Summary Report for HIV Random Clinical Trial Conducted in 2009-2014

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Abstract

In this report we summarize results from clinical trials carried out at Mass General Hospital during the period 2009-2014. The design of the clinical trials was based on dynamical mathematical models developed and calibrated with earlier data from patients in previous treatment protocols. Although enrollment was limited, the findings are in agreement with the model predications.

Key Words: Randomized clinical trials, HIV dynamical model based design, inverse problems
1 Introduction

We used modifications [3] of earlier developed and data validated dynamical models [1] to develop predictions of outcomes of several treatment strategies for HIV. In these randomized clinical trial, patients were randomized to receive either no therapy or 12 weeks therapy or 32 weeks therapy. The goal of this trial was to determine whether treatment initiated during acute HIV infection followed by terminal interruption resulted in a lower viral load level and higher CD4 cell count than no treatment and to determine whether the duration of treatment is important.

Specifically, our primary objectives are

(P1) to determine whether or not there is a difference in the CD4+ T cell count between the group without treatment at 48 weeks after randomization and the group with treatment at 48 weeks after discontinuation of treatment,

(P2) to determine whether or not there is a difference in the viral load level between the group without treatment at 48 weeks after randomization and the group with treatment at 48 weeks after discontinuation of treatment.

The primary endpoints for each patient are the average of the last two HIV log_{10} RNA viral load measurements and the average of the last two log CD4+ T cell measurements determined 48 weeks after discontinuation of treatment in patients randomized to receive therapy and 48 weeks after randomization for patients assigned to no treatment. Specifically, for patients randomized to receive 12 weeks (32 weeks) therapy, these endpoints are the average of two HIV log_{10} RNA viral load measurements and the average of two log CD4+ T cell measurements taken at 58 and 60 weeks (78 and 80 weeks) after randomization. For patients randomized to receive no treatment, they are the averages of two observations taken at 46 and 48 weeks after randomization.

The secondary objectives are

(S1) to determine whether or not there is a difference in the CD4+ T cell count between the group assigned to 12 weeks therapy at 48 weeks after discontinuation of treatment and the group assigned to 32 weeks therapy at 48 weeks after discontinuation of treatment,

(S2) to determine whether or not there is a difference in the viral load level between the group assigned to 12 weeks therapy at 48 weeks after discontinuation of treatment and the group assigned to 32 weeks therapy at 48 weeks after discontinuation of treatment.

As in the calculations of primary endpoints above, the secondary endpoints for each patient are the average of two HIV log_{10} RNA viral load measurements and the average of two log CD4+ T cell measurements determined 48 weeks after discontinuation of treatment.
2 Clinical Data

There are total 18 patients who were randomized for the clinical trial; here 9 patients were randomized to receive no therapy, 4 patients were randomized to receive 12 weeks therapy, and 5 patients were randomized to receive 32 weeks therapy. However, only 8 patients completed the study protocols: 2 of them are from no therapy group, 4 of them are from 12 weeks therapy group and the rest of the 2 patients are from 32 weeks therapy group. The detailed information for the patients in each group is given below.

2.1 Patients: Randomized to Receive No Therapy

There are 9 patients that were randomized to receive no therapy: CR0685X, CR0699Y, CR0823S, CR0826V, CR0860Q, CR0870, CR0920Y, CR0923N, and CR1033R. However, there are only 2 patients (CR0685X and CR0699Y) who completed study protocols (the plots for their clinical data are given in Figure 1). For the rest of the 7 patients, 4 of them (CR0826V, CR0860Q, CR0870 and CR0923N) developed other ineligibility criteria and hence they were eventually off study (the plots are shown in Figure 2), 2 of them (CR0920Y and CR1033R) went off study with withdrawn consent (the plots are given in Figure 3), and the last one, CR0823S, went off study because he/she cannot be contacted for follow-up (with the plots given in Figure 4).

![Figure 1](image1.png)

Figure 1: Plots of total number of CD4 T cells and viral load levels for those patients who were randomized to receive no therapy and completed the study protocols, where solid green lines along the x-axis indicate periods when the patient is on ART treatment.

Based on the medical change history, we found that we need to exclude patient CR0860Q from our analysis as this patient started the therapy on day 65 after he/she was randomized to receive no therapy (see upper right panel of Figure 2 for details).
Figure 2: Plots of total number of CD4 T cells and viral load levels for those patients who were randomized to receive no therapy but eventually went off study due to developing other ineligibility criteria, where solid green lines along the x-axis indicate periods when the patient is on ART treatment.
Figure 3: Plots of total number of CD4 T cells and viral load levels for those patients who were randomized to receive no therapy and went off study with withdrawn consent.

Figure 4: Plots of total number of CD4 T cells and viral load levels for those patients who were randomized to receive no therapy but went off study due to no contact for follow up.
2.2 Patients: Randomized to Receive 12 Weeks Therapy

There are 4 patients who were randomized to receive 12 weeks therapy: CR0697W, CR0719S, CR0846P, and CR0937Q. They all completed study protocols. However, we see that patients CR0846P and CR0937Q started therapy again in less than 48 weeks after discontinuation of the assigned treatment.

Figure 5: Plots of total number of CD4 T cells and viral load levels for those patients who were randomized to receive 12 weeks therapy, where solid green lines along the x-axis indicate periods when the patient is on ART treatment.
2.3 Patients: Randomized to Receive 32 Weeks Therapy

There are 5 patients who were randomized to receive 32 weeks therapy: CR0684W, CR0700Z, CR0882Y, CR0888R, CR0993X. However, there are only 2 patients, patients CR0888R and CR0993X, who completed the study protocols, even though patient CR0888R started therapy again in less than 48 weeks after discontinuation of the assigned treatment. For the rest of the 3 patients, patient CR0684W stayed in study for only 103 days (less than 15 weeks) and then cannot be contacted for follow-up, and hence cannot be used for our analysis. The other 2 patients went off study with withdrawn consent.

Figure 6: Plots of total number of CD4 T cells and viral load levels for those patients who received 32 weeks therapy and completed study protocols, where solid green lines along the x-axis indicate periods when the patient is on ART treatment.

Figure 7: Plots of total number of CD4 T cells and viral load levels for those patients who received 32 weeks therapy but went off study with withdrawn consent, where solid green lines along the x-axis indicate periods when the patient is on ART treatment.
3 Inverse Problem Approach

The above section reveals that there are 18 patients in this clinical trial and that two of them need to be excluded from statistical analysis. This leaves us 16 patients (8 of them randomized to receive no therapy, 4 of them assigned to 12 weeks therapy, and the remaining 4 patients assigned to 32 weeks therapy) with half of them not completing the study protocols. In addition, even for those patients who finished the study protocols, the observation times and intervals vary among patients. Moreover, there are some patients who started therapy again in less than 48 weeks after discontinuation of the assigned treatment (e.g., patients CR0846P and CR0937Q). This means that the endpoints are usually missing and hence we cannot directly use the recorded data for analysis. To partially alleviate this difficulty, we propose to use mathematical modeling combined with an inverse problem approach to obtain the predicated values of those endpoints for our analysis.

3.1 Mathematical Model

The model we used is adopted from [3] with descriptions of the state variables given in Table 1 and the schematic in Figure 8. The model has been carefully validated with multiple data sets as described in [2, 3, 4].

<table>
<thead>
<tr>
<th>States</th>
<th>Units</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1^*$</td>
<td>cells/µl-blood</td>
<td>uninfected activated CD4+ T cells</td>
</tr>
<tr>
<td>$T_1$</td>
<td>cells/µl-blood</td>
<td>infected activated CD4+ T cells</td>
</tr>
<tr>
<td>$T_2$</td>
<td>cells/µl-blood</td>
<td>uninfected resting CD4+ T cells</td>
</tr>
<tr>
<td>$T_2^*$</td>
<td>cells/µl-blood</td>
<td>infected resting (or latently infected) CD4+ T cells</td>
</tr>
<tr>
<td>$V_I$</td>
<td>RNA copies/ml-plasma</td>
<td>free infectious virus</td>
</tr>
<tr>
<td>$V_{NI}$</td>
<td>RNA copies/ml-plasma</td>
<td>free noninfectious virus</td>
</tr>
<tr>
<td>$E_1$</td>
<td>cells/µl-blood</td>
<td>HIV-specific effector CD8+ T cells</td>
</tr>
<tr>
<td>$E_2$</td>
<td>cells/µl-blood</td>
<td>HIV-specific memory CD8+ T cells</td>
</tr>
</tbody>
</table>

Table 1: Model States and their corresponding units and descriptions.
The treatment factors with an initial condition (with an initial condition describing the relative effectiveness of reverse transcriptase inhibitor (RTI), ε sent the effective treatment impact, consisting of efficacy factors ε of protease inhibitor (PI), and a time-dependent treatment function \( u(t) \) (0 ≤ u(t) ≤ 1).

The corresponding compartmental ordinary differential equation (ODE) model is given by

\[
\begin{align*}
\dot{T}_1 &= -d_1 T_1 - (1 - \xi_1(t)) k_1 V_1 T_1 - \gamma T_1 + p \left( \frac{\alpha r V_I}{V_I+K_V} + a_A \right) T_2, \quad (3.1) \\
\dot{T}_1^* &= (1 - \xi_1(t)) k_1 V_1 T_1 - \delta T_1^* - m E_1 T_1^* - \gamma T_1^* + p \left( \frac{\alpha r V_I}{V_I+K_V} + a_A \right) T_2^*, \quad (3.2) \\
\dot{T}_2 &= \lambda T_1 \frac{K}{V_I + K_a} + \gamma T_1 - d_2 T_2 - (1 - f \xi_1(t)) k_2 V_2 T_2 - \left( \frac{\alpha r V_I}{V_I+K_V} + a_A \right) T_2, \quad (3.3) \\
\dot{T}_2^* &= \gamma T_1 T_2^* + (1 - f \xi_1(t)) k_2 V_2 T_2 - d_2 T_2^* - \left( \frac{\alpha r V_I}{V_I+K_V} + a_A \right) T_2^*, \quad (3.4) \\
\dot{V}_1 &= (1 - \xi_2(t)) 10^3 N_T \delta T_1^* - c V_I - 10^3 [(1 - \xi_1(t)) k_1 T_1 + (1 - f \xi_1(t)) k_2 T_2] V_1, \quad (3.5) \\
\dot{V}_{NI} &= \xi_2(t) 10^3 N_T \delta T_1^* - c V_{NI}, \quad (3.6) \\
\dot{E}_1 &= \lambda E + \frac{b_{EI} T_1^*}{T_1^* + K_{a_1}} E_1 - \frac{d_{g} T_1^*}{T_1^* + K_{g_1}} E_1 - \delta E_1 E_1 - \gamma E T_1 T_1^* E_1 + \frac{p \gamma a V_I}{V_I + K_V} E_2, \quad (3.7) \\
\dot{E}_2 &= \gamma E T_1 T_1^* E_1 + \frac{b_{EI} K_{a_2}}{E_2 + K_{a_2}} E_2 - \delta E_2 E_2 - \frac{a r V_I}{V_I + K_V} E_2, \quad (3.8)
\end{align*}
\]

with an initial condition

\[
(T_1(0), T_1^*(0), T_2(0), T_2^*(0), V_1(0), V_{NI}(0), E_1(0), E_2(0))^T = (T_1^0, T_1^{0*}, T_2^0, T_2^{0*}, V_1^0, V_{NI}^0, E_1^0, E_2^0)^T.
\]

The treatment factors \( \xi_1(t) = \epsilon_1 u(t) \) in (3.1)-(3.4) and \( \xi_2(t) = \epsilon_2 u(t) \) in (3.5)-(3.6) represent the effective treatment impact, consisting of efficacy factors \( \epsilon_1 \) modeling the relative effectiveness of reverse transcriptase inhibitor (RTI), \( \epsilon_2 \) describing the relative effectiveness of protease inhibitor (PI), and a time-dependent treatment function \( u(t) \) (0 ≤ u(t) ≤ 1).
representing HAART drug level, where \( u(t) = 0 \) is fully off and \( u(t) = 1 \) is fully on. Since HIV treatments are nearly always administered as combination therapy, we do not consider the possibility of monotherapy, even for a limited period of time, though this could be implemented by considering separate treatment functions.

In (3.1), \( d_1T_1 \) denotes the natural death of \( T_1 \), and \((1 - \xi_1(t))k_1V_IT_1 \) is used to represent the infection process that results from encounters between the uninfected activated CD4+ T cells \( T_1 \) and free virus \( V_I \). The term \( \gamma_1T_1 \) is used to account for the phenomenon of differentiation of uninfected activated CD4+ T cells into uninfected resting CD4+ T cells \( T_2 \). In (3.2), \( \delta T_1 \) denotes the loss of infected activated CD4+ T cells due to the cytopathic effect of HIV, and the corresponding gain term for \( V_I \) include a multiplicative factor \( N_T \) to account for the number of RNA copies produced during this process. The term \( mE_1T_1^* \) is used to account for the elimination of the infected activated CD4+ T cells by the HIV-specific effector CD8+ T cells, and \( \gamma_1T_1^* \) is used to account for the phenomenon of differentiation of infected activated CD4+ T cells into latently infected CD4+ T cells \( T_2^* \) at rate \( \gamma_T \).

In (3.3), \( \lambda_T \frac{K_a}{V_I + K_a} \) is used to account for the source rate of naive CD4+ T cells, and \( d_2T_2 \) denotes the natural death of \( T_2 \). The infection process that results from encounters between the uninfected resting CD4+ T cells \( T_2 \) and free virus \( V_I \) is represented by \((1 - f\xi_1(t))k_2V_IT_2 \), where the parameter \( f \) (\( 0 \leq f \leq 1 \)) is used to account for the fact that treatment is potentially less effective in \( T_2 \) than in \( T_1 \). The term \( \left( \frac{a_TV_I}{V_I + K_V} + a_A \right)T_2 \) denotes the activation of the uninfected resting CD4+ T cells, and the corresponding gain term for \( T_1 \) include a multiplicative factor \( p_T \) to account for the net proliferation due to clonal expansion and programmed contraction. Similarly, \( \left( \frac{a_TV_I}{V_I + K_V} + a_A \right)T_2^* \) in (3.4) is used to account for the activation of latently infected CD4+ T cells, and the corresponding gain term for \( T_1^* \) also includes a multiplicative factor \( p_T \). The natural death of \( T_2^* \) is represented by \( d_2T_2^* \).

In (3.5) and (3.6), \( cV_I \) and \( cV_{NI} \) respectively denote the clearance of free infectious virus \( V_I \) and free noninfectious virus \( V_{NI} \), and the factor \( 10^3 \) is introduced to convert between microliter and milliliter scales. The term \( 10^3[(1 - \xi_1(t))k_1T_1 + (1 - f\xi_1(t))k_2T_2)V_I \) in (3.5) is used to account for the removal of free virus that takes place when free virus infects \( T_1 \) and \( T_2 \), where one free virus particle is assumed to be responsible for each new infection.

The first four terms in the right hand side of (3.7) denotes the source, nonlinear infected cell-dependent birth, nonlinear infected cell-dependent death, and constant death, respectively. The term \( \gamma_E \frac{T_1 + T_2}{T_1 + T_2 + K_\gamma}E_1 \) is used to include the essential role that activated CD4+ T cells play in the generation of memory CD8+ T cells, where the parameter \( K_\gamma \) is a half-saturation constant and \( \gamma_E \) is the maximum rate at which \( E_1 \) differentiates into \( E_2 \). In (3.8), \( \frac{b_EK_{EI}}{E_2 + K_{EI}}E_2 - \delta_{E2}E_2 \) is used to denote the homeostatic regulation of \( E_2 \) with \( b_{E2} \) being the maximum proliferation rate and \( \delta_{E2} \) being the death rate. The term \( \frac{a_EV_I}{V_I + K_V}E_2 \) denotes reactivation of HIV-specific memory CD8+ T cells, and the corresponding gain terms for \( E_1 \) include a multiplicative factor \( p_E \) to account for the net proliferation due to clonal expansion and programmed contraction.
3.2 Inverse Problem

Based on Section 2 (see also [1, 2]), we know that the observables are the total number of CD4+ T cells per µl-blood and the viral load per ml-plasma. For model (3.1)-(3.8), these two observables are respectively represented by

\[
\begin{align*}
\bar{z}_1(t; \bar{q}) &= T_1^*(t; \bar{q}) + T_2^*(t; \bar{q}) + T_1(t; \bar{q}) + T_2(t; \bar{q}), \\
\bar{z}_2(t; \bar{q}) &= V_I(t; \bar{q}) + V_{NI}(t; \bar{q}),
\end{align*}
\]

where \(\bar{q}\) is a column vector for those model parameters and initial conditions that need to be estimated. With regard to the viral load measurements, it is worth noting that if the measurements of RNA copies are below the limit of quantification for the assay used (48 copies/ml-plasma or 20 copies/ml-plasma), then the observed viral load value is censored to be at its detection limit; that is, in these cases the observed values do not represent the true data values anymore. Furthermore, observations of viral load and CD4+ may not be at the same time points and the observation times and intervals vary among patients. So, in general, for the \(j\)th patient we have CD4+ T-cell data pairs \((t_{ij}^1, \bar{y}_{ij}^1)\), \(i = 1, \ldots, N_j^1\), and potentially different time point viral RNA data pairs \((t_{ij}^2, \bar{y}_{ij}^2)\), \(i = 1, \ldots, N_j^2\), \(j = 1, 2, 3, \ldots, 16\) (patients are ordered as follows: the first 8 patients are those randomized to receive no therapy, the next 4 patients are those assigned to 12 weeks therapy and the last 4 patients are the ones assigned to 32 weeks therapy).

To obtain those individual-specific parameter estimates for the model, we carry out an inverse problem for each patient using his/her corresponding clinical data (that is, individuals are fitted individually). The algorithm we use in this paper is the same as the one in [3], where a statistically-based censored data method, an expectation maximization algorithm, was used.

For the simulation results shown below, we first estimated all the model parameters (31) and initial conditions (8) for each patient. We then fixed 14 parameters at the population averages across these 16 patients and re-estimated the remaining 25 parameters for each patient, where these 14 parameters are chosen based on the sensitivity analysis (results are given in Appendix A) and are given in Table 2 along with their corresponding values.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
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<td>(\epsilon_1)</td>
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<tr>
<td>(f)</td>
<td>5.303e-01</td>
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<tr>
<td>(k_2)</td>
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<td>(\lambda_E)</td>
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<td>(K_{b1})</td>
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<tr>
<td>(K_{b2})</td>
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<td>(\gamma_E)</td>
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<tr>
<td>(K_\gamma)</td>
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<td>(K_s)</td>
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</tr>
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<td>(T_2^{0})</td>
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</tr>
<tr>
<td>(V_I^{0})</td>
<td>4.486e+05</td>
</tr>
<tr>
<td>(V_{NI}^{0})</td>
<td>8.469e+02</td>
</tr>
<tr>
<td>(E_1^{0})</td>
<td>1.502e-02</td>
</tr>
</tbody>
</table>

Table 2: Results for those parameters whose values are fixed at the population averages across the 16 patients investigated.

After we estimate the reduced set of 25 parameters, we simulated the CD4+ T-cell and viral load trajectories over the full time span of the patient’s observations by using the parameter
values obtained and compared these to the experimental data. Model fitting results for those patients who were randomized to receive no therapy are given in Section 3.2.1, and the ones for those patients who were randomized to receive 12 (32) weeks therapy are illustrated in Section 3.2.2 (Section 3.2.3). In all these figures, time zero denotes the time point for which we have the first observation, the solid green lines along the x-axis indicate periods when the patient is on ART treatment, and gray circles denote the predicted censored data values. From these figures, we see that the fits are either very good or reasonably well.

3.2.1 Patients: Randomized to Receive No Therapy

Figure 9: Results for those patients who were randomized to receive no therapy and completed the study protocols, where the solid green lines along the x-axis indicate periods when the patient is on ART treatment, and gray circles denote the predicted censored data values.
Figure 10: Results for those patients who were randomized to receive no therapy and were taken off study due to developing other ineligibility criteria.
Figure 11: Results for those patients who were randomized to receive no therapy and were taken off study because of withdrawn consent.

Figure 12: Results for those patients who were randomized to receive no therapy and were taken off study due to no contact for follow-up.
3.2.2 Patients: Randomized to Receive 12 Weeks Therapy

Figure 13: Results for those patients who were randomized to receive 12 weeks therapy and completed the study protocols.
3.2.3 Patients: Randomized to Receive 32 Weeks Therapy

Figure 14: Results for those patients who were randomized to receive 32 weeks therapy and completed the study protocols.

Figure 15: Results for those patients who were randomized to receive 32 weeks therapy and were taken off study because of withdrawn consent.
3.3 Statistical Analysis

The Mann-Whitney U test [5], also called Wilcoxon rank-sum test, can be used to determine whether or not there is a difference in the viral load level and CD4+ T cell count between the group without treatment (8 patients) and the group with treatment (8 patients). It can also be used to determine whether or not there is a difference in the viral load level and CD4+ T cell count between the group assigned to 12 weeks therapy (4 patients) and the group assigned to 32 weeks therapy (4 patients). The Mann-Whitney U test is a nonparametric test that can be used to determine whether or not two random variables $X_1$ and $X_2$ have the same mean, and the associated statistic is based on the sum of ranks of assigned to the realizations of one random variable (i.e., either $X_1$ or $X_2$) when one orders the combined samples of $X_1$-realizations and $X_2$-realizations from least to greatest. For more information on this test, we refer the interested reader to [5, Chapter4].

Let $t_{\text{no}1}^{\text{no}}$ and $t_{\text{no}2}^{\text{no}}$ represent the two time points at which the measurements are taken to determine the primary endpoints for the patients randomized to receive no therapy, $t_{\text{12w}1}^{\text{12w}}$ and $t_{\text{12w}2}^{\text{12w}}$ for the patients assigned to 12 weeks therapy, and $t_{\text{32w}1}^{\text{32w}}$ and $t_{\text{32w}2}^{\text{32w}}$ for the patients assigned to 32 weeks therapy. In addition, we let $\hat{q}^j$ denote the estimated parameter values for the $j$th patient, $j = 1, 2, 3, \ldots, 16$.

For the primary objective (P1), the null hypothesis $H_0$ is that there is no difference in the CD4+ T cell count between the group without treatment and the group with treatment (that is, treatment has no discernable effect 48 weeks after cessation of treatment), while the alternative hypothesis $H_1$ is that there is difference in the CD4+ T cell count between these two groups. The primary endpoint $\text{PEP}_1^j$ for the $j$th patient is calculated as follows:

$$\text{PEP}_1^j = \begin{cases} 
\frac{1}{2} (\log_{10}(\tilde{z}_1(t_{\text{no}1}^{\text{no}}, \hat{q}^j)) + \log_{10}(\tilde{z}_1(t_{\text{no}2}^{\text{no}}, \hat{q}^j))), & \text{if } j \in \{1, 2, 3, \ldots, 8\}, \\
\frac{1}{2} (\log_{10}(\tilde{z}_1(t_{\text{12w}1}^{\text{12w}}, \hat{q}^j)) + \log_{10}(\tilde{z}_1(t_{\text{12w}2}^{\text{12w}}, \hat{q}^j))), & \text{if } j \in \{9, 10, 11, 12\}, \\
\frac{1}{2} (\log_{10}(\tilde{z}_1(t_{\text{32w}1}^{\text{32w}}, \hat{q}^j)) + \log_{10}(\tilde{z}_1(t_{\text{32w}2}^{\text{32w}}, \hat{q}^j))), & \text{if } j \in \{13, 14, 15, 16\}.
\end{cases}$$

(3.10)

(Recall that the first 8 patients are those patients randomized to receive no therapy, the next 4 patients are those assigned to 12 weeks therapy and the last 4 patients are the ones assigned to 32 weeks therapy.) Thus, for the primary objective (P1), the observations for the group without treatment and the ones for the group with treatment are respectively given by

$$\mathbb{P}_{\text{no}} = \{\text{PEP}_1^1, \text{PEP}_1^2, \text{PEP}_1^3, \ldots, \text{PEP}_1^8\},$$

$$\mathbb{P}_{\text{treat}} = \{\text{PEP}_1^9, \text{PEP}_1^{10}, \text{PEP}_1^{11}, \ldots, \text{PEP}_1^{16}\}.$$ 

(3.11)

Similarly, for the primary objective (P2), the null hypothesis $H_0$ is that there is no difference in the viral load level between the group without treatment and the group with treatment, while the alternative hypothesis $H_1$ is that there is difference in the viral load level between
these two groups. The primary endpoint PEP² for the jth patient is calculated as follows:

\[
\text{PEP}_2^j = \begin{cases} 
  \frac{1}{2} \log_{10}(\tilde{z}_2(t_{p,1}^{w}, \hat{\theta}^j)) + \log_{10}(\tilde{z}_2(t_{p,2}^{w}, \hat{\theta}^j)), & \text{if } j \in \{1, 2, 3, \ldots, 8\}, \\
  \frac{1}{2} \log_{10}(\tilde{z}_2(t_{12w}^{p}, \hat{\theta}^j)) + \log_{10}(\tilde{z}_2(t_{12w}^{p}, \hat{\theta}^j)), & \text{if } j \in \{9, 10, 11, 12\}, \\
  \frac{1}{2} \log_{10}(\tilde{z}_2(t_{32w}^{p}, \hat{\theta}^j)) + \log_{10}(\tilde{z}_2(t_{32w}^{p}, \hat{\theta}^j)), & \text{if } j \in \{13, 14, 15, 16\}. 
\end{cases}
\]  

Thus, for the primary objective (P2), the observations for the group without treatment and the ones for the group with treatment are respectively given by

\[
\begin{align*}
\mathbb{P}^{\text{no}}_2 &= \{\text{PEP}_2^1, \text{PEP}_2^2, \text{PEP}_2^3, \ldots, \text{PEP}_2^8\}, \\
\mathbb{P}^{\text{treat}}_2 &= \{\text{PEP}_2^9, \text{PEP}_2^{10}, \text{PEP}_2^{11}, \ldots, \text{PEP}_2^{16}\}.
\end{align*}
\]  

Using (3.11) and (3.13), we can then use Matlab command “ranksum” to obtain the p-values for the primary objectives (P1) and (P2). They are respectively given by 0.7984 and 0.6454. This indicates that there is no evidence that there is difference in the CD4+ T cell count and the viral load level between the group without treatment and the group with treatment. In other words, there is no evidence that treatment has an effect on the final set point values.

For the secondary objectives (S1), the observations for the group with 12 weeks treatment and the ones for the group with 32 weeks treatment are respectively given by

\[
\begin{align*}
\mathbb{S}_{12w}^1 &= \{\text{PEP}_1^0, \text{PEP}_1^{10}, \text{PEP}_1^{11}, \text{PEP}_1^{12}\}, \\
\mathbb{S}_{32w}^1 &= \{\text{PEP}_1^{13}, \text{PEP}_1^{14}, \text{PEP}_1^{15}, \text{PEP}_1^{16}\}.
\end{align*}
\]  

For the secondary objectives (S2), the observations for the group with 12 weeks treatment and the ones for the group with 32 weeks treatment are respectively given by

\[
\begin{align*}
\mathbb{S}_{12w}^2 &= \{\text{PEP}_2^0, \text{PEP}_2^{10}, \text{PEP}_2^{11}, \text{PEP}_2^{12}\}, \\
\mathbb{S}_{32w}^2 &= \{\text{PEP}_2^{13}, \text{PEP}_2^{14}, \text{PEP}_2^{15}, \text{PEP}_2^{16}\}.
\end{align*}
\]  

Using (3.14) and (3.15), we find that the p-values for the secondary objectives (S1) and (S2) are respectively given by 0.0571 and 0.3429. This indicates that there is no evidence that there is difference in the viral load level between the group assigned to 12 weeks therapy and the group assigned to 32 weeks therapy. We also fail to reject the null hypothesis of (S1) with 5% significance level.

4 Concluding Remarks

Our experimental findings support our earlier predictions with the mathematical model simulations. However we point out that because of the limited number of patients completing the study that the statistical analysis described above is far from conclusive.
5 Acknowledgements

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References


A Sensitivity Results

Sensitivity analysis was conducted for each patient with parameter values obtained for the case where we estimated all the model parameters and initial conditions (total 39 parameters). Due to the scale difference among model states and parameters, sensitivities of log-scaled model outputs (i.e., total CD4+ T cells and total viral load level) with respect to log-scaled parameters (except \( \epsilon_1, f, \epsilon_2 \)) were calculated. The overall influence of log-scaled parameters on the log-scaled model outputs over time for the \( j \)th patient were calculated as follows:

\[
S_{1,k}^j = \left( \frac{1}{N_1^j} \sum_{i=1}^{N_1^j} \left( \frac{\partial z_1}{\partial q_k}(t_{ij}^j; \hat{q}^j) \right)^2 \right)^{1/2}, \quad k = 1, 2, 3, \ldots, 39,
\]

\[
S_{2,k}^j = \left( \frac{1}{N_2^j} \sum_{i=1}^{N_2^j} \left( \frac{\partial z_2}{\partial q_k}(t_{ij}^j; \hat{q}^j) \right)^2 \right)^{1/2}, \quad k = 1, 2, 3, \ldots, 39.
\]

Here \( z_1 = \log_{10}(\tilde{z}_1) \) and \( z_2 = \log_{10}(\tilde{z}_2) \) with \( \tilde{z}_1 \) and \( \tilde{z}_2 \) defined in (3.9), and \( \hat{q}^j \) denotes the estimated value of log-scaled parameters for the \( j \)th patient. We then averaged these sensitivity results across these 16 investigated patients to identify the parameters to which both model outputs are least sensitive so that we can fix these parameters at the population averages. The results are shown in Table 3 and are ordered from the most sensitive to the least for each model output.
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Table 3: Sensitivity results.