$ dapat berkurang oleh kematian alami yaitu kematian yang terjadi bukan karena infeksi virus HIV dengan laju sebesar

$$\frac{dx}{dt} = -dx$$

Penyebaran infeksi virus HIV dalam populasi manusia terjadi antara populasi sel-$T\ CD4^+$ sehat dengan populasi sel-$T\ CD4^+$ yang terinfeksi. Kondisi ini mengakibatkan berkurangnya populasi sel-$T\ CD4^+$ yang sehat dengan laju β. Oleh karena itu, laju perubahan populasi sel-$T\ CD4^+$ yang sehat berbanding lurus dengan laju populasi sel-$T\ CD4^+$ sehat dan populasi sel-$T\ CD4^+$ terinfeksi, yaitu

$$\frac{dx}{dt} = -\beta xy$$

Dengan demikian laju perubahan populasi sel-$T\ CD4^+$ sehat (*uninfected*) terhadap waktu t dapat dinyatakan sebagai berikut

$$\frac{dx}{dt} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - \beta xy$$

3.1.2. Laju Perubahan Populasi Sel-$T\ CD4^+$ Terinfeksi (Infected)

Laju perubahan populasi sel-$T\ CD4^+$ terinfeksi terhadap waktu dipengaruhi parameter $\beta, a,$ dan l. Jumlah populasi sel-$T\ CD4^+$ terinfeksi dapat bertambah jika terdapat populasi sel-$T\ CD4^+$ sehat yang terinfeksi. Oleh karena itu, laju perubahan populasi sel-$T\ CD4^+$ terinfeksi berbanding lurus dengan populasi sel-$T\ CD4^+$ sehat dan sel-$T\ CD4^+$ terinfeksi, yaitu

$$\frac{dy}{dt} = \beta xy$$

Jumlah populasi sel-$T\ CD4^+$ terinfeksi dapat berkurang karena kematian alami dengan laju konstan a, yaitu

$$\frac{dy}{dt} = -ay$$

Jumlah populasi sel-$T\ CD4^+$ terinfeksi dapat berkurang karena interaksi dengan sel imun CTL yang mampu menghancurkan sel yang memproduksi virus (sel-$T\ CD4^+$ yang terinfeksi) dengan laju konstan l, yaitu

$$\frac{dy}{dt} = -lyz$$

Dengan demikian laju perubahan populasi sel-$T\ CD4^+$ terinfeksi (*infected*) terhadap waktu t dapat dinyatakan sebagai berikut

$$\frac{dy}{dt} = \beta xy - ay - lyz$$

3.1.3. Laju Perubahan Sel Imun CTL

Laju perubahan populasi sel imun CTL terhadap waktu yang dipengaruhi parameter s dan b. Akibat sel-$T\ CD4^+$ yang terinfeksi oleh virus HIV menyebabkan jumlah produksi sel CTL bertambah dengan laju konstan s, yaitu

$$\frac{dz}{dt} = sy$$

Jumlah populasi sel imun CTL dapat berkurang karena kematian alami dengan laju konstan b, yaitu

$$\frac{dz}{dt} = -bz$$

Dengan demikian laju perubahan populasi sel imun CTL terhadap waktu t dapat dinyatakan sebagai berikut

$$\frac{dz}{dt} = sy - bz$$

3.2. Titik Kesetimbangan

Titik kesetimbangan sistem persamaan (3.1) diperoleh jika

$$\frac{dx}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0$$

sehingga diperoleh

$$\lambda + px\left(1 - \frac{x}{T_m}\right) - dx - \beta xy = 0 \qquad (3.2a)$$

$$\beta xy - ay - lyz = 0 \qquad (3.2b)$$

$$sy - bz = 0 \qquad (3.2c)$$

Dari persamaan $(3.2b)$ dan $(3.2c)$ diperoleh

$$(\beta x - a - lz)y = 0 \implies y = 0, (\beta x - a - lz) = 0$$

$$z = \frac{\beta x - a}{l}$$

$$sy - bz = 0 \Longrightarrow y = \frac{b}{s}z$$

Berdasarkan perhitungan pada Lampiran 1 diperoleh dua titik kesetimbangan yaitu titik kesetimbangan sel-$T\ CD4^+$ sehat $E_0 = (x_0, 0,0)$ dan titik kesetimbangan sel-$T\ CD4^+$ yang terinfeksi $E^* = (x^*, y^*, z^*)$ dengan

$$x_0 = \frac{T_m}{2p}\left[(p-d) \pm \sqrt{(p-d)^2 + \frac{4\lambda p}{T_m}}\right] \qquad (3.3)$$

$$x^* = \frac{\left(p - d + \frac{ab\beta}{sl}\right) + \sqrt{\left(p - d + \frac{ab\beta}{sl}\right)^2 + 4\lambda\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)}}{2\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)} \qquad (3.4)$$

$$y^* = \frac{ab}{sl}(R_0 - 1) \qquad (3.5)$$

$$z^* = \frac{a}{l}(R_0 - 1) \qquad (3.6)$$

Perhatikan bahwa eksistensi y^* ditentukan oleh suatu bilangan

$$R_0 = \frac{\beta x^*}{a} \qquad (3.7)$$

yang disebut sebagai angka reproduksi dasar, yaitu angka yang menentukan ada tidaknya penyebaran penyakit pada suatu populasi.

3.3. Analisa Kestabilan Titik Kesetimbangan

Untuk mengetahui kestabilan titik kesetimbangan, perlu ditentukan matriks Jacobi sistem persamaan (3.1), yaitu

$$J = \begin{bmatrix} p - d - \dfrac{2px}{T_m} - \beta y & -\beta x & 0 \\ \beta y & \beta x - a - lz & -ly \\ 0 & s & -b \end{bmatrix}$$

3.3.1. Kestabilan Titik Kesetimbangan $\boldsymbol{E_0 = (x_0, 0, 0)}$

Matriks Jacobi dari titik $E_0 = (x_0, 0,0)$ adalah

$$J(E_0) = \begin{bmatrix} p - d - \dfrac{2px_0}{T_m} & -\beta x_0 & 0 \\ 0 & \beta x_0 - a & 0 \\ 0 & s & -b \end{bmatrix}$$

Persamaan karakteristik matriks Jacobi tersebut adalah

$$\left(N - p + d + \frac{2px_0}{T_m}\right)(N - \beta x_0 + a)(N + b) = 0$$

dengan nilai eigen

$$N_1 = p - d - \frac{2px_0}{T_m} = -\left(\frac{\lambda}{x_0} + \frac{px_0}{T_m}\right) < 0$$

$$N_2 = \beta x_0 - a \qquad (3.8)$$

$$N_3 = -b < 0$$

$E_0 = (x_0, 0,0)$ stabil asimtotik jika $R_0 < 1$ dan pelana (*saddle*) jika $R_0 > 1$.

3.3.2. Kestabilan Titik Kesetimbangan $\boldsymbol{E^* = (x^*, y^*, z^*)}$

Matriks Jacobi dari $E^* = (x^*, y^*, z^*)$ adalah

$$J(E^*) = \begin{bmatrix} p - d - \dfrac{2px^*}{T_m} - \beta y^* & -\beta x^* & 0 \\ \beta y^* & \beta x^* - a - lz^* & -ly^* \\ 0 & s & -b \end{bmatrix}$$

Persamaan karakteristik dari matriks Jacobi tersebut adalah

$$N^3 + AN^2 + BN + C = 0$$

dengan

$$A = \frac{\lambda}{x^*} + \frac{px^*}{T_m} + b > 0$$

$$B = b\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right) + \beta^2 x^* y^* + sly^* > 0 \tag{3.9}$$

$$C = sly^*\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right) + b\beta^2 x^* y^* > 0$$

Dari kriteria Routh-Hurwitz, syarat perlu dan cukup untuk stabil asimtotik adalah $AB - C > 0$, karena

$$\left(\frac{\lambda}{x^*} + \frac{px^*}{T_m} + b\right)\left[b\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right) + \beta^2 x^* y^* + sly^*\right] - \left[sly^*\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right) + b\beta^2 x^* y^*\right] > 0$$

3.4. Model HIV Dengan Pengobatan HAART

Berdasarkan pada persamaan (3.1), maka pada bagian ini terdapat suatu kontrol u yang menyatakan suatu pengobatan pada HIV. Kontrol $u(t)$ menunjukkan efisiensi dari HAART dalam menghambat produksi viral sehingga viral load dan tingkat infeksi berkurang. Sehingga persamaan (3.1) menjadi

$$\frac{dx}{dt} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - (1-u)\beta xy$$

$$\frac{dy}{dt} = (1-u)\beta xy - ay - lyz \tag{3.10}$$

$$\frac{dz}{dt} = sy - bz$$

Fungsi kontrol $u(t)$ memiliki nilai antara 0 dan 1: $u(t)$ = 1 menunjukkan suatu HAART yang efektif, sedangkan $u(t)$ = 0 menunjukkan tidak ada suatu pengobatan.

3.4.1 Kontrol Optimal Pada Pengobatan HAART

Tujuan dalam menyelesaikan kontrol optimal adalah memaksimumkan sel-$T\,CD4^+$ yang sehat, mengurangi laju infeksi, dan meminimumkan biaya pengobatan dengan memaksimumkan fungsi tujuan berikut

$$J(u(t)) = \int_0^T \{x(t) + z(t) - \frac{A}{2}u^2(t)\}dt \tag{3.11}$$

dengan sistem persamaan (3.10) sebagai kendala, sedangkan $A \geq 0$ bobot pada biaya pengobatan, dan interval waktu $[0, T]$. Sehingga $u^*(t)$ dapat dituliskan $J(u^*(t)) = \max\{J(u(t)) : u(t) \in U\}$ dan $U = \{u(t) : 0 \leq u(t) \leq 1, t \in [0, T]\}$.

Langkah awal untuk menentukan kontrol optimal adalah membentuk fungsi Lagrangian yaitu $L(t, x, y, z, u, \psi) = x(t) + z(t) - \frac{A}{2}u^2(t) + \sum_{i=1}^{3} \psi_i f_i$ dengan ψ_i dan f_i menyatakan variabel *co-state* dan kendala secara berturut – turut. Dengan menerapkan Prinsip Maksimum Pontryagin diperoleh Teorema 3.1 berikut.

Teorema 3.1. Suatu kontrol optimal $u^*(t)$, solusi kondisi optimal $x^*(t), y^*(t)$, dan $z^*(t)$ yang memaksimumkan fungsi tujuan $J(u(t))$. Variabel *co-state* $\psi_1(t), \psi_2(t)$, dan $\psi_3(t)$ yang memenuhi

$$\begin{aligned}
\frac{d\psi_1}{dt} &= -1 + \psi_1\left(\frac{2px^*}{T_m} + d - p\right) + \beta y^*(1 - u^*)(\psi_1 - \psi_2) \\
\frac{d\psi_2}{dt} &= \beta x^*(1 - u^*)(\psi_1 - \psi_2) + \psi_2(a + lz^*) - \psi_3 s \\
\frac{d\psi_3}{dt} &= -1 + \psi_2 l y^* + \psi_3 b
\end{aligned} \tag{3.12}$$

dengan kondisi transversal $\psi_1(T) = \psi_2(T) = \psi_3(T) = 0$. Selanjutnya, kontrol optimal diberikan oleh

$$u^*(t) = \min\left(1, max\left(0, \frac{\beta x^*(t) y^*(t)\big(\psi_1(t) - \psi_2(t)\big)}{A}\right)\right) \tag{3.13}$$

Bukti: Persamaan *co-state* dan kondisi transversal diperoleh dengan menggunakan Prinsip Maksimum Pontryagin yaitu

$$\frac{d\psi_1(t)}{dt} = -\frac{\partial L}{\partial x} = -1 + \psi_1\left(\frac{2px^*}{T_m} + d - p\right) + \beta y^*(1 - u^*)(\psi_1 - \psi_2)$$

$$\frac{d\psi_2(t)}{dt} = -\frac{\partial L}{\partial y} = \beta x^*(1 - u^*)(\psi_1 - \psi_2) + \psi_2(a + lz^*) - \psi_3 s$$

$$\frac{d\psi_3(t)}{dt} = -\frac{\partial L}{\partial z} = -1 + \psi_2 l y^* + \psi_3 b$$

Dengan menggunakan kondisi stasioner yaitu $\frac{\partial L}{\partial u} = 0$, maka

$$-Au + \psi_1 \beta xy - \psi_2 \beta xy = 0 \leftrightarrow \bar{u}(t) = \frac{\beta x^*(t) y^*(t)\left(\psi_1(t) - \psi_2(t)\right)}{A}$$

Karena $0 \leq u(t) \leq 1$ sehingga

$$u^*(t) = \begin{cases} 0 & , \bar{u}(t) \leq 0 \\ \bar{u}(t) & , 0 < \bar{u}(t) < 1 \\ 1 & , \bar{u}(t) \geq 1 \end{cases}$$

Jadi kontrol optimal

$$u^*(t) = \min\left(1, max\left(0, \frac{\beta x^*(t) y^*(t)\left(\psi_1(t) - \psi_2(t)\right)}{A}\right)\right) \quad \blacksquare$$

3.5. Model HIV Dengan Kombinasi Pengobatan HAART Dan Immunotherapy

Pada bagian ini menggunakan dua control u_1 dan u_2 untuk pengobatan pada HIV. Kontrol $u_1(t)$ menunjukkan efisiensi dari HAART dalam menghambat produksi viral sehingga viral load dan tingkat infeksi berkurang, sedangkan kontrol $u_2(t)$ menunjukkan efisiensi Immunotherapy menggunakan Interleukin-2 dalam menstimulasi respon imun untuk memulihkan pertahanan imun. Sehingga berdasarkan dua kontrol u_1 dan u_2, persamaan (3.1) menjadi

$$\begin{aligned} \frac{dx}{dt} &= \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - (1 - u_1)\beta xy + u_2 x \\ \frac{dy}{dt} &= (1 - u_1)\beta xy - ay - lyz \\ \frac{dz}{dt} &= sy - bz \end{aligned} \tag{3.14}$$

dimana $x(0) = x_0, y(0) = y_0$ dan $z(0) = z_0$. Kontrol $u_1(t)$ merupakan fungsi dengan nilai antara 0 dan 1: $u_1(t)$ = 1 menunjukkan suatu HAART yang efektif, sedangkan $u_1(t) = 0$ menunjukkan tidak ada suatu pengobatan. $u_1(t)$ digunakan untuk mengurangi laju viral load, sehingga terdapat suatu pergandaan βxy dengan $(1 - u)$, dimana β merupakan laju infeksi sel dan laju replikasi virus. Kontrol $u_2(t)$ merupakan suatu fungsi dengan nilai antara 0.0001 dan 0.003: $u_2(t)$ = 0.0001 untuk pasien dosis rendah, sedangkan $u_2(t)$ = 0.003 untuk dosis non toksin toleransi maksimal.

3.5.1. Kontrol Optimal Pada Pengobatan HAART Dan Immunotherapy

Seperti halnya pada terapi HAART, tujuan dalam menyelesaikan kontrol optimal pada kombinasi terapi yaitu HAART dan Immunotherapy ini adalah memaksimumkan sel-$T\ CD4^+$ yang sehat, mengurangi laju infeksi, dan meminimumkan biaya pengobatan dengan memaksimumkan fungsi tujuan berikut

$$J(u_1, u_2) = \int_0^T \left\{ x(t) + z(t) - \left[\frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \right] \right\} dt \tag{3.15}$$

dengan sistem persamaan (3.14) sebagai kendala, sedangkan $A_1 \geq 0$ dan $A_2 \geq 0$ bobot pada biaya pengobatan, dan interval waktu $[0, T]$. Kemudian akan diperoleh $u_1^*(t)$ dan $u_2^*(t)$ sehingga berlaku $J(u_1^*(t), u_2^*(t)) = \max\{J\big(u_1(t), u_2(t)\big) : (u_1(t), u_2(t)) \in U\}$ dengan $U = \big\{\big(u_1(t), u_2(t)\big) : 0 \leq u_1(t) \leq 1, 0.0001 \leq u_2(t) \leq 0.003, t \in [0, T]\big\}$.

Langkah awal untuk menentukan kontrol optimal adalah membentuk fungsi Lagrangian yaitu $L(t, x, y, z, u, \psi) = x(t) + z(t) - \left[\frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t)\right] + \sum_{i=1}^{3} \psi_i f_i$ dengan ψ_i dan f_i menyatakan variabel *costate* dan kendala secara berturut – turut. Dengan menerapkan Prinsip Maksimum Pontryagin diperoleh Teorema 3.2 berikut.

Teorema 3.2. Terdapat kontrol optimal $u_1^*(t)$ dan $u_2^*(t)$, solusi kondisi optimal $x^*(t), y^*(t)$, dan $z^*(t)$ yang memaksimumkan fungsi tujuan $J\big(u_1(t), u_2(t)\big)$. Selain itu, terdapat variabel *co-state* $\psi_1(t), \psi_2(t)$, dan $\psi_3(t)$ yang memenuhi

$$\begin{aligned}
\frac{d\psi_1}{dt} &= -1 + \psi_1 \left(\frac{2px^*}{T_m} + d - p - u_2^* \right) + \beta y^* (1 - u_1^*)(\psi_1 - \psi_2) \\
\frac{d\psi_2}{dt} &= \beta x^* (1 - u_1^*)(\psi_1 - \psi_2) + \psi_2 (a + l z^*) - \psi_3 s \\
\frac{d\psi_3}{dt} &= -1 + \psi_2 l y^* + \psi_3 b
\end{aligned} \tag{3.16}$$

dengan kondisi transversal $\psi_1(T) = \psi_2(T) = \psi_3(T) = 0$. Selanjutnya, kontrol optimal diberikan oleh

$$u_1^*(t) = \min\left(1, max\left(0, \frac{\beta x^*(t) y^*(t) \big(\psi_1(t) - \psi_2(t)\big)}{A_1}\right)\right) \tag{3.17}$$

dan

$$u_2^*(t) = \min\left(0.003, max\left(0.0001, \frac{x^*(t)\psi_1(t)}{A_2}\right)\right) \tag{3.18}$$

Bukti: Persamaan *co-state* dan kondisi transversal diperoleh dengan menggunakan Prinsip Maksimum Pontryagin yaitu

$$\frac{d\psi_1(t)}{dt} = -\frac{\partial L}{\partial x} = -1 + \psi_1\left(\frac{2px^*}{T_m} + d - p - u_2^*\right) + \beta y^*(1 - u_1^*)(\psi_1 - \psi_2)$$

$$\frac{d\psi_2(t)}{dt} = -\frac{\partial L}{\partial y} = \beta x^*(1 - u_1^*)(\psi_1 - \psi_2) + \psi_2(a + lz^*) - \psi_3 s$$

$$\frac{d\psi_3(t)}{dt} = -\frac{\partial L}{\partial z} = -1 + \psi_2 l y^* + \psi_3 b$$

Dengan menggunakan kondisi stasioner yaitu $\frac{\partial L}{\partial u_1} = 0$ dan $\frac{\partial L}{\partial u_2} = 0$, maka

$$-Au + \psi_1\beta xy - \psi_2\beta xy = 0 \leftrightarrow \bar{u}_1(t) = \frac{\beta x^*(t)y^*(t)\big(\psi_1(t) - \psi_2(t)\big)}{A_1}$$

dan

$$-A_2u_2 + \psi_1 x = 0 \leftrightarrow \bar{u}_2(t) = \frac{x^*(t)\psi_1(t)}{A_2}$$

Karena $0 \le u_1(t) \le 1$ sehingga

$$u_1^*(t) = \begin{cases} 0 & ,\bar{u}_1(t) \le 0 \\ \bar{u}_1(t) & ,0 < \bar{u}_1(t) < 1 \\ 1 & ,\bar{u}_1(t) \ge 1 \end{cases}$$

dan

Karena $0.0001 \le u_1(t) \le 0.003$ sehingga

$$u_2^*(t) = \begin{cases} 0.0001 & ,\bar{u}_2(t) \le 0 \\ \bar{u}_2(t) & ,0 < \bar{u}_2(t) < 1 \\ 0.003 & ,\bar{u}_2(t) \ge 1 \end{cases}$$

Jadi kontrol optimal

$$u_1^*(t) = \min\left(1, max\left(0, \frac{\beta x^*(t)y^*(t)\big(\psi_1(t) - \psi_2(t)\big)}{A_1}\right)\right)$$

dan

$$u_2^*(t) = \min\left(0.003, max\left(0.0001, \frac{x^*(t)\psi_1(t)}{A_2}\right)\right)$$ ■

BAB IV
SOLUSI NUMERIK

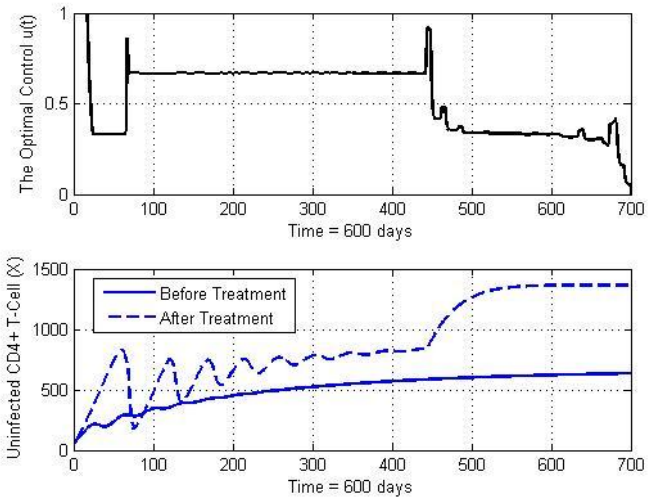
4.1 Interpretasi Solusi Numerik

Periode yang digunakan dalam simulasi numerik pada sistem persamaan dinamik ini adalah 700 $days$ dan parameter – parameter sebagai berikut.

Parameter	Nilai
λ	$10\ mm^{-3}day^{-1}$
β	$0.002\ mm^{-3}day^{-1}$
d	$0.01\ mm^{-3}day^{-1}$
p	$0.03\ mm^{-3}day^{-1}$
a	$0.24\ mm^{-3}day^{-1}$
l	$0.001\ mm^{-3}day^{-1}$
s	$0.2\ mm^{-3}day^{-1}$
b	$0.02\ mm^{-3}day^{-1}$
T_m	$1500\ mm^{-3}day^{-1}$

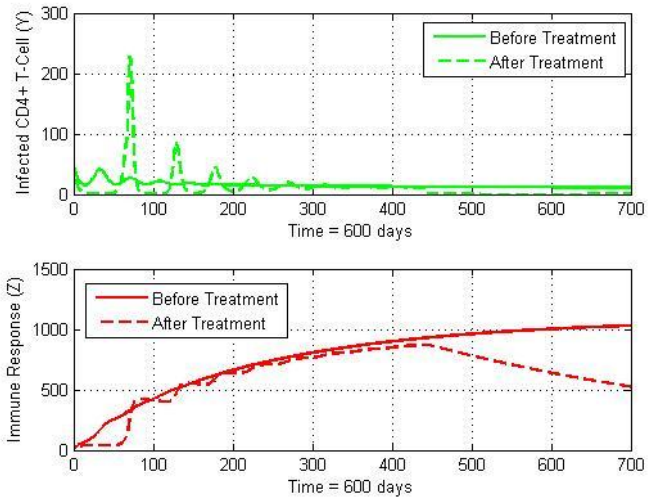
Tabel 1. Nilai Parameter

Berdasarkan parameter – parameter tersebut, maka diperoleh grafik sebagai berikut.



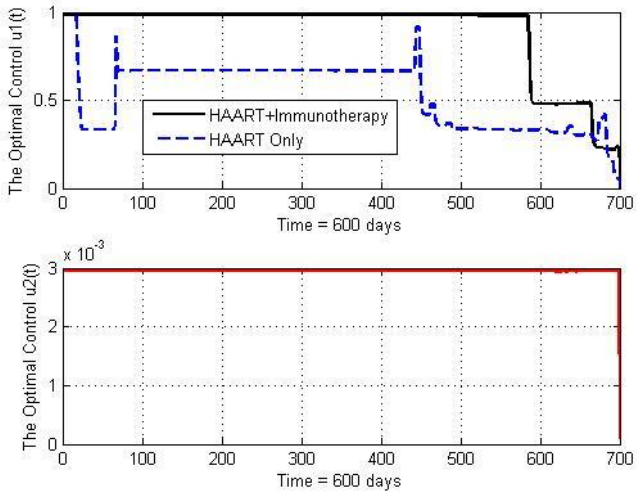
Gambar 1. Kontrol Optimal $u(t)$ dan Sel-$T\ CD4^+$ Sehat dengan Pengobatan HAART dan Tanpa Pengobatan

Gambar 1, nilai kontrol optimal $u(t)$ mencapai maksimum $u = 1$, hal ini menjelaskan terdapat suatu terapi HAART yang maksimum pada tahap AIDS. Kemudian, sekitar 30 hari pertama mengalami penurunan terapi dengan nilai kontrol optimal mencapai $u(t) < 0.5$. Sekitar dari hari ke-70 mengalami kestabilan kontrol optimal mencapai $u(t) > 0.5$. Kontrol optimal mengalami penurunan yang drastis dengan nilai mencapai $u(t) = 0$ pada akhir dari periode terapi, sekitar dari hari ke-665. Dari Gambar 1 menunjukkan bahwa dengan terapi HAART yang diberikan, tingkat sel-$T\ CD4^+$ Sehat mengalami peningkatan dan mencapai nilai maksimum lebih dari 1200 $mm^{-3}day^{-1}$ selama masa terapi 700 hari.



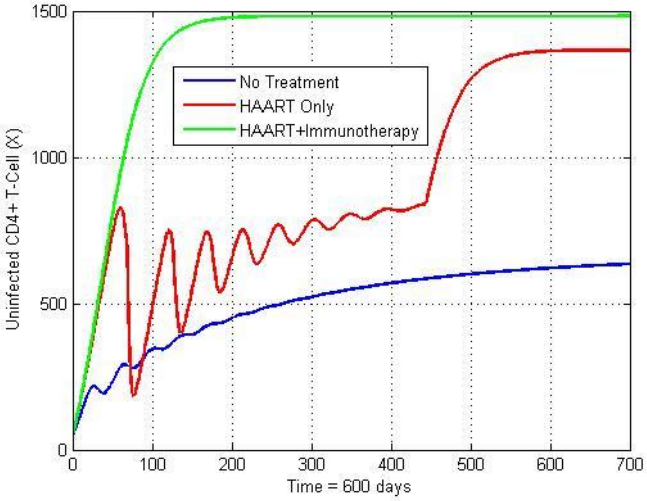
Gambar 2. Sel-$T\ CD4^+$ Terinfeksi dan Respon Imun Sel CTL

Gambar 2 menjelaskan suatu perbedaan yang signifikan pada jumlah sel-$T\ CD4^+$ Terinfeksi saat diberikan terapi HAART. Penurunan sel-$T\ CD4^+$ Terinfeksi dimulai dari hari ke-300 selama periode 700 hari. Gambar 2 menunjukkan suatu penurunan jumlah respon imun sel CTL setelah diberikan terapi HAART. Penurunan terapi pada Gambar 1, terjadi saat respon imun sel CTL meningkat. Selama periode respon imun sel CTL efektif, terapi HAART sedikit diperlukan, karena dalam ini sistem imun berperan penting dalam mengendalikan virus HIV pada tahap AIDS. Sehingga penurunan terapi HAART bergantung pada stimulasi imun dan kekuatan sistem sel imun CTL melawan virus HIV.



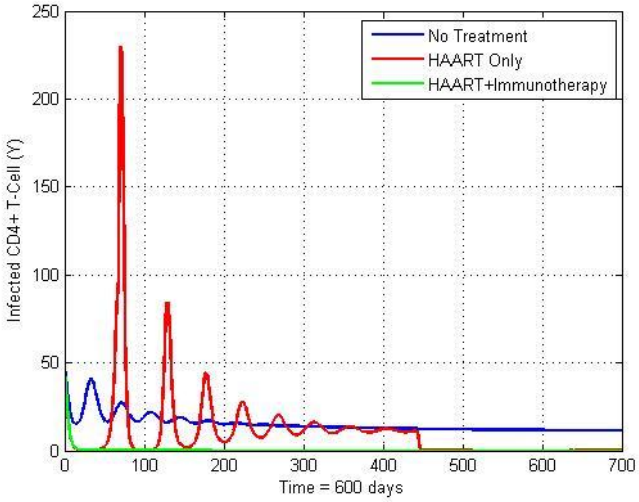
Gambar 3. Kontrol Optimal $u_1(t)$ dan $u_2(t)$ dengan Kombinasi Pengobatan HAART + Immunotherapy, Pengobatan HAART, dan Tanpa Pengobatan

Gambar 3 menjelaskan bahwa dengan kombinasi pengobatan HAART + Immunotherapy paling optimal jika dibandingkan dengan hanya pengobatan HAART dan tanpa pengobatan.



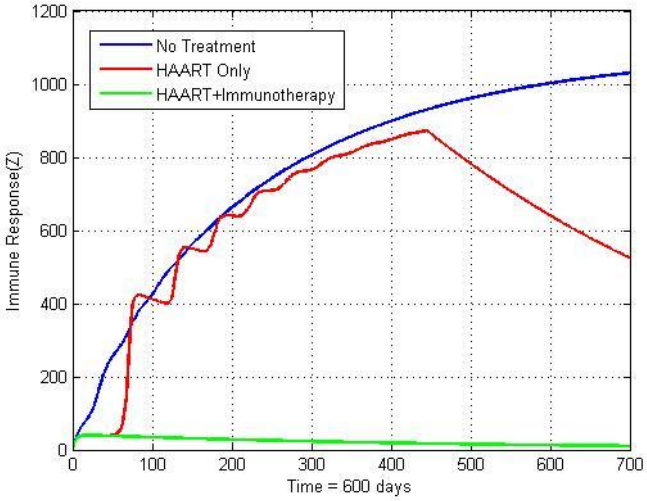
Gambar 4. Sel-$T\ CD4^+$ Sehat

Gambar 4 menunjukkan bahwa dengan kombinasi pengobatan HAART + Immunotherapy mengakibatkan sel-$T\ CD4^+$ sehat meningkat dengan nilai hampir mencapai 1500 $mm^{-3}day^{-1}$ jika dibandingkan hanya dengan pengobatan HAART dan tanpa pengobatan.



Gambar 5. Sel-$T\ CD4^+$ Terinfeksi

Gambar 5 menunjukkan bahwa dengan kombinasi pengobatan HAART + Immunotherapy mengakibatkan sel-$T\ CD4^+$ terinfeksi menurun dengan nilai dibawah 25 $mm^{-3}day^{-1}$ jika dibandingkan hanya dengan pengobatan HAART dan tanpa pengobatan dikarenakan sistem imun yang semakin meningkat.



Gambar 6. Respon Imun Sel CTL

Gambar 7 menunjukkan bahwa dengan kombinasi pengobatan HAART + Immunotherapy mengakibatkan respon imun menurun jika dibandingkan dengan hanya pengobatan HAART dan tanpa pengobatan. Hal ini dikarenakan kombinasi pengobatan HAART + Immunotherapy bekerja sangat efektif.

BAB V
PENUTUP

5.1 Kesimpulan

Dari hasil pembahasan dan analisa pada dinamika penyebaran virus HIV dengan pengobatan HAART dan Immunotherapy menggunakan Interleukin-2, maka dapat disimpulkan

1. Model Dasar Matematika Virus dapat dituliskan sebagai.

$$\frac{dx}{dt} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - \beta xy$$

$$\frac{dy}{dt} = \beta xy - ay - lyz \tag{5.1}$$

$$\frac{dz}{dt} = sy - bz$$

Model Matematika Pengobatan HAART

$$\frac{dx}{dt} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - (1-u)\beta xy$$

$$\frac{dy}{dt} = (1-u)\beta xy - ay - lyz \tag{5.2}$$

$$\frac{dz}{dt} = sy - bz$$

dan Model Matematika Pengobatan HAART + Immunotherapy

$$\frac{dx}{dt} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - (1-u_1)\beta xy + u_2 x$$

$$\frac{dy}{dt} = (1-u_1)\beta xy - ay - lyz \tag{5.3}$$

$$\frac{dz}{dt} = sy - bz$$

2.

3. Pengobatan HAART dan Immunotherapy menggunakan Interleukin-2 dapat mengurangi konsentrasi terapi antiretroviral selama 200 hari pertama dan tetap maksimum tingkat sel-$T\ CD4^{+}$ yang sehat dan tingkat infeksi yang sangat rendah hingga akhir dari pengobatan. Pengobatan HAART dan Immunotherapy menggunakan Interleukin-2 tidak hanya mampu memaksimumkan jumlah sel-$T\ CD4^{+}$ yang sehat, mengurangi tingkat infeksi dan meminimumkan biaya pengobatan selama periode pengobatan, namun juga dapat mengurangi konsentrasi HAART, sehingga dapat memperbaiki kualitas hidup pasien dengan mengurangi efek samping yang tinggi dan penggunaan yang berkelanjutan dari obat – obatan.

LAMPIRAN

Lampiran 1. Titik Kesetimbangan

$$\frac{dx}{dt} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - \beta xy$$

$$\frac{dy}{dt} = \beta xy - ay - lyz$$

$$\frac{dz}{dt} = sy - bz$$

$$R_+^3 = \{(x, y, z) \in R^3, x \geq 0, y \geq 0, z \geq 0\}$$

Misal $\frac{dx}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0$, maka

$$\lambda + px\left(1 - \frac{x}{T_m}\right) - dx - \beta xy = 0 \qquad (L1.1)$$

$$\beta xy - ay - lyz = 0 \qquad (L1.2)$$

$$sy - bz = 0 \qquad (L1.3)$$

Dari persamaan ($L1.2$) diperoleh

$$\beta xy - ay - lyz = 0 \Longrightarrow (\beta x - a - lz)y = 0$$

$y = 0$ atau $\beta x - a - lz = 0$

Dari persamaan ($L1.3$) diperoleh

$$sy - bz = 0 \Longrightarrow sy = bz \Leftrightarrow y = \frac{b}{s}z$$

$$y_0 = 0, z_0 = 0$$

Substitusikan ke persamaan ($L1.1$) diperoleh

$$\lambda + px_0\left(1 - \frac{x_0}{T_m}\right) - dx_0 = 0$$

$$\lambda + px_0 - \frac{px_0^2}{T_m} - dx_0 = 0$$

$$\lambda + (p-d)x_0 - \frac{px_0^2}{T_m} = 0$$

$$\frac{px_0^2}{T_m} - (p-d)x_0 - \lambda = 0$$

$$x_{0_{1,2}} = (p-d) \pm \frac{\sqrt{(p-d)^2 + \frac{4\lambda p}{T_m}}}{\frac{2p}{T_m}}$$

$$x_{0_{1,2}} = \frac{T_m}{2p}\left[(p-d) \pm \sqrt{(p-d)^2 + \frac{4\lambda p}{T_m}}\right]$$

$$x_0 = \frac{T_m}{2p}\left[(p-d) \pm \sqrt{(p-d)^2 + \frac{4\lambda p}{T_m}}\right]$$

Jadi diperoleh titik kesetimbangan untuk sel-$T\ CD4^+$ yang sehat $E_0 = (x_0, 0,0)$ dengan

$$x_0 = \frac{T_m}{2p}\left[(p-d) \pm \sqrt{(p-d)^2 + \frac{4\lambda p}{T_m}}\right]$$

Dari persamaan $(L1.2)$ diperoleh

$$(\beta x - a - lz) = 0 \Longrightarrow z^* = \frac{\beta x^* - a}{l}$$

Substitusikan ke $y = \frac{b}{s}z$ diperoleh

$$y^* = \frac{b}{s}z^* = \frac{b}{s}\left(\frac{\beta x^* - a}{l}\right) = \frac{b}{sl}(\beta x^* - a)$$

Substitusikan $y^* = \frac{b}{sl}(\beta x^* - a)$ ke persamaan $(L1.1)$ diperoleh

$$\lambda + px^*\left(1 - \frac{x^*}{T_m}\right) - dx^* - \beta x^*\left(\frac{b}{sl}(\beta x^* - a)\right) = 0$$

$$\lambda + px^* - \frac{px^{*2}}{T_m} - dx^* - \frac{b\beta^2 x^{*2}}{sl} + \frac{ab\beta x^*}{sl} = 0$$

$$\lambda + \left(p - d + \frac{ab\beta}{sl}\right)x^* - \left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)x^{*2} = 0$$

$$\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)x^{*2} - \left(p - d + \frac{ab\beta}{sl}\right)x^* - \lambda = 0$$

$$x^*_{1,2} = \frac{\left(p - d + \frac{ab\beta}{sl}\right) \pm \sqrt{\left(p - d + \frac{ab\beta}{sl}\right)^2 + 4\lambda\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)}}{2\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)}$$

$$x^* = \frac{\left(p - d + \frac{ab\beta}{sl}\right) + \sqrt{\left(p - d + \frac{ab\beta}{sl}\right)^2 + 4\lambda\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)}}{2\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)}$$

Jadi diperoleh titik kesetimbangan untuk sel-$T\ CD4^+$ yang terinfeksi $E^* = (x^*, y^*, z^*)$ dengan

$$x^* = \frac{\left(p - d + \frac{ab\beta}{sl}\right) + \sqrt{\left(p - d + \frac{ab\beta}{sl}\right)^2 + 4\lambda\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)}}{2\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)}$$

$$y^* = \frac{b}{sl}(\beta x^* - a)$$

$$z^* = \frac{\beta x^* - a}{l}$$

Lampiran 2. Analisis Kestabilan Titik Kesetimbangan

Dari persamaan $y^* = \frac{b}{sl}(\beta x^* - a) \Longrightarrow \frac{ab}{sl}\left(\frac{\beta}{a}x^* - 1\right)$

Jadi Angka Reproduksi Dasar (*Basic Reproduction Number*) adalah $R_0 = \frac{\beta}{a}x^*$. Sehingga untuk titik kesetimbangan $E^* = (x^*, y^*, z^*)$ dapat ditulis ulang sebagai berikut.

$$E^* = (x^*, y^*, z^*)$$

dengan

$$x^* = \frac{\left(p - d + \frac{ab\beta}{sl}\right) + \sqrt{\left(p - d + \frac{ab\beta}{sl}\right)^2 + 4\lambda\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)}}{2\left(\frac{p}{T_m} + \frac{b\beta^2}{sl}\right)}$$

$$y^* = \frac{ab}{sl}(R_0 - 1)$$

$$z^* = \frac{a}{l}(R_0 - 1)$$

Matriks Jacobi dari persamaan $(1a - 1c)$ adalah

$$J = \begin{bmatrix} p - d - \frac{2px}{T_m} - \beta y & -\beta x & 0 \\ \beta y & \beta x - a - lz & -ly \\ 0 & s & -b \end{bmatrix}$$

❖ Matriks Jacobi untuk titik kesetimbangan $E_0 = (x_0, 0,0)$ adalah

$$J(E_0) = \begin{bmatrix} p - d - \frac{2px_0}{T_m} & -\beta x_0 & 0 \\ 0 & \beta x_0 - a & 0 \\ 0 & s & -b \end{bmatrix}$$

$$\begin{vmatrix} N - p + d + \frac{2px_0}{T_m} & \beta x_0 & 0 \\ 0 & N - \beta x_0 + a & 0 \\ 0 & -s & N + b \end{vmatrix} = 0$$

Persamaan karakteristik dari matriks $J(E_0)$ adalah

$$\left(N - p + d + \frac{2px_0}{T_m}\right)(N - \beta x_0 + a)(N + b) = 0$$

Nilai eigen dari matriks $J(E_0)$ adalah

$N_1 = p - d - \frac{2px_0}{T_m}$

Dari persamaan $\lambda + px_0\left(1 - \frac{x_0}{T_m}\right) - dx_0 = 0 \Longrightarrow \lambda + px_0 - \frac{px_0^2}{T_m} = 0$

$$\Leftrightarrow \lambda + px_0 - \frac{2px_0^2}{T_m} + \frac{px_0^2}{T_m} - dx_0 = 0$$

$$\Leftrightarrow \lambda + px_0 - \frac{2px_0^2}{T_m} + \frac{px_0^2}{T_m} - dx_0 = 0$$

Bagi kedua ruas dengan x_0 diperoleh

$$\frac{\lambda}{x_0} + p - \frac{2px_0}{T_m} + \frac{px_0}{T_m} - d = 0$$

$$\Leftrightarrow p - d - \frac{2px_0}{T_m} = -\left(\frac{\lambda}{x_0} + \frac{px_0}{T_m}\right)$$

Sehingga N_1 menjadi

$N_1 = p - d - \frac{2px_0}{T_m} = -\left(\frac{\lambda}{x_0} + \frac{px_0}{T_m}\right) < 0$

$N_2 = \beta x_0 - a$ $(L2.1)$

$N_3 = -b < 0$

Persamaan $(L2.1)$ menjadi stabil jika $R_0 < 1$, karena nilai $N_1, N_2, N_3 < 0$. Namun, menjadi pelana (*saddle*) jika $R_0 > 1$, karena nilai $N_1, N_3 < 0$ dan $N_2 > 0$.

❖ Matriks Jacobi untuk titik kesetimbangan $E^* = (x^*, y^*, z^*)$ adalah

$$J(E^*) = \begin{bmatrix} p - d - \frac{2px^*}{T_m} - \beta y^* & -\beta x^* & 0 \\ \beta y^* & \beta x^* - a - lz^* & -ly^* \\ 0 & s & -b \end{bmatrix}$$

atau

$$J(E^*) = \begin{bmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ 0 & a_{32} & a_{33} \end{bmatrix}$$

dengan

$$a_{11} = p - d - \frac{2px^*}{T_m} - \beta y^*$$

$$a_{12} = -\beta x^*$$

$$a_{21} = \beta y^*$$

$$a_{22} = \beta x^* - a - lz^*$$

$$a_{23} = -ly^*$$

$$a_{32} = s$$

$$a_{33} = -b$$

$$\begin{vmatrix} N - a_{11} & -a_{12} & 0 \\ -a_{21} & N - a_{22} & -a_{23} \\ 0 & -a_{32} & N - a_{33} \end{vmatrix} = 0$$

Persamaan karakteristik dari matriks $J(E^*)$ adalah

$$(N - a_{11})(N - a_{22})(N - a_{33}) - [a_{23}a_{32}(N - a_{11}) + a_{12}a_{21}(N - a_{33})] = 0$$

$$(N^2 - a_{22}N - a_{11}N + a_{11}a_{22})(N - a_{33}) - [a_{23}a_{32}N - a_{11}a_{23}a_{32} + a_{12}a_{21}N - a_{12}a_{21}a_{33}] = 0$$

$$(N^2 - (a_{11} + a_{22})N + a_{11}a_{22})(N - a_{33}) - [(a_{12}a_{21} + a_{23}a_{32})N - (a_{11}a_{23}a_{32} + a_{12}a_{21}a_{33})] = 0$$

$$[N^3 - (a_{11} + a_{22})N^2 + a_{11}a_{22}N - a_{33}N^2 + a_{33}(a_{11} + a_{22})N - a_{11}a_{22}a_{33}] - [(a_{12}a_{21} + a_{23}a_{32})N - (a_{11}a_{23}a_{32} + a_{12}a_{21}a_{33})] = 0$$

$$N^3 - (a_{11} + a_{22} + a_{33})N^2 + (a_{11}a_{22} + a_{33}(a_{11} + a_{22}) - a_{12}a_{21} - a_{23}a_{32})N + a_{11}a_{23}a_{32} + a_{12}a_{21}a_{33} - a_{11}a_{22}a_{33} = 0$$

$$N^3 + AN^2 + BN + C = 0$$

dengan

$$A = -(a_{11} + a_{22} + a_{33})$$

$$B = (a_{11}a_{22} + a_{33}(a_{11} + a_{22}) - a_{12}a_{21} - a_{23}a_{32})$$

$$C = a_{11}a_{23}a_{32} + a_{12}a_{21}a_{33} - a_{11}a_{22}a_{33}$$

$$A = -(a_{11} + a_{22} + a_{33})$$

$$= -\left[\left(p - d - \frac{2px^*}{T_m} - \beta y^*\right) + (\beta x^* - a - lz^*) + (-b)\right]$$

$$= -p + d + \frac{2px^*}{T_m} + \beta y^* - \beta x^* + a + lz^* + b$$

$$= -p + d + \frac{2px^*}{T_m} + \beta\left[\frac{b}{sl}(\beta x^* - a)\right] - \beta x^* + a + l\left[\frac{(\beta x^* - a)}{l}\right] + b$$

$$= -p + d + \frac{2px^*}{T_m} + \frac{b\beta}{sl}(\beta x^* - a) - \beta x^* + a + \beta x^* - a + b$$

$$= -p + d + \frac{2px^*}{T_m} + \frac{b\beta}{sl}(\beta x^* - a) + b$$

Dari persamaan $\lambda + px^*\left(1 - \frac{x^*}{T_m}\right) - dx^* - \beta x^* y^* = 0$ dan $y^* = \frac{b}{sl}(\beta x^* - a)$, diperoleh

$$\lambda + px^*\left(1 - \frac{x^*}{T_m}\right) - dx^* - \beta x^*\left[\frac{b}{sl}(\beta x^* - a)\right] = 0$$

$$\lambda + px^*\left(1 - \frac{x^*}{T_m}\right) - dx^* = \beta x^*\left[\frac{b}{sl}(\beta x^* - a)\right]$$

Bagi kedua ruas dengan x^*, diperoleh

$$\frac{\lambda}{x^*} + p\left(1 - \frac{x^*}{T_m}\right) - d = \beta\left[\frac{b}{sl}(\beta x^* - a)\right]$$

$$\frac{\lambda}{x^*} + p\left(1 - \frac{x^*}{T_m}\right) - d = \frac{b\beta}{sl}(\beta x^* - a)$$

Sehingga

$$A = -p + d + \frac{2px^*}{T_m} + \frac{b\beta}{sl}(\beta x^* - a) + b$$

$$= -p + d + \frac{2px^*}{T_m} + \left[\frac{\lambda}{x^*} + p\left(1 - \frac{x^*}{T_m}\right)\right] + b$$

$$= -p + d + \frac{2px^*}{T_m} + \frac{\lambda}{x^*} + p - \frac{px^*}{T_m} + b$$

$$A = \frac{\lambda}{x^*} + \frac{px^*}{T_m} + b > 0$$

$$B = (a_{11}a_{22} + a_{33}(a_{11} + a_{22}) - a_{12}a_{21} - a_{23}a_{32})$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)(\beta x^* - a - lz^*)$$
$$+ (-b)\left(p - d - \frac{2px^*}{T_m} - \beta y^* + \beta x^* - a - lz^*\right) - (-\beta x^*)(\beta y^*)$$
$$- (-ly^*)(s)$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)(\beta x^* - a - lz^*) - b\left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)$$
$$- b(\beta x^* - a - lz^*) + \beta^2 x^* y^* + sly^*$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)[(\beta x^* - a - lz^*) - b] - b(\beta x^* - a - lz^*) + \beta^2 x^* y^*$$
$$+ sly^*$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)\left[\left(\beta x^* - a - l\left[\frac{\beta x^* - a}{l}\right]\right) - b\right]$$
$$- b\left(\beta x^* - a - l\left[\frac{\beta x^* - a}{l}\right]\right) + \beta^2 x^* y^* + sly^*$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)[(\beta x^* - a - (\beta x^* - a)) - b]$$
$$- b(\beta x^* - a - (\beta x^* - a)) + \beta^2 x^* y^* + sly^*$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)(-b) - b(0) + \beta^2 x^* y^* + sly^*$$

$$= (-b)\left(p - d - \frac{2px^*}{T_m} - \beta y^*\right) + \beta^2 x^* y^* + sly^*$$

Dari persamaan

$$\lambda + px^*\left(1 - \frac{x^*}{T_m}\right) - dx^* - \beta x^* y^* = 0$$

Bagi kedua ruas dengan x^*, diperoleh

$$\frac{\lambda}{x^*} + p\left(1 - \frac{x^*}{T_m}\right) - d - \beta y^* = 0 \Leftrightarrow \frac{\lambda}{x^*} + p - \frac{px^*}{T_m} - d - \beta y^* = 0$$

$$\Leftrightarrow \frac{\lambda}{x^*} + p - \frac{2px^*}{T_m} + \frac{px^*}{T_m} - d - \beta y^* = 0$$

$$\Leftrightarrow p - d - \frac{2px^*}{T_m} - \beta y^* = -\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right)$$

Sehingga

$$B = (-b)\left(p - d - \frac{2px^*}{T_m} - \beta y^*\right) + \beta^2 x^* y^* + sly^*$$

$$= (-b)\left[-\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right)\right] + \beta^2 x^* y^* + sly^*$$

$$B = b\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right) + \beta^2 x^* y^* + sly^* > 0$$

$$C = a_{11}a_{23}a_{32} + a_{12}a_{21}a_{33} - a_{11}a_{22}a_{33}$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)(-ly^*)(s) + (-\beta x^*)(\beta y^*)(-b)$$
$$- \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)(\beta x^* - a - lz^*)(-b)$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)[-sly^* - b(\beta x^* - a - lz^*)] + b\beta^2 x^* y^*$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)\left[-sly^* - b\left(\beta x^* - a - l\left[\frac{\beta x^* - a}{l}\right]\right)\right] + b\beta^2 x^* y^*$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)[-sly^* - b(\beta x^* - a - (\beta x^* - a))] + b\beta^2 x^* y^*$$

$$= \left(p - d - \frac{2px^*}{T_m} - \beta y^*\right)[-sly^* - b(0)] + b\beta^2 x^* y^*$$

$$= (-sly^*)\left(p - d - \frac{2px^*}{T_m} - \beta y^*\right) + b\beta^2 x^* y^*$$

$$= (-sly^*)\left[-\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right)\right] + b\beta^2 x^* y^*$$

$$C = sly^*\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right) + b\beta^2 x^* y^* > 0$$

Dari kriteria Routh-Hurwitz, syarat perlu dan cukup untuk stabil asimtotik adalah $AB - C > 0$, karena

$$\left(\frac{\lambda}{x^*} + \frac{px^*}{T_m} + b\right)\left[b\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right) + \beta^2 x^* y^* + sly^*\right] - \left[sly^*\left(\frac{px^*}{T_m} + \frac{\lambda}{x^*}\right) + b\beta^2 x^* y^*\right] > 0$$

Lampiran 3. Prinsip Maksimum Pontryagin

A. Kontrol Optimal Highly Active Antiretroviral Therapy (HAART)

$$\frac{dx}{dt} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - (1-u)\beta xy$$

$$\frac{dy}{dt} = (1-u)\beta xy - ay - lyz$$

$$\frac{dz}{dt} = sy - bz$$

1). Fungsi Tujuan/ Objektif (*Performance Index*)

$$J(u) = \int_0^T \left[x(t) + z(t) - \frac{A}{2}u^2(t)\right] dt \qquad (L3.1)$$

dengan $A \geq 0$

2). Kontrol Optimal u Dan Himpunan Kontrol U

$$J(u^*) = \max_{u \in U} J(u)\,, U = \{0 \leq u(t) \leq 1, t \in [0,T]\} \qquad (L3.2)$$

3). Berdasarkan $(L3.1)$ dan $(L3.2)$ diperoleh Persamaan Lagrangian sebagai berikut.

$$L = x + z - \frac{A}{2}u^2 + \psi_1\left[\lambda + px\left(1 - \frac{x}{T_m}\right) - dx - (1-u)\beta xy\right] + \psi_2[(1-u)\beta xy - ay - lyz] + \psi_3[sy - bz] + w_1 u + w_2(1-u)$$

dengan

$$w_1 \geq 0, w_2 \geq 0$$

$$w_1 u = 0$$

$$w_2(1-u) = 0$$

Syarat perlu yang dibentuk oleh Prinsip Maksimum Pontryagin adalah Kondisi Stasioner dari Persamaan Lagrangian, persamaan *state*, dan persamaan *co-state*.

4). Persamaan *state* dan *co-state*.

$$x' = \frac{\partial L}{\partial \psi_1} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - (1-u)\beta xy$$

$$y' = \frac{\partial L}{\partial \psi_2} = (1-u)\beta xy - ay - lyz$$

$$z' = \frac{\partial L}{\partial \psi_3} = sy - bz$$

$$\psi_1' = -\frac{\partial L}{\partial x} = -\left[1 + \psi_1 p - \psi_1 \frac{2px^*}{T_m} - \psi_1 d - \psi_1(1-u^*)\beta y^* + \psi_2(1-u^*)\beta y^*\right]$$

$$= -\left[1 + \psi_1\left(\frac{2px^*}{T_m} + p - d\right) + \beta y^*(1-u^*)(\psi_2 - \psi_1)\right]$$

$$= -1 + \psi_1\left(\frac{2px^*}{T_m} + d - p\right) + \beta y^*(1-u^*)(\psi_1 - \psi_2)$$

$$\psi_2' = -\frac{\partial L}{\partial y} = -[-\psi_1(1-u^*)\beta x^* + \psi_2(1-u^*)\beta x^* - \psi_2 a - \psi_2 l z^* + \psi_3 s]$$

$$= -[\beta x^*(1-u^*)(\psi_2 - \psi_1) - \psi_2(a + lz^*) + \psi_3 s]$$

$$= \beta x^*(1-u^*)(\psi_1 - \psi_2) + \psi_2(a + lz^*) - \psi_3 s$$

$$\psi_3' = -\frac{\partial L}{\partial z} = -[1 - \psi_2 l y^* - \psi_3 b] = -1 + \psi_2 l y^* + \psi_3 b$$

dengan $x(0) = x_0, y(0) = y_0, z(0) = z_0$ dan $\psi_1(T) = \psi_2(T) = \psi_3(T) = 0$ (kondisi transversal).

$$\frac{\partial L}{\partial u} = -Au + \psi_1 \beta x^* y^* - \psi_2 \beta x^* y^* + w_1 - w_2$$

$$\frac{\partial^2 L}{\partial u^2} = -A$$

$A \geq 0$, maka $\frac{\partial^2 L}{\partial u^2} \leq 0$ (memenuhi syarat cukup untuk mencapai nilai maksimum).

5). Persamaan Stasioner

$\frac{\partial L}{\partial u} = 0$, sehingga diperoleh

$$-Au + \psi_1 \beta x^* y^* - \psi_2 \beta x^* y^* + w_1 - w_2 = 0 \Longrightarrow u = \frac{\beta x^* y^* (\psi_1 - \psi_2) + w_1 - w_2}{A}$$

dengan $w_1 \geq 0, w_2 \geq 0$

$$w_1 u = 0$$

$$w_2 (1 - u) = 0$$

(i) Untuk $0 < u < 1$, $w_1 = w_2 = 0$, sehingga

$$0 = \frac{\beta x^* y^* (\psi_1 - \psi_2)}{A}$$

(ii) Untuk $u = 1$, $w_1 = 0$, sehingga

$$u = \frac{\beta x^* y^* (\psi_1 - \psi_2) - w_2}{A} = 1$$

$$\beta x^* y^* (\psi_1 - \psi_2) - w_2 = A$$

$$w_2 = \beta x^* y^* (\psi_1 - \psi_2) - A \geq 0$$

Akibatnya

$$A \leq \beta x^* y^* (\psi_1 - \psi_2)$$

$$\frac{\beta x^* y^* (\psi_1 - \psi_2)}{A} \geq 1$$

(iii) Untuk $u = 0, w_2 = 0$, sehingga

$$u = \frac{\beta x^* y^* (\psi_1 - \psi_2) + w_1}{A} = 0$$

$$w_1 = -\beta x^* y^* (\psi_1 - \psi_2) \geq 0$$

Akibatnya

$$-\beta x^* y^* (\psi_1 - \psi_2) \geq 0$$

$$\beta x^* y^* (\psi_1 - \psi_2) \leq 0$$

$$\frac{\beta x^* y^* (\psi_1 - \psi_2)}{A} \leq 0$$

Karena $U = \{u(t) | 0 \leq u(t) \leq 1, t \in [0, T]\}$, $u(t) \in U$, maka

$$u^*(t) = \min\left(1, max\left(0, \frac{\beta x^* y^* (\psi_1 - \psi_2)}{A}\right)\right) \qquad (L3.3)$$

B. Kontrol Optimal HAART Dan Immunotherapy IL-2

$$\frac{dx}{dt} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - (1 - u_1)\beta xy + u_2 x$$

$$\frac{dy}{dt} = (1 - u_1)\beta xy - ay - lyz$$

$$\frac{dz}{dt} = sy - bz$$

1). Fungsi Tujuan/ Objektif (*Performance Index*)

$$J(u) = \int_0^T \left[x(t) + z(t) - \left[\frac{A_1}{2}u_1^2(t) + \frac{A_2}{2}u_2^2(t)\right]\right] dt \qquad (L3.4)$$

dengan $A_1 \geq 0, A_2 \geq 0$

2). Kontrol Optimal u_1, u_2 dan Himpunan Kontrol U

$$J(u_1^*, u_2^*) = \max_{u \in U} J(u_1, u_2) \qquad (L3.5)$$

$$U = \left\{\left(u_1(t), u_2(t)\right) : 0 \leq u_1(t) \leq 1, 0.0001 \leq u_2(t) \leq 0.003, t \in [0, T]\right\}$$

3). Berdasarkan $(L3.4)$ dan $(L3.5)$ diperoleh Persamaan Lagrangian sebagai berikut.

$$L = x + z - \frac{A_1}{2}u_1^2 - \frac{A_2}{2}u_2^2 + \psi_1\left[\lambda + px\left(1 - \frac{x}{T_m}\right) - dx - (1-u_1)\beta xy + u_2 x\right]$$
$$+ \psi_2[(1-u_1)\beta xy - ay - lyz] + \psi_3[sy - bz] + w_1 u_1$$
$$+ w_2(1-u_1) + p_1 u_2 + p_2(1-u_2)$$

dengan

$$w_1 \geq 0, w_2 \geq 0, p_1 \geq 0, p_2 \geq 0$$

$$w_1 u_1 = 0$$

$$w_2(1-u_1) = 0$$

$$p_1 u_2 = 0$$

$$p_2(1-u_2) = 0$$

Syarat perlu yang dibentuk oleh Prinsip Maksimum Pontryagin adalah Kondisi Stasioner dari Persamaan Lagrangian, persamaan *state*, dan persamaan *co-state*.

4). Persamaan *state* dan *co-state*.

$$x' = \frac{\partial L}{\partial \psi_1} = \lambda + px\left(1 - \frac{x}{T_m}\right) - dx - (1-u_1)\beta xy + u_2 x$$

$$y' = \frac{\partial L}{\partial \psi_2} = (1-u_1)\beta xy - ay - lyz$$

$$z' = \frac{\partial L}{\partial \psi_3} = sy - bz$$

$$\psi_1' = -\frac{\partial L}{\partial x} = -\left[1 + \psi_1 p - \psi_1 \frac{2px^*}{T_m} - \psi_1 d - \psi_1(1-u_1^*)\beta y^* + \psi_1 u_2^*\right.$$
$$\left. + \psi_2(1-u^*)\beta_1 y^*\right]$$

$$= -\left[1 + \psi_1\left(\frac{2px^*}{T_m} + p - d + u_2^*\right) + \beta y^*(1-u_1^*)(\psi_2 - \psi_1)\right]$$

$$= -1 + \psi_1\left(\frac{2px^*}{T_m} + d - p - u_2^*\right) + \beta y^*(1-u_1^*)(\psi_1 - \psi_2)$$

$$\psi_2' = -\frac{\partial L}{\partial y} = -[-\psi_1(1-u_1^*)\beta x^* + \psi_2(1-u^*)\beta x^* - \psi_2 a - \psi_2 l z^* + \psi_3 s]$$

$$= -[\beta x^*(1-u_1^*)(\psi_2-\psi_1) - \psi_2(a+lz^*) + \psi_3 s]$$

$$= \beta x^*(1-u_1^*)(\psi_1-\psi_2) + \psi_2(a+lz^*) - \psi_3 s$$

$$\psi_3' = -\frac{\partial L}{\partial z} = -[1-\psi_2 l y^* - \psi_3 b] = -1 + \psi_2 l y^* + \psi_3 b$$

dengan $x(0) = x_0, y(0) = y_0, z(0) = z_0$ dan $\psi_1(T) = \psi_2(T) = \psi_3(T) = 0$ (kondisi transversal).

$$\frac{\partial L}{\partial u_1} = -A_1 u_1 + \psi_1 \beta x^* y^* - \psi_2 \beta x^* y^* + w_1 - w_2$$

$$\frac{\partial^2 L}{\partial u_1^2} = -A_1$$

$A_1 \geq 0$, maka $\frac{\partial^2 L}{\partial u_1^2} \leq 0$ (memenuhi syarat cukup untuk mencapai nilai maksimum).

$$\frac{\partial L}{\partial u_2} = -A_2 u_2 + \psi_1 x^* + p_1 - p_2$$

$$\frac{\partial^2 L}{\partial u_2^2} = -A_2$$

$A_2 \geq 0$, maka $\frac{\partial^2 L}{\partial u_2^2} \leq 0$ (memenuhi syarat cukup untuk mencapai nilai maksimum).

5). Persamaan Stasioner

❖ $\frac{\partial L}{\partial u_1} = 0$, sehingga diperoleh

$$-A_1 u_1 + \psi_1 \beta x^* y^* - \psi_2 \beta x^* y^* + w_1 - w_2 = 0 \Longrightarrow u_1 = \frac{\beta x^* y^*(\psi_1 - \psi_2) + w_1 - w_2}{A_1}$$

dengan $w_1 \geq 0, w_2 \geq 0$

$$w_1 u_1 = 0$$

$$w_2(1-u_1)=0$$

(i) Untuk $0<u_1<1$, $w_1=w_2=0$, sehingga

$$0=\frac{\beta x^* y^*(\psi_1-\psi_2)}{A_1}$$

(ii) Untuk $u_1=1$, $w_1=0$, sehingga

$$u_1=\frac{\beta x^* y^*(\psi_1-\psi_2)-w_2}{A_1}=1$$

$$\beta x^* y^*(\psi_1-\psi_2)-w_2=A_1$$

$$w_2=\beta x^* y^*(\psi_1-\psi_2)-A_1\geq 0$$

Akibatnya

$$A_1\leq \beta x^* y^*(\psi_1-\psi_2)$$

$$\frac{\beta x^* y^*(\psi_1-\psi_2)}{A_1}\geq 1$$

(iii) Untuk $u_1=0, w_2=0$, sehingga

$$u_1=\frac{\beta x^* y^*(\psi_1-\psi_2)+w_1}{A_1}=0$$

$$w_1=-\beta x^* y^*(\psi_1-\psi_2)\geq 0$$

Akibatnya

$$-\beta x^* y^*(\psi_1-\psi_2)\geq 0$$

$$\beta x^* y^*(\psi_1-\psi_2)\leq 0$$

$$\frac{\beta x^* y^*(\psi_1-\psi_2)}{A_1}\leq 0$$

❖ $\frac{\partial L}{\partial u_2}=0$, sehingga diperoleh

$$-A_2u_2 + x^*(t)\psi_1 + p_1 - p_2 = 0 \Longrightarrow u_2 = \frac{x^*(t)\psi_1 + p_1 - p_2}{A_2}$$

dengan $p_1 \geq 0, p_2 \geq 0$

$$p_1u_2 = 0$$

$$p_2(1 - u_2) = 0$$

(i) Untuk $0 < u_2 < 1$, $p_1 = p_2 = 0$, sehingga

$$0 = \frac{x^*(t)\psi_1}{A_2}$$

(ii) Untuk $u_2 = 1$, $p_1 = 0$, sehingga

$$u_1 = \frac{x^*(t)\psi_1 - p_2}{A_2} = 1$$

$$x^*(t)\psi_1 - p_2 = A_2$$

$$p_2 = x^*(t)\psi_1 - A_2 \geq 0$$

Akibatnya

$$A_2 \leq x^*(t)\psi_1$$

$$\frac{x^*(t)\psi_1}{A_2} \geq 1$$

(iii) Untuk $u_2 = 0, p_2 = 0$, sehingga

$$u_2 = \frac{x^*(t)\psi_1 + p_1}{A_2} = 0$$

$$p_1 = -x^*(t)\psi_1 \geq 0$$

Akibatnya

$$-x^*(t)\psi_1 \geq 0$$

$$x^*(t)\psi_1 \leq 0$$

$$\frac{x^*(t)\psi_1}{A_2} \leq 0$$

Karena

$U = \{u_1(t), u_2(t) | 0 \leq u_1(t) \leq 1, 0.0001 \leq u_2(t) \leq 0.003, t \in [0, T]\}$,

$u_1(t), u_2(t) \in U$, maka

$$u_1^*(t) = \min\left(1, max\left(0, \frac{\beta x^* y^*(\psi_1 - \psi_2)}{A_1}\right)\right) \qquad (L3.6)$$

$$u_2^*(t) = \min\left(0.003, max\left(0.0001, \frac{x^*(t)\psi_1}{A_2}\right)\right) \qquad (L3.7)$$

SOURCE CODE (HAART) DAN (HAART + Immunotherapy)

No	Function (HAART) AND (HAART + Immunotherapy Using IL-2)

```
function
[t,f]=simulation_HIV(lamda,beta,d,p,a,l,s,b,Tm,T,X0,Y0,Z0,A,A1,A2)
N=1000;
t=linspace(0,T,N+1);
h=T/N;
h2=h/2;
%State Without Control
X=zeros(1,N+1);
Y=zeros(1,N+1);
Z=zeros(1,N+1);
X(1)=X0;
Y(1)=Y0;
Z(1)=Z0;

%State With Control (HAART)
stateX=zeros(1,N+1);
stateY=zeros(1,N+1);
stateZ=zeros(1,N+1);
stateX(1)=X0;
stateY(1)=Y0;
stateZ(1)=Z0;

%Co-State (HAART)
co_stateX=zeros(1,N+1);
co_stateY=zeros(1,N+1);
co_stateZ=zeros(1,N+1);

%Control HAART
u=zeros(1,N+1);

%State With Control (HAART+Immunotherapy IL-2)
X2=zeros(1,N+1);
Y2=zeros(1,N+1);
Z2=zeros(1,N+1);
X2(1)=X0;
```

```
Y2(1)=Y0;
Z2(1)=Z0;

%Co-State (HAART+Immunotherapy IL-2)
PX2=zeros(1,N+1);
PY2=zeros(1,N+1);
PZ2=zeros(1,N+1);

%Control HAART+Immunotherapy IL-2
ucomb1=zeros(1,N+1);
ucomb2=zeros(1,N+1);
iteration=0;
for i=1:N
    iteration=iteration+1;
    oldu=u;
    olducomb1=ucomb1;
    olducomb2=ucomb2;
    %fprintf('iterasi ke= %i\n',iteration);

    %Part1 State With Control HAART
    for i=1:N
        value_stateX=lamda+p*stateX(i)*(1-stateX(i)/Tm)-
d*stateX(i)-(1-u(i))...
            *beta*stateX(i)*stateY(i);
        value_stateY=(1-u(i))*beta*stateX(i)*stateY(i)-
a*stateY(i)-l*stateY(i)...
            *stateZ(i);
        value_stateZ=s*stateY(i)-b*stateZ(i);
        %-----------------------------------------------------------
---------
        value_state2X=lamda+p*(stateX(i)+h2*value_stateX)...
            *(1-(stateX(i)+h2*value_stateX)/Tm)-
d*(stateX(i)+h2*value_stateX)...
            -(1-
0.5*(u(i)+u(i+1)))*beta*(stateX(i)+h2*value_stateX)...
            *(stateY(i)+h2*value_stateY);
        value_state2Y=(1-
0.5*(u(i)+u(i+1)))*beta*(stateX(i)+h2*value_stateX)...
```

```
            *(stateY(i)+h2*value_stateY)-
a*(stateY(i)+h2*value_stateY)...
            -
l*(stateY(i)+h2*value_stateY)*(stateZ(i)+h2*value_stateZ);
        value_state2Z=s*(stateY(i)+h2*value_stateY)...
            -b*(stateZ(i)+h2*value_stateZ);
        %-------------------------------------------------------
---------
        value_state3X=lamda+p*(stateX(i)+h2*value_state2X)...
            *(1-(stateX(i)+h2*value_state2X)/Tm)-
d*(stateX(i)+h2*value_state2X)...
            -(1-
0.5*(u(i)+u(i+1)))*beta*(stateX(i)+h2*value_state2X)...
            *(stateY(i)+h2*value_state2Y);
        value_state3Y=(1-
0.5*(u(i)+u(i+1)))*beta*(stateX(i)+h2*value_state2X)...
            *(stateY(i)+h2*value_state2Y)-
a*(stateY(i)+h2*value_state2Y)...
            -
l*(stateY(i)+h2*value_state2Y)*(stateZ(i)+h2*value_state2Z);
        value_state3Z=s*(stateY(i)+h2*value_state2Y)...
            -b*(stateZ(i)+h2*value_state2Z);
        %-------------------------------------------------------
---------
        value_state4X=lamda+p*(stateX(i)+h*value_state3X)...
            *(1-(stateX(i)+h*value_state3X)/Tm)-
d*(stateX(i)+h*value_state3X)...
            -(1-u(i))*beta*(stateX(i)+h*value_state3X)...
            *(stateY(i)+h*value_state3Y);
        value_state4Y=(1-u(i))*beta*(stateX(i)+h*value_state3X)...
            *(stateY(i)+h*value_state3Y)-
a*(stateY(i)+h*value_state3Y)...
            -
l*(stateY(i)+h*value_state3Y)*(stateZ(i)+h*value_state3Z);
        value_state4Z=s*(stateY(i)+h*value_state3Y)...
            -b*(stateZ(i)+h*value_state3Z);
        %-------------------------------------------------------
---------
```

```
stateX(i+1)=stateX(i)+(h/6)*(value_stateX+2*value_state2X...
            +2*value_state3X+value_state4X);

stateY(i+1)=stateY(i)+(h/6)*(value_stateY+2*value_state2Y...
            +2*value_state3Y+value_state4Y);

stateZ(i+1)=stateZ(i)+(h/6)*(value_stateZ+2*value_state2Z...
            +2*value_state3Z+value_state4Z);
    end;
    %End Of Part1


    %Part2 Co-State HAART
    for i=1:N
        j=N+2-i;
        value_stateX=-1+co_stateX(j)*((2*p*stateX(j)/Tm)+d-p)+...
            beta*stateY(j)*(1-u(j))*(co_stateX(j)-co_stateY(j));
        value_stateY= beta*stateY(j)*(1-u(j))*(co_stateX(j)-
co_stateY(j))...
            +co_stateY(j)*(a+l*stateZ(j))-co_stateZ(j)*s;
        value_stateZ=-1+co_stateY(j)*l*stateY(j)+co_stateZ(j)*b;
        %-------------------------------------------------------
---------
        value_state2X=-1+(co_stateX(j)-h2*value_stateX)...
            *((2*p*0.5*(stateX(j)+stateX(j-1))/Tm)+d-p)...
            +beta*(stateY(j)+stateY(j-1))*(1-0.5*(u(j)+u(j-1)))...
            *((co_stateX(j)-h2*value_stateX)-(co_stateY(j)-
h2*value_stateY));
        value_state2Y= beta*0.5*(stateY(j)+stateY(j-1))*(1-
0.5*(u(j)+u(j-1)))...
            *((co_stateX(j)-h2*value_stateX)-(co_stateY(j)-
h2*value_stateY))...
            +(co_stateY(j)-
h2*value_stateY)*(a+l*0.5*(stateZ(j)+stateZ(j-1)))...
            -(co_stateZ(j)-h2*value_stateZ)*s;
        value_state2Z=-1+(co_stateY(j)-h2*value_stateY)...
            *l*0.5*(stateY(j)+stateY(j-1))+(co_stateZ(j)-
h2*value_stateZ)*b;
        %-------------------------------------------------------
---------
```

```
        value_state3X=-1+(co_stateX(j)-h2*value_state2X)...
            *((2*p*0.5*(stateX(j)+stateX(j-1))/Tm)+d-p)...
            +beta*0.5*(stateY(j)+stateY(j-1))*(1-0.5*(u(j)+u(j-
1)))...
            *((co_stateX(j)-h2*value_state2X)...
            -(co_stateY(j)-h2*value_state2Y));
        value_state3Y= beta*0.5*(stateY(j)+stateY(j-1))*(1-
0.5*(u(j)+u(j-1)))...
            *((co_stateX(j)-h2*value_state2X)-(co_stateY(j)-
h2*value_state2Y))...
            +(co_stateY(j)-h2*value_state2Y)...
            *(a+l*0.5*(stateZ(j)+stateZ(j-1)))...
            -(co_stateZ(j)-h2*value_state2Z)*s;
        value_state3Z=-1+(co_stateY(j)-h2*value_state2Y)...
            *l*0.5*(stateY(j)+stateY(j-1))+(co_stateZ(j)-
h2*value_state2Z)*b;
        %-------------------------------------------------------
---------
        value_state4X=-1+(co_stateX(j)-h*value_state3X)...
            *((2*p*(stateX(j-1))/Tm)+d-p)...
            +beta*(stateY(j-1))*(1-u(j))...
            *((co_stateX(j)-h*value_state3X)-(co_stateY(j)-
h*value_state3Y));
        value_state4Y= beta*(stateY(j-1))*(1-u(j))...
            *((co_stateX(j)-h*value_state3X)-(co_stateY(j)-
h*value_state3Y))...
            +(co_stateY(j)-h*value_state3Y)...
            *(a+l*(stateZ(j-1)))...
            -(co_stateZ(j)-h*value_state3Z)*s;
        value_state4Z=-1+(co_stateY(j)-h*value_state3Y)...
            *l*(stateY(j-1))...
            +(co_stateZ(j)-h*value_state3Z)*b;
        %-------------------------------------------------------
---------
        co_stateX(j-1)=co_stateX(j)-
(h/6)*(value_stateX+2*value_state2X...
            +2*value_state3X+value_state4X);
        co_stateY(j-1)=co_stateY(j)-
(h/6)*(value_stateY+2*value_state2Y...
```

```
            +2*value_state3Y+value_state4Y);
        co_stateZ(j-1)=co_stateZ(j)-
(h/6)*(value_stateZ+2*value_state2Z...
            +2*value_state3Z+value_state4Z);
        %-------------------------------------------------------
---------
        u(j)=min(1,max(0,(beta*stateX(j)*stateY(j)...
            *(co_stateX(j)-co_stateY(j)))/A));
    end;
    %End Of Part2

    %Part3 State Without Control
    for i=1:N
        valueX=lamda+p*X(i)*(1-X(i)/Tm)-d*X(i)-beta*X(i)*Y(i);
        valueY=beta*X(i)*Y(i)-a*Y(i)-l*Y(i)*Z(i);
        valueZ=s*Y(i)-b*Z(i);
        %-------------------------------------------------------
---------
        value2X=lamda+p*(X(i)+h2*valueX)*(1-
(X(i)+h2*valueX)/Tm)...
            -d*(X(i)+h2*valueX)-
beta*(X(i)+h2*valueX)*(Y(i)+h2*valueY);
        value2Y=beta*(X(i)+h2*valueX)*(Y(i)+h2*valueY)...
            -a*(Y(i)+h2*valueY)-
l*(Y(i)+h2*valueY)*(Z(i)+h2*valueZ);
        value2Z=s*(Y(i)+h2*valueY)-b*(Z(i)+h2*valueZ);
        %-------------------------------------------------------
---------
        value3X=lamda+p*(X(i)+h2*value2X)*(1-
(X(i)+h2*value2X)/Tm)...
            -d*(X(i)+h2*value2X)-
beta*(X(i)+h2*value2X)*(Y(i)+h2*value2Y);
        value3Y=beta*(X(i)+h2*value2X)*(Y(i)+h2*value2Y)...
            -a*(Y(i)+h2*value2Y)-
l*(Y(i)+h2*value2Y)*(Z(i)+h2*value2Z);
        value3Z=s*(Y(i)+h2*value2Y)-b*(Z(i)+h2*value2Z);
        %-------------------------------------------------------
---------
        value4X=lamda+p*(X(i)+h*value3X)*(1-
```

```
(X(i)+h*value3X)/Tm)...
            -d*(X(i)+h*value3X)-
beta*(X(i)+h*value3X)*(Y(i)+h*value3Y);
        value4Y=beta*(X(i)+h*value3X)*(Y(i)+h*value3Y)...
            -a*(Y(i)+h*value3Y)-
l*(Y(i)+h*value3Y)*(Z(i)+h*value3Z);
        value4Z=s*(Y(i)+h*value3Y)-b*(Z(i)+h*value3Z);
        %-------------------------------------------------------
---------
        X(i+1)=X(i)+(h/6)*(valueX+2*value2X+2*value3X+value4X);
        Y(i+1)=Y(i)+(h/6)*(valueY+2*value2Y+2*value3Y+value4Y);
        Z(i+1)=Z(i)+(h/6)*(valueZ+2*value2Z+2*value3Z+value4Z);
    end;
    %End of Part3

    %Part4 State With Control HAART+Immunotherapy IL-2
    for i=1:N
        combX=lamda+p*X2(i)*(1-X2(i)/Tm)-d*X2(i)-(1-ucomb1(i))...
            *beta*X2(i)*Y2(i)+ucomb2(i)*X2(i);
        combY=(1-ucomb1(i))*beta*X2(i)*Y2(i)-a*Y2(i)-l*Y2(i)...
            *Z2(i);
        combZ=s*Y2(i)-b*Z2(i);
        %-------------------------------------------------------
---------
        comb2X=lamda+p*(X2(i)+h2*combX)...
            *(1-(X2(i)+h2*combX)/Tm)-d*(X2(i)+h2*combX)-0.5*(2-
ucomb1(i)...
            -
ucomb1(i+1))*beta*(X2(i)+h2*combX)*(Y2(i)+h2*combY)...
            +ucomb2(i)*(X2(i)+h2*combX);
        comb2Y=0.5*(2-ucomb1(i)-
ucomb1(i+1))*beta*(X2(i)+h2*combX)...
            *(Y2(i)+h2*combY)-a*(Y2(i)+h2*combY)...
            -l*(Y2(i)+h2*combY)*(Z2(i)+h2*combZ);
        comb2Z=s*(Y2(i)+h2*combY)-b*(Z2(i)+h2*combZ);
        %-------------------------------------------------------
---------
        comb3X=lamda+p*(X2(i)+h2*comb2X)...
            *(1-(X2(i)+h2*comb2X)/Tm)-d*(X2(i)+h2*comb2X)-0.5*(2-
```

```
ucomb1(i)...
            -
ucomb1(i+1))*beta*(X2(i)+h2*comb2X)*(Y2(i)+h2*comb2Y)...
            +ucomb2(i)*(X2(i)+h2*comb2X);
        comb3Y=0.5*(2-ucomb1(i)-
ucomb1(i+1))*beta*(X2(i)+h2*comb2X)...
            *(Y2(i)+h2*comb2Y)-a*(Y2(i)+h2*comb2Y)...
            -l*(Y2(i)+h2*comb2Y)*(Z2(i)+h2*comb2Z);
        comb3Z=s*(Y2(i)+h2*comb2Y)-b*(Z2(i)+h2*comb2Z);
        %-------------------------------------------------------
---------
        comb4X=lamda+p*(X2(i)+h*comb3X)...
            *(1-(X2(i)+h*comb3X)/Tm)-d*(X2(i)+h*comb3X)-0.5*(2-
ucomb1(i)...
            -
ucomb1(i+1))*beta*(X2(i)+h*comb3X)*(Y2(i)+h*comb3Y)...
            +ucomb2(i)*(X2(i)+h*comb3X);
        comb4Y=0.5*(2-ucomb1(i)-
ucomb1(i+1))*beta*(X2(i)+h*comb3X)...
            *(Y2(i)+h*comb3Y)-a*(Y2(i)+h*comb3Y)...
            -l*(Y2(i)+h*comb3Y)*(Z2(i)+h*comb3Z);
        comb4Z=s*(Y2(i)+h*comb3Y)-b*(Z2(i)+h*comb3Z);
        %-------------------------------------------------------
---------
        X2(i+1)=X2(i)+(h/6)*(combX+2*comb2X+2*comb3X+comb4X);
        Y2(i+1)=Y2(i)+(h/6)*(combY+2*comb2Y+2*comb3Y+comb4Y);
        Z2(i+1)=Z2(i)+(h/6)*(combZ+2*comb2Z+2*comb3Z+comb4Z);
    end;
    %End Of Part4

    %Part5 Co-State HAART+Immunotherapy Using IL-2
    for i=1:N
       j=N+2-i;
        combX=-1+PX2(j)*((2*p*X2(j)/Tm)+d-p-ucomb2(j))+...
            beta*Y2(j)*(1-ucomb1(j))*(PX2(j)-PY2(j));
        combY= beta*Y2(j)*(1-ucomb1(j))*(PX2(j)-PY2(j))...
            +PY2(j)*(a+l*Z2(j))-PZ2(j)*s;
        value_stateZ=-1+PY2(j)*l*Y2(j)+PZ2(j)*b;
        %-------------------------------------------------------
```

```
---------
        comb2X=-1+(PX2(j)-h2*combX)*((2*p*0.5*(stateX(j)...
            +X2(j-1))/Tm)+d-p-0.5*(2-ucomb2(j)-ucomb2(j-1)))...
            +beta*(Y2(j)+Y2(j-1))*0.5*(2-ucomb1(j)-ucomb1(j-1))...
            *((PX2(j)-h2*combX)-(PY2(j)-h2*combY));
        comb2Y= beta*0.5*(Y2(j)+Y2(j-1))*0.5*(2-ucomb1(j)-
ucomb1(j-1))...
            *((PX2(j)-h2*combX)-(PY2(j)-h2*combY))...
            +(PY2(j)-h2*combY)*(a+l*0.5*(Z2(j)+Z2(j-1)))-(PZ2(j)-
h2*combZ)*s;
        comb2Z=-1+(PY2(j)-h2*combY)*l*0.5*(Y2(j)+Y2(j-1))...
            +(PZ2(j)-h2*combZ)*b;
        %-------------------------------------------------------
---------
        comb3X=-1+(PX2(j)-h2*comb2X)*((2*p*0.5*(stateX(j)...
            +X2(j-1))/Tm)+d-p-0.5*(2-ucomb2(j)-ucomb2(j-1)))...
            +beta*(Y2(j)+Y2(j-1))*0.5*(2-ucomb1(j)-ucomb1(j-1))...
            *((PX2(j)-h2*comb2X)-(PY2(j)-h2*comb2Y));
        comb3Y= beta*0.5*(Y2(j)+Y2(j-1))*0.5*(2-ucomb1(j)-
ucomb1(j-1))...
            *((PX2(j)-h2*comb2X)-(PY2(j)-h2*comb2Y))...
            +(PY2(j)-h2*comb2Y)*(a+l*0.5*(Z2(j)+Z2(j-1)))-(PZ2(j)-
h2*comb2Z)*s;
        comb3Z=-1+(PY2(j)-h2*comb2Y)*l*0.5*(Y2(j)+Y2(j-1))...
            +(PZ2(j)-h2*comb2Z)*b;
        %-------------------------------------------------------
---------
        comb4X=-1+(PX2(j)-h*comb3X)*((2*p*0.5*(stateX(j)...
            +X2(j-1))/Tm)+d-p-0.5*(2-ucomb2(j)-ucomb2(j-1)))...
            +beta*(Y2(j)+Y2(j-1))*0.5*(2-ucomb1(j)-ucomb1(j-1))...
            *((PX2(j)-h*comb3X)-(PY2(j)-h*comb3Y));
        comb4Y= beta*0.5*(Y2(j)+Y2(j-1))*0.5*(2-ucomb1(j)-
ucomb1(j-1))...
            *((PX2(j)-h*comb3X)-(PY2(j)-h*comb3Y))...
            +(PY2(j)-h*comb3Y)*(a+l*0.5*(Z2(j)+Z2(j-1)))-(PZ2(j)-
h*comb3Z)*s;
        comb4Z=-1+(PY2(j)-h*comb3Y)*l*0.5*(Y2(j)+Y2(j-1))...
            +(PZ2(j)-h*comb3Z)*b;
        %-------------------------------------------------------
```

```
---------
        PX2(j-1)=PX2(j)-(h/6)*(combX+2*comb2X+2*comb3X+comb4X);
        PY2(j-1)=PY2(j)-(h/6)*(combY+2*comb2Y+2*comb3Y+comb4Y);
        PZ2(j-1)=PZ2(j)-(h/6)*(combZ+2*comb2Z+2*comb3Z+comb4Z);
        %-------------------------------------------------------------
---------
        ucomb1(j)=min(1,max(0,(beta*X2(j)*Y2(j)...
            *(PX2(j)-PY2(j)))/A1));
        ucomb2(j)=min(0.003,max(0.0001,X2(j)*PX2(j)/A2));
    end;
    %End Of Part5

    temp=(beta*stateX.*stateY.*(co_stateX-co_stateY))/A;
    u1=min(1,max(0,temp));
    u=0.5*(u1+oldu);

    tempcomb1=(beta*X2.*Y2.*(PX2-PY2))/A1;
    u2=min(1,max(0,tempcomb1));
    ucomb1=0.5*(u2+olducomb1);

    tempcomb2=(X2.*PX2)/A2;
    u3=min(0.003,max(0.0001,tempcomb2));
    ucomb2=0.5*(u3+olducomb2);
end;
f(1,:)=X;
f(2,:)=Y;
f(3,:)=Z;
f(4,:)=stateX;
f(5,:)=stateY;
f(6,:)=stateZ;
f(7,:)=u;
f(8,:)=X2;
f(9,:)=Y2;
f(10,:)=Z2;
f(11,:)=ucomb1;
f(12,:)=ucomb2;
```

No	Main Program

```
clear all;
clc;
lamda=10;
beta=0.002;
d=0.01;
p=0.03;
a=0.24;
l=0.001;
s=0.2;
b=0.002;
Tm=1500;
T=600;
X0=50;
Y0=50;
Z0=2;
A=2;
A1=10;
A2=20;
[t
f1]=simulation_HIV(lamda,beta,d,p,a,l,s,b,Tm,T,X0,Y0,Z0,A,A1,A2);
figure(1)
subplot(2,1,1);plot(t,f1(7,:),'black','Linewidth',2);
subplot(2,1,1);xlabel('Time = 600 days');
subplot(2,1,1);ylabel('The Optimal Control u(t)');
grid on;
------------------------------------------------------------------
--------
subplot(2,1,2);plot(t,f1(1,:),'blue','Linewidth',2);
hold on;
subplot(2,1,2);plot(t,f1(4,:),'--blue','Linewidth',2);
subplot(2,1,2);xlabel('Time = 600 days');
subplot(2,1,2);ylabel('Uninfected CD4+ T-Cell (X)');
legend('Before Treatment','After Treatment');
grid on;
%-----------------------------------------------------------------
---------
figure(2)
subplot(2,1,1);plot(t,f1(2,:),'green','Linewidth',2);
```

```
hold on;
subplot(2,1,1);plot(t,f1(5,:),'--green','Linewidth',2);
subplot(2,1,1);xlabel('Time = 600 days');
subplot(2,1,1);ylabel('Infected CD4+ T-Cell (Y)');
legend('Before Treatment','After Treatment');
grid on;
%-------------------------------------------------------------------
---------
subplot(2,1,2);plot(t,f1(3,:),'red','Linewidth',2);
hold on;
subplot(2,1,2);plot(t,f1(6,:),'--red','Linewidth',2);
subplot(2,1,2);xlabel('Time = 600 days');
subplot(2,1,2);ylabel('Immune Response (Z)');
legend('Before Treatment','After Treatment');
grid on;
figure(3);
%Combination between HAART and Immunotherapy Using IL-2
subplot(2,1,1);plot(t,f1(11,:),'black','Linewidth',2);
hold on;
subplot(2,1,1);plot(t,f1(7,:),'--blue','Linewidth',2);
subplot(2,1,1);xlabel('Time = 600 days');
subplot(2,1,1);ylabel('The Optimal Control u1(t)');
legend('HAART+Immunotherapy','HAART Only');
grid on;
hold on;
subplot(2,1,2);plot(t,f1(12,:),'red','Linewidth',2);
subplot(2,1,2);xlabel('Time = 600 days');
subplot(2,1,2);ylabel('The Optimal Control u2(t)');
grid on;
figure(4);
plot(t,f1(1,:),'blue','Linewidth',2);
hold on;
plot(t,f1(4,:),'red','Linewidth',2);
hold on;
plot(t,f1(8,:),'green','Linewidth',2);
hold on;
xlabel('Time = 600 days');
ylabel('Uninfected CD4+ T-Cell (X)');
legend('No Treatment','HAART Only','HAART+Immunotherapy');
```

```
grid on;
figure(5);
plot(t,f1(2,:),'blue','Linewidth',2);
hold on;
plot(t,f1(5,:),'red','Linewidth',2);
hold on;
plot(t,f1(9,:),'green','Linewidth',2);
hold on;
xlabel('Time = 600 days');
ylabel('Infected CD4+ T-Cell (Y)');
legend('No Treatment','HAART Only','HAART+Immunotherapy');
grid on;
figure(6);
plot(t,f1(3,:),'blue','Linewidth',2);
hold on;
plot(t,f1(6,:),'red','Linewidth',2);
hold on;
plot(t,f1(10,:),'green','Linewidth',2);
hold on;
xlabel('Time = 600 days');
ylabel('Immune Response(Z)');
legend('No Treatment','HAART Only','HAART+Immunotherapy');
grid on;
```

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Two Therapeutic Approaches for the Treatment of HIV Infection in AIDS Stage

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Abstract

In this paper, we propose an optimal control approach for adequate therapeutic strategy design for HIV infection. Starting from a system of ordinary differential equations modeling the human immunodeficiency virus (HIV) infection and its interaction with the immune system, we introduce first a control representing a treatment using highly active antiretroviral therapy (HAART), then we introduce a control characterizing a combination treatment of both highly active antiretroviral therapy (HAART) and immunotherapy using the Interleukin-2. A comparison of the results allows us to choose which treatment strategy is able to reduce the viral load and the side effects, maximize the immune response level and the number of healthy $CD4^+$ T-cells while minimizing the cost of treatment. The Pontryagin's maximum principle is used to characterize the optimal controls. The optimality system is derived and solved numerically using an iterative method with a Runge-Kutta fourth order scheme.

Mathematics Subject Classification: 34H01, 49J15

Keywords: HIV infection, Optimal control, Interleukin-2, Highly Active Antiretroviral Therapy, Runge-Kutta fourth order scheme

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1 Introduction

In recent decades, the AIDS has generated much interest among scientists in general and more precisely mathematicians. For over 20 years, many scientists have focused on this disease and several mathematical models have been proposed in order to better understand the disease and try to find a proper treatment that minimizes the viral load, side effects and the cost of treatment.

Mathematical models proposed by Arnaout, Wodarz and Nowak [1] show that people with AIDS who are able to maintain a high level of CTL cells remain healthy longer hence the importance of the action of CTL cells in a possible treatment. Other models such as Kirschner and Webb [7] are based on the immunotherapy using the Interleukin-2 (IL-2) which is a type of cytokine that stimulates lymphocyte proliferation and immune response and it's necessary for the growth, proliferation and differentiation of T-cells to become 'effector' T-cells. They developed a mathematical model of dynamics of disease progression and IL-2 treatment of the HIV-infected immune system. Their model is based upon the key markers of HIV progression, $CD4^+$ T-cells level and viral levels in the plasma, and the model agrees with preliminary results from clinical trials. They also predict that immunotherapy administered during the early stages of disease progression is most beneficial for raising $CD4^+$ T-cells count. Some authors have proposed mathematical models of HIV treatment using the optimal control theory. Kirschner, Lenhart and Serbin [6] have established optimal regimens for a scenario in which the treatment reduces the viral production rate. However Fister, Lenhart and McNally [4] have established results for a similar model to that discussed in [6] but by introducing a control represented by a drug that reduces the infectivity rate. In these last two models of HIV treatment, the optimal controls were generally monotonous and decreasing.

In the study [5], the patients with less than 200 healthy $CD4^+$ T-cells per $mm^{-3}day^{-1}$ who received low doses of Interleukin-2 less than $12,500$ IU per day, their $CD4^+$ T-cells level declined however the other patients who received a maximal nontoxic tolerated dose of IL-2 in the range of $187,000$-$250,000$ IU per day, their $CD4^+$ T-cells level increased with a mean monthly gain of 27 units of healthy $CD4^+$ T-cells per micrometer of blood and per month. Other clinical studies [11] have demonstrated that exogenous human recombinant IL-2 can be safely administered concurrently with potent antiretroviral therapy to HIV-infected patients. These studies also provide that therapeutic immunization in the presence of HAART may be more effective.

Among those different studies, the basic virus infection model (BVIM) introduced by Priti Kumar Roy and Amar Nath Chatterjee [10] is widely used in studies of virus infection dynamic. This model typically considered uninfected (x) and infected (y) $CD4^+$ T-cells and the immune response (z)

measured by the rate of the CTL immune cells. The dynamics of BVIM are governed by the following equations:

$$\begin{aligned} \frac{dx}{dt} &= \lambda + px(1 - \frac{x}{T_m}) - dx - \beta xy, \\ \frac{dy}{dt} &= \beta xy - ay - lyz, \\ \frac{dz}{dt} &= sy - bz. \end{aligned} \tag{1}$$

where the parameters model are defined in the following section of our work.

In this work we take the basic virus infection model (1) appeared in [10] in which we will introduce optimal controls characterizing different treatments. This paper is organized as follows: Section 2 describes mathematical models of HIV with control terms, the first part presents a treatment using highly active antiretroviral therapy, and the second one presents a treatment using a combination of both highly active antiretroviral therapy and immunotherapy. The analysis of optimization problems is also presented in the same section. In section 3, we present the numerical iterative method used and the simulations corresponding results and we discuss the numerical results obtained in this paper while comparing them with other results established in similar works. Finally we compare the results of these two therapeutic approaches in conclusion in section 4.

2 Mathematical models

2.1 Therapeutic approach using highly active antiretroviral therapy (HAART)

2.1.1 Presentation of the model without HIV treatment

Here we introduce the ODE modeling of the immune dynamics of an HIV-infected immune system (1). We note that these equations model an untreated individual, treatment will be introduced in the next subsection via an optimal control. For analysis of the system, we will be forced to link this system to the following initial conditions: Let $C = C([0, T], \mathbb{R}^3)$ be the Banach space of continuous functions mapping the interval $[0, T]$ into $\mathbb{R}^3$ with the topology of uniform convergence. It easy to show that there exists a unique solution $(x(t), y(t), z(t))$ of system (1) with initial data $(x_0, y_0, z_0) \in C$.
In addition, for biological reasons, we assume that the initial data for system (1) satisfy:

$$x_0 = 50 \geq 0, \quad y_0 = 50 \geq 0, \quad z_0 = 2 \geq 0. \tag{2}$$

The definitions and descriptions of above model parameters (1) are listed in the following table:

Parameters	Descriptions
λ	Production rate of healthy $CD4^+$ T cells
β	Infection rate and viral replication rate
d	Natural mortality rate of healthy $CD4^+$ T cells
p	Maximum proliferation rate of healthy $CD4^+$ T cells
a	Natural mortality rate of infected $CD4^+$ T cells
l	Mortality rate of virus-producing cells by CTL cells
s	Production rate of CTL cells
b	Natural mortality rate of CTL cells
T_m	Number of $CD4^+$ T cells after a maximum proliferation

Table 1: The description of parameters used.

2.1.2 Presentation of the model with HIV treatment.

In this section, we introduce a control u that characterizes the treatment to the above mentioned model (1). The control $u(t)$ represents the efficiency of the highly active antiretroviral therapy (HAART) in inhibiting viral production for reducing the viral load and the infection level. Our HIV model is given by the following system of ordinary differential equations:

$$\begin{aligned} \frac{dx}{dt} &= \lambda + px(1 - \frac{x}{T_m}) - dx - (1-u)\beta xy, \\ \frac{dy}{dt} &= (1-u)\beta xy - ay - lyz, \\ \frac{dz}{dt} &= sy - bz. \end{aligned} \tag{3}$$

Our goal is obviously to try to maximize the levels of healthy $CD4^+$ T cells as well as the immune response for reducing the infection rate and subsequent the viral load while minimizing the cost of treatment. Our control is a function $u(t)$ taking values between 0 and 1 : $u(t) = 1$ represents a completely effective highly active antiretroviral therapy, while $u(t) = 0$ represents no treatment.

2.1.3 The optimal control problem.

The problem is to maximize the objective functional:

$$J(u) = \int_0^T \{x(t) + z(t) - \frac{A}{2}u^2(t)\}dt, \tag{4}$$

where the parameter $A \geq 0$ is based on the benefits and costs of the treatment.

Since our optimal control is primarily designed to reduce the rate of viral replication and therefore the most logical is to multiply the term 'βxy' by $(1-u)$. In our case the constant 'β' represents both the rate of cell infection and the rate of viral replication that may well give us a pretty clear idea about drugs to prescribe. Our target is to maximize the objective functional defined in equation (4) by increasing the number of the uninfected cells, maximizing immune response by CTLs, decreasing the viral load and minimizing the cost of treatment. In other words, we are seeking an optimal control $u^* \in U$ such that:

$$J(u^*) = \max_{u \in U} J(u), \tag{5}$$

where U is the control set defined by

$$U = \{u \; Lebesgue - measurable, 0 \leq u(t) \leq 1, t \in [0, T]\},$$

The Pontryagin's maximum principle [12] provides necessary conditions for an optimal control problem. This principle converts into a problem of maximizing the Lagrangian L, pointwisely with respect to u:

$$\begin{aligned} L(t,x,y,z,u,\psi) &= x + z - \frac{A}{2}u^2 \\ &+ \psi_1[\lambda + px(1 - \frac{x}{T_m}) - dx - (1-u)\beta xy] \\ &+ \psi_2[(1-u)\beta xy - ay - lyz] \\ &+ \psi_3[sy - bz], \end{aligned}$$

The ψ_j where $j = 1, 2, 3$ are our adjoint variables that determine the adjoint system which satisfies the optimality necessary conditions.

By applying the Pontryagin's maximum principle [9] and the existence result for the optimal control from [13], we obtain the following theorem:

Theorem 2.1 *Given optimal control u and solutions x, y and z of the corresponding state system (3), there exists adjoint variables ψ_1, ψ_2 and ψ_3 satisfying the following equations:*

$$\begin{aligned} \psi_1^{'} &= -1 + \psi_1(\frac{2px^*}{T_m} + d - p) + \beta y^*(1-u^*)(\psi_1 - \psi_2), \\ \psi_2^{'} &= \beta x^*(1-u^*)(\psi_1 - \psi_2) + \psi_2(a + lz^*) - \psi_3 s, \\ \psi_3^{'} &= -1 + \psi_2 l y^* + \psi_3 b. \end{aligned} \tag{6}$$

with transversality conditions

$$\psi_i(T) = 0, i = 1, ..., 3.$$

Moreover, the optimal control is given by:

$$u^*(t) = \min(1, \max(0, \frac{\beta x^*(t) y^*(t)(\psi_1(t) - \psi_2(t))}{A})). \tag{7}$$

Proof. Due to the convexity of integrand of J with respect to u, a priori boundedness of the state solutions and the Lipschitz property of the state system with respect to the state variables. The existence of an optimal control has been given by [10] (see Corollary 4.1). The adjoint equations and transversality conditions can be obtained by using Pontryagin's maximum principle such that:

$$\begin{aligned} \psi_1' &= -\frac{\partial L}{\partial x}, \\ \psi_2' &= -\frac{\partial L}{\partial y}, \\ \psi_3' &= -\frac{\partial L}{\partial z}. \end{aligned} \tag{8}$$

The optimal control u^* can be solve from the optimality conditions:

$$\frac{\partial L}{\partial u} = 0.$$

By the bounds in U of the control, it is easy to obtain u^* in the form of (7).

2.2 Therapeutic approach using a combination treatment of both HAART and Immunotherapy.

2.2.1 Presentation of the model with HIV treatment.

In this section, we introduce a control u=(u_1,u_2) to the above mentioned model (1). The control $u_1(t)$ represents the efficiency of the highly active antiretroviral therapy (HAART) in inhibiting viral production for reducing the viral load and the infection level, and the control $u_2(t)$ represents the efficiency of the immunotherapy (using Interleukin-2) in stimulating immune response for restoring immune defenses. Our HIV model is given by the following system of ordinary differential equations:

$$\begin{aligned} \frac{dx}{dt} &= \lambda + px(1 - \frac{x}{T_m}) - dx - (1-u_1)\beta xy + u_2 x, \\ \frac{dy}{dt} &= (1-u_1)\beta xy - ay - lyz, \\ \frac{dz}{dt} &= sy - bz. \end{aligned} \tag{9}$$

where $x(0)$=x_0, $y(0)$=y_0, $z(0)$=z_0 are given and the definitions of above model parameters have been previously defined. The control functions: $u_1(t)$ and $u_2(t)$, are bounded and Lebesgue integrable functions. The control $u_1(t)$ is a function with values normalised to be between 0 and 1: $u_1(t)$=1 represents a

completely effective highly active antiretroviral therapy, while $u_1(t)$=0 represents no treatment. Since $u_1(t)$ is primarily designed to reduce the rate of viral load and therefore the most logical is to multiply the term 'βxy' by $(1-u)$ since 'β' represents both the rate of cell infection and the rate of viral replication. The control $u_2(t)$ is a function with values normalised to be between 0.0001 and 0.003: $u_2(t)$=0.0001 for the low dose patients and $u_2(t) = 0.003$ for the maximal tolerated nontoxic dose that will produce the desired effect without unacceptable toxicity [5].

2.3 The optimal control problem.

The problem is to maximize the objective functional:

$$J(u_1, u_2) = \int_0^T \{x(t) + z(t) - [\frac{A_1}{2}u_1^2(t) + \frac{A_2}{2}u_2^2(t)]\}dt, \tag{10}$$

where the parameters $A_1 \geq 0$ and $A_2 \geq 0$ are based on the benefits and costs of the treatment. Our target is to maximize the objective functional defined in equation (10) by increasing the number of the uninfected target cells, maximizing immune response, decreasing the infection level and minimizing the cost of treatment. In other words, we are seeking optimal control pair (u_1^*, u_2^*) such that:

$$J(u_1^*, u_2^*) = \max\{J(u_1, u_2) : (u_1, u_2) \in U\}, \tag{11}$$

where U is the control set defined by

$$U = \{u = (u_1, u_2) : u_i \; measurable, 0 \leq u_i(t) \leq 1, t \in [0, T], i = 1, 2\},$$

The Pontryagin's maximum principle [9] provides necessary conditions for an optimal control problem. This principle converts into a problem of maximizing the Lagrangian L, pointwisely with respect to u_1 and u_2:

$$\begin{aligned} L(t, x, y, z, u, \psi) &= x + z - (\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2) \\ &+ \psi_1[\lambda + px(1 - \frac{x}{T_m}) - dx - (1-u_1)\beta xy + u_2 x] \\ &+ \psi_2[(1-u_1)\beta xy - ay - lyz] \\ &+ \psi_3[sy - bz]. \end{aligned}$$

The ψ_j where $j = 1, 2, 3$ are our adjoint variables that determine the adjoint system which satisfies the optimality necessary conditions.

By applying the Pontryagin's maximum principle [9] and the existence result for the optimal control from[13], we obtain the following theorem:

Theorem 2.2 *Given optimal controls u_1^* and u_2^* and solutions x, y and z of the corresponding state system (9), there exists adjoint variables ψ_1, ψ_2 and ψ_3 satisfying the following equations:*

$$\begin{aligned}
\psi_1^{'}(t) &= -1 + \psi_1(\frac{2px^*}{T_m} + d - p - u_2^*) + \beta y^*(1-u_1^*)(\psi_1 - \psi_2),\\
\psi_2^{'}(t) &= \beta x^*(1-u_1^*)(\psi_1 - \psi_2) + \psi_2(a + lz^*) - \psi_3 s,\\
\psi_3^{'}(t) &= -1 + \psi_2 l y^* + \psi_3 b.
\end{aligned} \tag{12}$$

with transversality conditions

$$\psi_i(T) = 0, i = 1, ..., 3.$$

Moreover, the optimal control is given by:

$$u_1^*(t) = \min(1, \max(0, \frac{\beta x^*(t) y^*(t)(\psi_1(t) - \psi_2(t))}{A_1})), \tag{13}$$

and

$$u_2^*(t) = \min(0.003, \max(0.0001, \frac{x^*(t)\psi_1(t)}{A_2})). \tag{14}$$

Proof. Due to the convexity of integrand of J with respect to u, a priori boundedness of the state solutions, and the Lipschitz property of the state system with respect to the state variables. The existence of an optimal control has been given by[13] (see Corollary 4.1). The adjoint equations and transversality conditions can be obtained by using Pontryagin's maximum principle such that:

$$\begin{aligned}
\psi_1^{'} &= -\frac{\partial L}{\partial x},\\
\psi_2^{'} &= -\frac{\partial L}{\partial y},\\
\psi_3^{'} &= -\frac{\partial L}{\partial z}.
\end{aligned} \tag{15}$$

The optimal controls u_1^* and u_2^* can be solve from the optimality conditions:

$$\frac{\partial L}{\partial u_1} = 0 \; and \; \frac{\partial L}{\partial u_2} = 0$$

By the bounds in U of the controls, it is easy to obtain u_1^* and u_2^* in the form of (13) and (14), respectively.

3 Numerical Simulation

3.1 Summary of parameters and values used

A wide range of values is proposed for modeling of HIV infection in the presence the immune response compartment [1]. We specify that the detailed description of the parameters is given above in the presentation of the model without HIV treatment and we note that HIV-specific parameters are given in units of cells per $mm^{-3}day^{-1}$.

We can say that it is difficult to assign a set of parameters to persons with different clinical outcomes. However, since the interest is due to the initiation of any treatment by the introduction of an optimal control in the ODE system (1), we keep the values of the parameters found in [10] and we state that the stability properties of the model are stored for these parameters which have rearranged in the following table:

Parameters	Values
λ	$10mm^{-3}day^{-1}$
β	$0.002mm^{-3}day^{-1}$
d	$0.01day^{-1}$
p	$0.03day^{-1}$
a	$0.24day^{-1}$
l	$0.001mm^{-3}day^{-1}$
s	$0.2day^{-1}$
b	$0.02day^{-1}$
T_m	$1500mm^{-3}$

Table 2: The different parameters and values used.

We note that the period of the therapy considered is T=600 days, it's the necessary observed period which allows us to obtain good results.

3.2 Numerical results

To solve numerically this problem, namely to find an optimal control u^* that maximizes the objective function $J(u)$, many methods and techniques of programming can be used. The method we chose for solving the optimality system optimally is generally known under the name of 'Forward Backward Sweep Method' [12]. The optimality system is solved using an iterative method with a Runge-Kutta fourth order scheme. The state system with an initial guess is solved forward in time and then the adjoint system is solved backward in time. The iterations continue until convergence is achieved. Finally, we note that all informations about the convergence of this method is given in [8].

3.2.1 Therapeutic approach using highly active antiretroviral therapy (HAART).

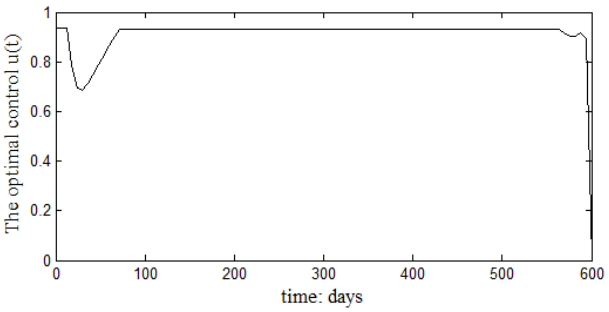

Figure 1: **The Optimal control** $u^*(t)$**.**

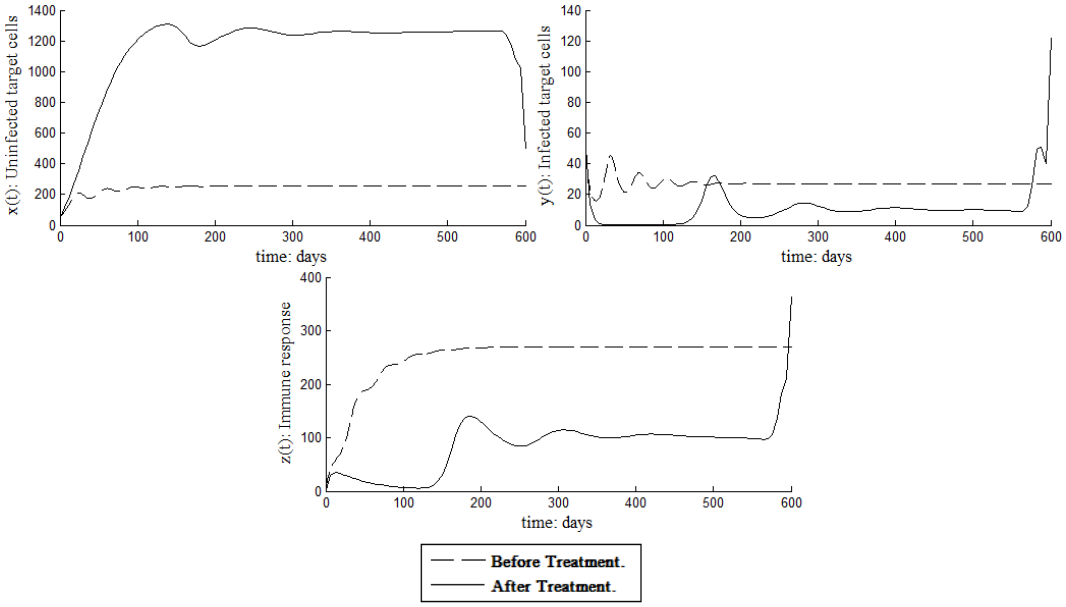

Figure 2: **The graphics of the states** $x(t)$**,** $y(t)$ **and** $z(t)$ **before and after treatment with (**$x(0)$=$50mm^{-3}day^{-1}$**,** $y(0)$=$50mm^{-3}day^{-1}$ **and** $z(0)$=$2mm^{-3}day^{-1}$**).**

As is shown in Figure 2, we find that following the initial values of healthy and infected $CD4^+$ T-cells and CTL immune cells, the patient in question in this HIV mathematical model is in AIDS stage, this phase is characterized by the weakening of the immune system and the development of all kinds of opportunistic infections that take advantage of the weakness of the immune

system to invade the body. Generally during this period of the disease, the rate of healthy CD4$^+$ T-cells is less than 200 $mm^{-3}day^{-1}$ [3].

Taking into account these facts and characteristics of the disease in AIDS stage, our optimal control starts at a maximum value near $u = 0.94$, which corresponds to a complete treatment of highly active antiretroviral therapy (Figure 1). Subsequently and after an initial decline that will last for the first 30 days of treatment, the optimal control reaches a value $u = 0.69$ then the treatment rises during the next 40 days and stabilizes from the $70th$ day at the value $u = 0.93$ and then keeps a constant value. Our optimal control eventually falls sharply to the value $u = 0$ at the end of the treatment period and more precisely from the $565th$ day.

Early findings graphs (Figure 2) lead us to say that our optimal treatment protocol has a very beneficial effect on the population of healthy CD4$^+$ T-cells that reaching maximum values more than 1200 $mm^{-3}day^{-1}$ throughout most of the duration of treatment lasting 600 days. As the results in [1], although HIV does not target the CTLs directly, it has been noted clinically for some time that individuals who maintain a high level of CTLs remain healthy longer. Despite the fact that the infection isn't eradicated during the treatment period, but it reached very low levels less than 10 $mm^{-3}day^{-1}$, we simply note that a significant growth of the infection was observed towards the end of treatment, followed by a drop in the population of healthy CD4$^+$ T-cells and a maximum stimulation of immune response, this increase in the level of infection is very logical and normal at that stage of the disease and after a sudden interruption of the treatment acting mainly on viral load. We also note that the increase in the level of infection is followed immediately by a corresponding increase of the natural immune response that eliminates infected CD4$^+$ T-cells.

The sudden and severe decrease in the level of our optimal control in the last 35 days of treatment logically implies a significant increase in the level of infection, which leads to a considerable drop in the level of healthy CD4$^+$ T-cells especially for patients in AIDS stage. But in parallel, we note with great interest the maximum growth of immune response and significant stimulation of CTL in the period following the increase in the viral load level. It's also noted that the population of healthy CD4$^+$ T-cells is around 500 units per microliter of blood towards the end of the treatment period, which is significantly higher than the initial level that didn't exceed 50 units per microliter of blood. We finally concluded that the immune system at this stage of HIV infection is still able to reduce and stabilize the viral load and partially restore the immune response system.

By studying the shape of our optimal control's graph (Figure 1), we note the initial decrease of the treatment with great interest, this happens at the same time as the growth of the immune response, we can deduce that during periods when the immune response is effective, the recourse to treatment acting

on viral load is less necessary because at this time, the immune system plays its role perfectly in controlling the disease.

After comparing our results with those established in [6] and [4], we find that our optimal control behaves differently from controls used in models that don't present explicitly a compartment of the immune response. In [6], the optimal control was either monotonically decreasing from its maximum value or peaked just after the start of treatment and then declined thereafter.

However, we observe that the behavior of our optimal control takes into account the evolution of the disease and the level of infection in every moment of the treatment period and acts according to these circumstances by adopting optimal strategies specific to each situation corresponding such as the increase or the decrease of the treatment regimen. We believe that the decline of treatment depends mainly on immune stimulation and action of the immune response via the CTL immune cells, thus our optimal treatment is reduced over a period of time while the immune response takes over. Any subsequent increase in the level of treatment is considered after the sudden reappearance of the disease disorders characterized by an increase in viral load. And finally maintaining a constant optimal control for any period is recommended to consolidate the treatment and cope with the instability of the HIV infection at this stage of the disease.

3.2.2 Therapeutic approach using a combination treatment of both HAART and Immunotherapy.

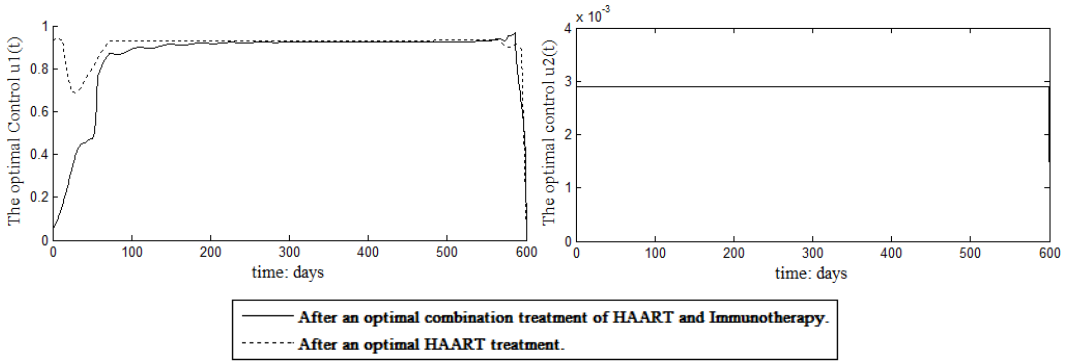

Figure 3: **The graphics of the optimal controls $u_1^*(t)$ and $u_2^*(t)$.**

As is shown in Figure 3, we note with interest a decrease in the concentration of the antiretroviral therapy after the introduction of new combination treatment of both HAART and immunotherapy especially during the first four months of treatment.

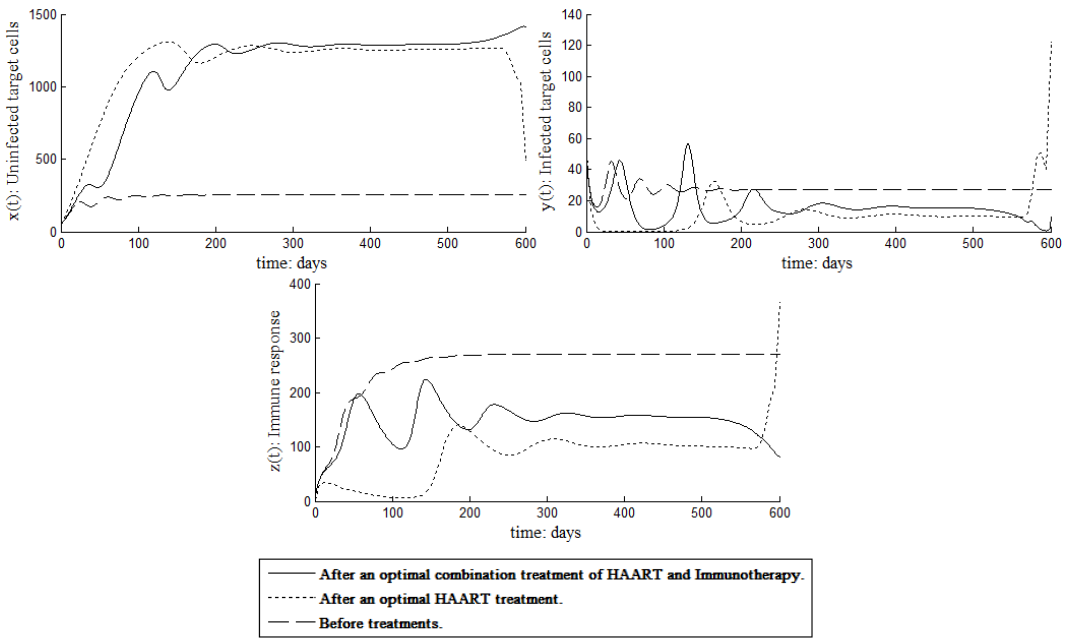

Figure 4: **The graphics of the states $x(t)$, $y(t)$ and $z(t)$ before and after treatments with ($x(0)$=$50mm^{-3}day^{-1}$, $y(0)$=$50mm^{-3}day^{-1}$ and $z(0)$=$2mm^{-3}day^{-1}$).**

Taking into account the initial values of $x(t)$, $y(t)$ and $z(t)$ and the characteristics of the AIDS stage, as was the case in some studies [5], our optimal treatment strategy adopts a control representing immunotherapy by means of a model of daily injections of IL-2 where the treatment function $u_2(t)$ is taken to be constant assuming the treatment can be approximately by a continuous process where $u_2 = 0.00290625$. However, the control $u_1(t)$ that represents the HAART begins with a minimum value $u_1 = 0.05$ and increases progressively to reach its maximum value $u_1 = 0.93$ from the $200th$ day, then the control remains constant until the $585th$ day when it drops sharply and reaches the value $u_1 = 0$ at the end of the treatment period.

Compared with the optimal treatment using the HAART (Figure 3), we note with interest that the introduction of an optimal combination treatment of HAART and immunotherapy allows us to reduce the concentration of the antiretroviral therapy during the first 200 days and keep a maximum level of healthy $CD4^+$ T-cells and a very low level of infection even at the end of the treatment.

The introduction of immunotherapy using the Interleukin-2 administered to AIDS patients under the highly active antiretroviral therapy (HAART) has enabled us to achieve all the goals we set in the optimal control problem

(Figure 4), throughout the duration of treatment, which lasts 600 days, we were able to keep a high level of immune response that allowed us to maximize the population of healthy CD4$^+$ T-cells more than 1200 $mm^{-3}day^{-1}$ and even if the infection is not totally eradicated but it reached very low levels less than 20 $mm^{-3}day^{-1}$ and it didn't rise at the end of the optimal treatment which obviously would alleviate the antiretroviral therapy and subsequently reduce the side effects. We finally concluded that the implementation of treatments that stimulate the immune response is very beneficial as a complement to the HAART treatment.

4 Conclusion

In order to get the most optimal treatment for HIV infection in AIDS stage, firstly, we adopted a therapeutic strategy that aims to introduce a control characterizing HAART and we obtained thereafter very good results by maximizing the level of the immune response and the number of healthy CD4$^+$ T-cells and minimizing the level of infection and the cost of treatment but we note however that from the moment when the control decreases towards the end of the treatment period, the level of infection increases sharply which leads subsequently a declining in the population of healthy CD4$^+$ T-cells. Taking into account these results and the specific characteristics of HIV infection in AIDS stage, we opted for another treatment strategy in the second part of this work. This new therapeutic approach consists to introduce two controls, the first one characterizing the HAART and the other one characterizing the immunotherapy using interleukin-2 by tolerated doses, the introduction of this treatment combination has enabled us not only to maximize the number of healthy CD4$^+$ T-cells, reduce the level of infection and minimize treatment cost throughout the treatment period but it could also reduce the concentration of the HAART which allowed us to improve the patient's quality of life by reducing the side effects of heavy and continuous use of antiretroviral drugs.

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