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# A dynamical modeling approach for analysis of longitudinal clinical trials in the presence of missing endpoints

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ABSTRACT

Randomized longitudinal clinical trials are the gold standard to evaluate the effectiveness of interventions among different patient treatment groups. However, analysis of such clinical trials becomes difficult in the presence of missing data, especially in the case where the study endpoints become difficult to measure because of subject dropout rates or/and the time to discontinue the assigned interventions are different among the patient groups. Here we report on using a validated mathematical model combined with an inverse problem approach to predict the values for the missing endpoints. A small randomized HIV clinical trial where endpoints for most of patients are missing is used to demonstrate this approach.



## 1. Introduction

Even though most randomized clinical trials are carefully designed, it often becomes inevitable for participants to go off the study or discontinue the assigned intervention before study completion. This is especially true for longitudinal clinical trials conducted over a substantial period of time in which new or alternative strategies are introduced into clinical practice which may effect continued participation of study subjects, resulting in an incomplete or difficult to analyze data set. The impact of conducting of an incomplete or altered clinical trial is large, especially given the expense and time involved for study subjects and investigators. However, it is often the case that information contained in the data collected for an early termination time is useful. Consequently, the question of how to efficiently use the collected data and appropriately handle missing data points has become one of the important problems in analysis of clinical trials. This is especially important in cases where the clinical trials involve a small number of participants.

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To minimize the number of subjects who are eliminated from the analysis, imputation methods are often used to handle missing data. A number of ad-hoc imputation approaches have been proposed in the literature including the commonly used last-observation-carried-forward, baseline observation carried forward, and intent to treat (ITT) methods. However, these methods do not work well for those longitudinal clinical trials where dropout or discontinuation of the assigned interventions occurs early and the outcomes of interest are changing over time. They may also provide biased treatment comparisons if dropout rates or/and times to dropout are different among the intervention groups. For more information on these methods, we refer interested readers to [1,2] and the references therein.

To partially alleviate the difficulty encountered by the traditional methods, we propose to use mathematical/dynamical modeling combined with an inverse problem approach to analyze longitudinal clinical trials in the presence of missing endpoints. A randomized trial of treatment versus no treatment in subjects with acute HIV infection is used to illustrate the proposed approach, where the model used to predict the missing endpoints was carefully validated by multiple data sets collected previously. The remainder of this paper is organized as follows: we first give a brief introduction of this clinical trial, and then we talk about how to use the proposed method to analyze this trial. Finally we conclude the paper by some remarks.

## 2. An HIV randomized clinical trial

The randomized clinical trial used to illustrate our approach was conducted in Massachusetts General Hospital from 2009 to 2014. This trial was approved by the Massachusetts General Hospital human subject protection committee ([IRB]) In this trial, subjects identified with acute HIV infection were randomized to receive either no therapy, 12 weeks therapy, or 32 weeks therapy. The goal of this trial is to determine whether treatment initiated during acute HIV infection followed by terminal interruption results in a lower HIV viral load level and higher CD4+ T cell count than no treatment and to determine whether the length of time in treatment before discontinuation plays an important role. Below we will give detailed information on the objectives and the associated endpoints for this study as well as the data collected.

### *2.1. Objectives and endpoints*

As we stated earlier, there were two objectives in our study. The primary objectives were to determine whether treatment initiated during acute HIV infection is beneficial as measured by the following primary (P) and secondary (S) study endpoints: (P1) To determine whether or not there is a difference in the *CD4+ T cell count* between the group without treatment at 46–48 weeks after randomization and the group with treatment at 46–48 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 46–48 weeks after randomization and the group with treatment at 46–48 weeks after discontinuation of treatment. The primary endpoints were determined for each study subject by taking the average of two HIV $\log_{10}$ RNA viral load measurements and the average of two log CD4+ T cell measurements determined 46–48 weeks after discontinuation of treatment in subjects randomized to receive therapy and 46–48 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. While for subjects randomized to receive no treatment, they are the averages of two observations taken at 46 and 48 weeks after randomization.

The secondary objectives are to determine whether the duration of treatment before interruption is important, and these are detailed as follows: (S1) To determine whether or not there is a difference at 46–48