Modeling the Causal Effect of Treatment Initiation Time on Survival: Application to HIV/TB Co-infection

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Abstract

Timing of combinational antiretroviral therapy (cART) initiation is important in HIV/Tuberculosis (TB) co-infection. Early initiation during TB treatment increases drug toxicity, the risk of inflammatory immune reconstitution, and cost burden; late initiation increases risk for morbidity and mortality associated with HIV/AIDS. Evidence from recent RCTs and observational studies generally supports early initiation. However, existing studies do not give specifics about optimal initiation time or precise recommendations for those with CD4>100. We use data from a large observational cohort to gain more detailed information about treatment effects in practical settings. We formulate a causal structural model that flexibly captures the joint effects of treatment initiation time and treatment duration using smoothing splines, and develop methods for fitting the model to observational data with complicated censoring patterns where both treatment and outcome are event times and subject to censoring. Our methods can generate survival curves corresponding to specific treatment times; and can separately characterize effects of timing and duration on treatment. We fit the model to data from 4903 individuals in a large HIV treatment program in Kenya, and use it to estimate optimal initiation times by CD4 subgroups. Our findings are consistent with RCTs but have "higher resolution" in the sense of generating CD4-specific rules that can be used to complement current treatment guidelines.

Keywords: Causal inference; HIV/TB co-infection; Missing data; Survival analysis; Optimal cART initiation time; Inverse weighting

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1 Introduction

1.1 Overview and objectives

Integration of combined antiretroviral therapy (cART) with tuberculosis (TB) treatment has received significant attention in the care management of patients coinfected with TB and human immunodeficiency virus (HIV). The World Health Organization (WHO) guidelines recommend concomitant treatment of the two diseases (WHO 2013). However, the optimal timing of cART initiation during the TB treatment period is difficult to determine (Abdool Karim et al. 2011, Severe et al. 2010). Initiating cART too early increases the potential drug toxicity and the risk of TB-associated immune reconsititution inflammatory syndrome (IRIS) (Breen et al. 2004, Burman et al. 2007, Havlir et al. 2011). On the other hand, late initiation of cART increases risk for morbidity and mortality associated with AIDS (Abdool Karim et al. 2010).

The CD4 cell count serves as the major laboratory indicator of immune function in HIV-infected patients, and it is an important factor in determining the urgency of cART initiation. Evidence from randomized controlled trial (RCT) (Abdool Karim et al. 2010 2011, Blanc et al. 2011, Havlir et al. 2011) and observational studies (Franke et al. 2011, Velasco et al. 2009, Westreich et al. 2012) generally support early initiation of cART for patients with low CD4 count. However, these studies do not give precise recommendations for those with CD4 greater than 100, nor do they give specifics about optimal starting time for different types of patients. These studies generally compare groups of individuals and several regimes, not the actual timing. Furthermore, the sample sizes of the RCT studies are smaller than large observational cohorts.

Our objective is to draw inferences about the effect of timing of cART initiation on mortality. We investigate the issue using data drawn from the electronic medical records (EMR) system of the Academic Model Providing Access to Healthcare (AMPATH), a program delivering HIV care in western Kenya (Einterz et al. 2007). The AMPATH program has developed its own treatment guideline in consultation with the Kenyan National AIDS and STI Control Program (NASCOP); see Table 2. The data have rich information, but the observational nature of the data poses complications for our analysis. First, treatment initiation time is not randomly allocated. Second, in many cases we have incomplete information on exposure, outcome, or both. In the maximum information setting, we would observe for all patients cART initiation time first, and then death time. However, some patients died before initiating cART, which censors cART initiation time. For other patients, incomplete follow up leads to censoring of death time, cART initiation time, or both. Figure 1 shows the four observed data patterns of cART initiation and mortality following initiation of the TB treatment.

Our approach is to formulate model that captures the effects of both timing and duration of cART. We formulate a marginal structural proportional hazards model with an unspecified smooth function capturing the effect of timing of cART initiation, and a second unspecified smooth function capturing the effect of duration on cART, once initiated. We develop methods for fitting our structural model to complex observational data wherein initiation time is nonrandomly assigned, and both mortality and cART initiation time are subject to censoring. We then use output from the fitted model to estimate CD4-specific optimal initiation times that are tailored to CD4 count at the initiation of TB treatment. The optimality criterion is one-year survival, although any feature of the survival distribution can be used.

Our paper makes use of a large observational data drawn from the AMPATH program,

examines the effect of cART timing on continuous scale, estimates the CD4-specific optimal cART initiation time, and investigates whether our analyses results are consistent with general RCT findings. Furthermore, the larger sample size in our data affords the potential to examine the issue in greater details.

This paper is organized as follows: Section 1 introduces HIV and TB co-infection and marginal structural models. Section 2 describes notation, defines optimal initiation time and formulates a marginal structural model for mortality. Section 3 develops the methods for fitting our structural model to complex observational data, wherein both exposure and outcome are subject to censoring. Section 4 presents results from applying our method on AMPATH data. In Section 5 we put the results in context by comparing them with RCT findings and current treatment guidelines.

1.2 Treatment of individuals coinfected with HIV and tuberculosis

Generally, treatment of TB is a 6-month regimen, starting with 2-month administration of isoniazid, rifampin, pyrazinamide and ethambutol, and continuing with isoniazid and rifampin for another 4 months (WHO 2010). The treatment guidelines for TB are summarized in Table 1.

While the optimal time cART initiation time is not yet clear, and may depend on CD4 count and other indicators of HIV disease stage, the WHO recommends that TB treatment should be initiated first and cART be started within the first 8 weeks for all patients and within the first 2 weeks for those with CD4 less than 50 (WHO 2013). However, complications associated with early initiation of cART may discourage treatment adherence and cause adverse effects, drug interactions and IRIS (WHO 2013). In developing countries, HIV treatment decisions are often based on both clinical and immunological markers (e.g., CD4 cell count). Patients in the 4-point WHO scale stage 3 or 4, or with a CD4 count below 250, are eligible for cART at initiation of TB treatment. In consultation with the Kenyan National AIDS and STI Control Program (NASCoP), the AMPATH program has developed its own treatment guidelines for patients with HIV/TB co-infection. The guidelines for initiating cART for patients with different levels of CD4 count at the initiation of TB treatment are shown in Table 2.

1.3 Statistical methods for time-dependent treatment regimes

Marginal structural models (MSMs) are a class of statistical models to estimate the causal effect of a time-varying treatment on an outcome of interest while accounting for time-dependent confounding (Robins 1999, Robins et al. 1998). Marginal structural models (MSMs) have become a popular tool to study the causal effect of a treatment regime (Hernán et al. 2001, Murphy et al. 2001, Robins 1999, Robins et al. 2000).

In comparing the effect of cART initiation time, Franke et al. (2011) applied g-computation formula to simulate the potential 2-year survival curves that would be observed under five cART initiation regimes. When a treatment is continuous, the g-computation algorithm requires model-dependent, computationally-intensive integration over the distribution of time-dependent confounders. Moreover, the g-computation algorithm can suffer from the g-null paradox under some modeling choices for time-varying covariates (Daniel et al. 2013): that with the parametric version of the g-computation formula, given enough data, one would reject of causal null hypothesis of no causal effect of treatment even when it is true.

Work by Johnson and Tsiatis (2005) develops methods for estimating the effect of treatment *duration* on the mean of a single endpoint. Our work deals with the related but different problem of *timing of treatment initiation*. In addition, we use the survival distribution,

rather than a univariate measure, as the outcome of interest. Our parametrization of causal effect of initiation time captures separately the influence of both timing and duration; these components are represented using unspecified smooth functions of time, providing flexibility for modeling and generating interpretable data-driven representations of the overall treatment effect. Our method can be used to generate the full distribution of potential outcomes corresponding to specific cART initiation times, and to derive covariate-specific optimal initiation times.

2 Formulation of potential outcomes model

2.1 Notation for potential outcomes and observed data

Let t denote time elapsed from the initiation of TB therapy, and let t_{max} denote a fixed period of interest. All event times are measured in terms of elapsed time from $t = 0$. Let $T_a > 0$ denote the potential outcome corresponding to time of death if cART is initiated at time a, where $a \geq 0$ is continuous. We use T_∞ to denote death time corresponding to any $a > t_{\text{max}}$.

Information on potential outcomes is observed according to the cases depicted in Figure 1. Let A be the random variable representing cART initiation time, and let $T = T_A$ denote the survival time corresponding to initiating cART at A. As shown in Figure 1, either or both of A and T_A may be right censored, for example due to loss to follow up. Let C denote a censoring time. We can now describe precisely the observed data that are available for drawing inference about the distribution of potential outcomes.

The observed follow up time for the mortality outcome is $T^* = \min(T, C)$, and the event indicator is $\Delta^T = I(T < C)$. Similarly, the observed follow up time for cART initiation time is $A^* = \min(A, T^*) = \min(A, T, C)$, with another indicator $\Delta^A = I(A < T^*)$. Notice that A can be right censored by T, as shown in Case II of Figure 1. We administratively censor A at t_{max} for cases where $A > t_{\text{max}}$ and $T^* > t_{\text{max}}$.

Each individual has a $p \times 1$ vector L of covariates, some of which may be time varying. We use $L(t)$, $t \geq 0$ to denote the most recently observed value of the covariate vector at time t, and use $\overline{L}(t) = \{L(s) : 0 \leq s < t\}$ to denote the observed covariate history up to but not including t. For each individual, therefore, we observe a copy of $\left\{\overline{L}(A^*), T^*, \Delta^T, A^*, \Delta^A\right\}$.

2.2 Defining optimal initiation time

Optimal initiation time is defined as the value of a that maximizes an objective function written in terms of a functional of the distribution of potential outcomes. Specifically, let $F_a(t) = P(T_a \leq t)$ denote the CDF associated with T_a, and let $\theta_a = \theta(F_a)$ denote a scalar functional of F_a. For example, $\int t \; dF_a(t)$ is the mean of T_a, and $F_a^{-1}(\frac{1}{2})$ is the median. For a given functional θ_a, the optimal initiation time is given as $a_{\text{opt}} = \arg\max_a \theta_a$, or the value of a that maximizes the functional. For our application to the AMPATH data, we fix a time t_0 and set $\theta_a = \theta_a(t_0) = 1 - F_a(t_0)$, the survival fraction at time t_0; note that the optimal initiation time $a_{\text{opt}}(t_0) = \arg\max_a\{\theta_a(t_0)\}$ is therefore a function of t_0. Our data analysis in Section 4 sets t_0 to be one year past initiation of TB therapy.

2.3 Marginal structural model for mortality

We assume T_a follows a marginal structural proportional hazards model of the form

$$\lambda_a(t) \quad = \quad \lambda_\infty(t) \; r(t, a), \tag{1}$$

where $\lambda_a(t)$ is the hazard function for T_a, $\lambda_\infty(t)$ is the reference hazard for T_∞, and $r(t,a) > 0$ is the hazard ratio function which can be time dependent. We parameterize $r(t,a)$ in terms of two components: $h_1(a)$ and $h_2(t-a)$, denoting effect of timing and effect of duration, respectively. Both are unspecified. In our application, we assume

$$r(t,a) \quad = \quad \exp[I(a \leq t)\{h_1(a) + h_2(t-a)\}], \tag{2}$$

where $h_1(\cdot)$ and $h_2(\cdot)$ are unspecified smooth functions that are twice continuously differentiable, with the second derivative set to zero at the endpoints of a and $t-a$. We also allow the function $r(t,a)$ to depend on baseline covariates $V \subseteq L(0)$ by elaborating model (2). We describe this in detail in Section 4.

The model can be understood by considering some simple cases. Let $h_1(a) = \beta_1$ be a constant and $h_2(t-a) = 0$; this implies that the log hazard of mortality is $\log\{\lambda_\infty(t)\}$ prior to treatment initiation ($t < a$) and $\beta_1 + \log\{\lambda_\infty(t)\}$ thereafter ($t \geq a$). This simple version also assumes the (instantaneous) effect of cART on hazard of mortality is the same, regardless of when cART is initiated; see Figure 2(a). If we allow $h_1(a)$ to vary with a, then the effect of cART initiation depends on its timing; see Figure 2(b).

Now consider models where $h_1(a)$ is arbitrary and $h_2(t-a) \neq 0$; a simple version is $h_2(t-a) = (t-a)\beta_2$, where β_2 is a scalar. This model implies that the instantaneous effect of initiating cART is $h_1(a)$, and that the effect of *being on* cART at any given time t depends on duration; see Figure 2(c). If $\beta_2 < 0$, then at any given time t, individuals at risk who have been on cART for longer will have lower rate of mortality. In general, $h_2(t-a) < 0$ (> 0) implies that, after the initiation of cART at time a, the effect of cART on the hazard of mortality diminishes (intensifies) over time. Figure 2 illustrates some simple versions of the hazard model and the corresponding survival models. For simplicity, models in Figure 2 assume $\lambda_\infty(t)$ is constant, but in our application it is left unspecified.

We parameterize $h_1(\cdot)$ and $h_2(\cdot)$ using natural cubic splines constructed from piecewise third-order polynomials that pass through a set of control points, or knots. In practice, we place the knots at quantiles of observed A for $h_1(\cdot)$ and observed $T^* - A$ for $h_2(\cdot)$, respectively. A natural cubic spline has continuous first and second derivatives at the knots, and is linear beyond the boundary knots. Basis functions generated under these constraints are called B-spline functions (Hastie et al. 2009). Parameterizing our model in terms of B-splines yields

$$\lambda_a(t) \quad = \quad \lambda_\infty(t) \exp\left[I(a < t)\left\{b_1(a)^\top \beta_1 + b_2(t-a)^\top \beta_2\right\}\right], \tag{3}$$

where $b_1(\cdot)^\top = (b_{1_1}(\cdot), \ldots, b_{1_{K_1}}(\cdot))$ is a B-spline basis function of degree K_1 in a, and $b_2(\cdot)^\top = (b_{2_1}(\cdot), \ldots, b_{2_{K_2}}(\cdot))$ is a B-spline basis function of degree K_2 in $t-a$. The parameters β_1 and β_2 are vectors of K_1 and K_2 coefficients for the basis functions $b_1(a)$ and $b_2(t-a)$, respectively. This yields $r(t,a) = \exp\{X(a,t)^\top \beta\}$, where

$$X(a,t)_{(K_1+K_2)\times 1} = I(a < t)[b_1(a)^\top, b_2(t-a)^\top]^\top \tag{4}$$

and $\beta_{(K_1+K_2)\times 1} = [\beta_1^\top, \beta_2^\top]^\top$. The causal effect of cART initiation time on survival distribution is therefore encoded in β.

3 Estimation of structural model and optimal initiation time

3.1 Overview

In a RCT, individuals would be randomly assigned to cART initiation time A according to some known probability density $f_A(\cdot)$. In observational data, A is not randomized and may be right censored. In our data, the decision to initiate cART depends on information avail-

able to the physician, and is therefore not randomly allocated. Moreover, A will be right censored when an individual dies or leaves the study before treatment initiation. Our methods use observed data $\left\{A_i^*, \Delta_i^A, T_i^*, \Delta_i^T, \overline{L}_i(A_i^*) \ : \ i = 1, \ \ldots, \ n\right\}$ to estimate parameters of the structural Cox model. We propose to use a weighted partial likelihood score (WPLS), with inverse probability weights (IPW) to address nonrandom allocation of treatment and potentially informative censoring. In the following, we discuss how to choose appropriate weights and propose methods for estimating them.

In deriving the weights, we first consider the hypothetical case where A is not randomized and where T is always observed. Next, we move to the case where A may be censored by T (i.e., where death occurs prior to treatment initiation), but there is no censoring by C. We then describe the case where A is not randomized, and possibly censored by T. Finally, we generalize our approach to allow for censoring by C, and consider cases where C may be either non-informative or informative. Following the development of inference for our causal structural model, we address the issue of estimating the optimal treatment initiation time.

3.2 Randomized treatment assignment

If treatment is randomly allocated according to $f_A(\cdot)$, then we can use the standard partial likelihood score equations to derive consistent estimators of β. Let $\{N^T(t) : t > 0\}$ denote the zero-one counting process associated with T, such that $N^T(t) = I\left\{T \leq t, \Delta^T = 1\right\}$. Let $Y(t) = 1$ if an individual is still at risk and under observation at t, and $Y(t) = 0$ otherwise. The partial likelihood score equations can be written $\sum_{i=1}^n D_i(\beta) = 0$, where

$$\begin{aligned} D_i(\beta) &= D(A_i, T_i; \beta) \\ &= \int_0^\infty \left\{X(A_i, t) - \overline{X}(t, \beta)\right\} dN_i^T(t), \end{aligned} \tag{5}$$

where $X(A_i, t)$ is the design matrix based on (4) and $\overline{X}(t, \beta) = \frac{\sum_k X(A_k,t)Y_k(t)r(A_k,t;\beta)}{\sum_k Y_k(t)r(A_k,t;\beta)}$. Let $E_R\{\cdot\}$ denote expectation under randomized treatment assignment. Under randomization of A, $(1/n)\sum_i D(A_i, T_i; \beta)$ is an unbiased estimator of $E_R\left\{D(A, T; \beta)\right\}$. The score function $\sum_i D_i(\beta)$ is a stochastic integral of a predictable process with respect to a martingale, and as such $E_R\left\{D(A, T; \beta_0)\right\} = 0$ at the true value β_0 of β; hence, the root $\widehat{\beta}$ of the unbiased estimating equation $\sum_{i=1}^n D_i(\beta) = 0$ is a consistent estimator of β (Fleming and Harrington 1991, pp. $297 - 298$).

Now consider the case where A is still randomly allocated, but death may occur before initiation of treatment, so that $A^* = \min(A, T)$ and $\Delta^A = I(A < T)$. We continue to assume no censoring by C. Following Johnson and Tsiatis (2005), the mean of an individual score contribution is $E_R\left\{D(A_i, T_i; \beta)\right\} = E_R\left\{\Delta_i^A D(A_i, T_i; \beta) + (1 - \Delta_i^A) D(A_i, T_i; \beta)\right\}$, with

$$\begin{aligned} E_R\left\{(1 - \Delta_i^A) D(A_i, T_i; \beta)\right\} &= E_R\left[E_R\left\{(1 - \Delta_i^A) D(A_i, T_i; \beta) \mid \Delta_i^A, A_i^*\right\}\right] \\ &= E_R\left[(1 - \Delta_i^A) E_R\left\{D(A_i, T_i; \beta) \mid \Delta_i^A, A_i^*\right\}\right] \\ &= E_R\left\{(1 - \Delta_i^A) \int_{A_i^*}^\infty D(a, T_i, \beta) dF_{A \mid A > A_i^*}(a)\right\} \\ &= E_R\left\{\frac{(1 - \Delta_i^A)}{1 - F_A(A_i^*)} \int_{A_i^*}^\infty D(a, T_i, \beta) dF_A(a)\right\}. \end{aligned} \tag{6}$$

To evaluate (6), note that $D(a, T_i; \beta) = \int_0^\infty \{X(a,t) - \overline{X}(t,\beta)\} dN_i^T(t)$, and recall that $X(a,t) = I(a < t)[b_1(a)^\top, b_2(t-a)^\top]^\top$, so that $X(a,t) = 0$ for $a \geq t$, and $D(a, T_i, \beta)$ is a constant function of a where $a \geq A_i^*$ and is evaluated at T_i as $-\overline{X}(T_i, \beta)$. Therefore, $\int_{A_i^*}^\infty D(a, T_i, \beta) dF_A(a) = (1 - F_A(A^*))\, \overline{X}(T_i, \beta)$ and equation (6) $= -E_R \left\{ (1 - \Delta_i^A) \overline{X}(T_i, \beta) \right\}$. Hence, when death may occur before treatment initiation, and when there is no censoring by C, $(1/n) \sum_i D_i(\beta)$ is an unbiased estimator of $E_R \left\{ \Delta^A D(A, T; \beta) - (1 - \Delta^A) \overline{X}(T, \beta) \right\}$. This implies that the solution $\widehat{\beta}$ to the modified estimating equations

$$\sum_{i=1}^{n} \left\{ \Delta_i^A D(A_i, T_i; \beta) - (1 - \Delta_i^A) \overline{X}(T_i, \beta) \right\} \;=\; 0 \tag{7}$$

will yield a consistent estimator of β.

3.3 Non-random allocation of treatment

Suppose now that A is not randomly allocated, but that treatment allocation can be considered ignorable in the sense that

$$\lambda^A \left\{ t \,|\, \overline{L}(t), \mathscr{T}_{\{a \geq t\}} \right\} \;=\; \lambda^A \left\{ t \,|\, \overline{L}(t) \right\}, \tag{8}$$

where $\mathscr{T}_{\{a \geq t\}} = \{T_a : a \geq t\}$ is the set of potential failure times associated with initiation times beyond t. This assumption states that initiation of treatment at time t is sequentially randomized in the sense that it is independent of future potential outcomes, conditionally on observed covariate history $\overline{L}(t)$ (Robins 1999). This is the key assumption we make for causal inference about the effect of A on T.

Let $\mathbb{P}_R(\cdot)$ denote the data distribution under randomized treatment, and let $\mathbb{P}_O(\cdot)$ denote the same under non-random allocation of treatment. Recall that the collection of data that can be observed for *all* individuals, under either randomized or non-randomized allocation of treatment, is $\{A^*, \Delta^A, T^*, \Delta^T\}$. Following Murphy et al. (2001) and Johnson and Tsiatis (2005), under the sequential randomization assumption in (8) and some regularity conditions, including that

$$\Pr \left\{ \lambda \left(t | \overline{L}(t) \right) > 0 \;\text{ for all }\; t \;\text{ such that }\; f_A(t) > 0 \right\} \;=\; 1, \tag{9}$$

the distribution of $\{A^*, \Delta^A, T^*, \Delta^T\}$ under $\mathbb{P}_R(\cdot)$ is absolutely continuous with respect to the distribution of $\{A^*, \Delta^A, T^*, \Delta^T\}$ under $\mathbb{P}_O(\cdot)$, and a version of the Radon-Nikodym (R-N) derivative is

$$E_O \Big\{ \Delta^A \frac{f_A(A^*)}{f_A(A^* \,|\, \overline{L}(A^*))} + (1 - \Delta^A) \frac{1 - F_A(A^*)}{1 - F_A(A^* \,|\, \overline{L}(A^*))} \Big| \; A^* = a, \Delta^A = \delta^A, T^* = t, \Delta^T = \delta^T \Big\}. \tag{10}$$

One consequence of the R-N derivative is that an estimating equation that is a function of observed data and is unbiased under the distribution of $\mathbb{P}_R(\cdot)$ can be re-weighted by the R-N derivative to obtain an unbiased estimating equation using the same observed data, but now under the distribution $\mathbb{P}_O(\cdot)$ (Murphy et al. 2001).

Define

$$W_{1i}^A(t) \;=\; \frac{f_A(t)}{f_A(t \,|\, \overline{L}_i(t))}, \quad W_{2i}^A(t) \;=\; \frac{1 - F_A(t)}{1 - F_A(t \,|\, \overline{L}_i(t))}.$$

The R-N derivative in (10) suggests using the weighted estimating equation

$$\sum_{i=1}^{n} \Delta_i^A D^*(A_i, T_i; \beta) W_{1i}^A(A_i) - (1 - \Delta_i^A)\overline{X}^*(T_i; \beta) W_{2i}^A(T_i) \quad = \quad 0, \tag{11}$$

where D^* and $\overline{X}^*$ are evaluated using weighted risk set indicators

$$Y_k^*(t) \quad = \quad Y_k(t) \left\{ I(A_k < t) W_{1k}^A(A_k) + I(A_k \geq t) W_{2k}^A(t) \right\}.$$

Up to now we have assumed no censoring by C. Let $A(t)$ be the counting process of treatment initiation, and $\overline{A}(t)$ denotes treatment history information up to time t. Suppose that censoring is non-informative such that

$$\lambda^C \left\{ t \,|\, \overline{A}(t),\ \mathscr{T}_{\{a \geq t\}} \right\} \quad = \quad \lambda^C \left\{ t \,|\, \overline{A}(t) \right\}, \tag{12}$$

i.e., that conditional on treatment history information, the hazard of censoring at time t does not depend on covariates or future potential outcomes. Censoring of T by C implies that contributions to (11) will be zero. Under the non-informative censoring assumption in (12), the WPLS estimating equation in (11) gives a consistent estimator for β.

We can relax the assumption by conditioning on covariates $L(t)$,

$$\lambda^C \left\{ t \,|\, \overline{A}(t),\ \overline{L}(t),\ \mathscr{T}_{\{a \geq t\}} \right\} \quad = \quad \lambda^C \left\{ t \,|\, \overline{A}(t),\ \overline{L}(t) \right\}.$$

This assumption states that occurrence of a censoring event at time t does not depend on future potential outcomes, conditionally on observed treatment and covariate history $\overline{L}(t)$. Define $W_i^C(t) = \dfrac{1 - F_C(t)}{1 - F_C(t \,|\, \overline{L}_i(t))}$. Individuals who are censored by C contribute to the risk set for all death times that occur before C. Our proposed WPLS estimating equation is then:

$$U_n(\beta) = \sum_{i=1}^{n} \Delta_i^T \ W_i^C(T_i) \left\{ \Delta_i^A D^{**}(A_i, T_i; \beta) W_{1i}^A(A_i) - (1 - \Delta_i^A)\overline{X}^{**}(T_i; \beta) W_{2i}^A(T_i) \right\}, \tag{13}$$

where D^{**} and $\overline{X}^{**}$ are evaluated using weighted risk set indicators

$$Y_k^{**}(t) \quad = \quad Y_k(t) \left\{ I(A_k < t) W_{1k}^A(A_k) + I(A_k \geq t) W_{2k}^A(t) \right\} W_k^C(t).$$

3.4 Estimation of the weights

The weights in our WPLS estimating equations in (13) depend on the marginal and conditional density functions of A and C. Let $\{N^A(t) : t > 0\}$ denote the zero-one counting processes associated with A, such that $N^A(t) = I(A \leq t, \Delta^A = 1)$. Let $N^C(t) = I(C \leq t, \Delta^T = 0)$. We can model the intensity processes of $N^A(t)$ and $N^C(t)$ separately.

To estimate $f_A(t \,|\, \overline{L}(t))$, we assume a proportional hazards model for $\lambda^A \left\{ t \,|\, \overline{L}(t) \right\}$, using a regression function parameterized in terms of a finite-dimensional parameter α,

$$\lambda^A \left\{ t \,|\, \overline{L}(t) \right\} \quad = \quad \lambda_0^A(t)\ q^A \left(\ \overline{L}(t);\ \alpha \ \right). \tag{14}$$

Using the approximation $e^{-x} \approx 1 - x$ for small x, and noting that $1 - F_A(t) = \exp\{-\Lambda(t)\}$, we have $1 - F_A(t \,|\, \overline{L}(t), \widehat{\alpha}) \approx \prod_{t_j \leq t} \left\{ 1 - \lambda^A(t_j \,|\, \overline{L}(t_j), \widehat{\alpha}) \right\}$. The conditional density function $f_A(t \,|\, \overline{L}(t))$ can be estimated as $\widehat{f}_A(t \,|\, \overline{L}(t)) = \lambda^A(t \,|\, \overline{L}(t), \widehat{\alpha}) \left\{ 1 - F_A(t \,|\, \overline{L}(t), \widehat{\alpha}) \right\}$, where t_j's are the unique observed treatment initiation times, and $\widehat{\alpha}$ is the maximum partial likelihood estimator for model (14).

To estimate the unknown marginal probability density $f_A(t)$, we use the Nelson-Aalen estimator $\widehat{\Lambda}^A(t)$ for the cumulative hazard rate function of the observed treatment initia-

tion, $\left\{A_i^*, \Delta_i^A, i = 1, \ldots, n\right\}$, with $\widehat{\lambda}^A(t) = \mathrm{d}\widehat{\Lambda}^A(t)$, hence $\widehat{f}_A(t) = \widehat{\lambda}^A(t)\left\{1 - \widehat{F}_A(t)\right\}$, where $1 - \widehat{F}_A(t) = \exp\left\{-\widehat{\Lambda}^A(t)\right\}$. Therefore,

$$\widehat{W}_{1i}^A(t) \;=\; \frac{\widehat{f}_A(t)}{\widehat{f}_A(t \,|\, \overline{L}_i(t))}, \quad \widehat{W}_{2i}^A(t) \;=\; \frac{1 - \widehat{F}_A(t)}{1 - F_A(t \,|\, \overline{L}_i(t), \widehat{\alpha})}.$$

The weights $W_i^C(t)$ can be estimated in a similar fashion by fitting a PH model for $\lambda^C\left\{t \,|\, \overline{A}(t),\ \overline{L}(t)\right\}$ and using N-A estimator $\widehat{\Lambda}^C(t)$ with $\widehat{\lambda}^C(t) = \mathrm{d}\widehat{\Lambda}^C(t)$ for estimating $f_C(t)$.

3.5 Optimal initiation time

With our structural model (3), the potential survival function for a given regime a is: $S_a(t) = \exp\{-\Lambda_a(t)\}$, where,

$$\begin{aligned}\Lambda_a(t) \;&=\; I(t < a)\Lambda_\infty(t) \\ &+\; I(t \geq a)\Big[\Lambda_\infty(a) + \int_a^t \exp\{h_1(a) + h_2(u - a)\}\mathrm{d}\Lambda_\infty(u)\Big].\end{aligned}$$

The estimated baseline cumulative hazard, $\hat{\Lambda}_\infty(t)$, is the Breslow estimate. For any given a and t, $h_1(a)$, $h_2(t - a)$ and $\Lambda_\infty(\cdot)$ are estimated using our WPLS estimating equation (13). Therefore, $S_a(t)$ can be estimated for any combination of a and t. We estimate the optimal initiation time as the value of a that maximizes expected one-year survival, $a_{\text{opt}}(t_0 = 52) = \arg\max_a\{\hat{S}_a(t_0 = 52)\}$.

4 Application to AMPATH data

We extracted AMPATH data on 6726 HIV/TB co-infected adult patients who initiated TB treatment between March 1, 2004 and April 18, 2008 and had a baseline CD4 count below 350. These patients were automatically eligible for cART initiation in resource constrained setting according to AMPATH guidelines. Baseline is defined as the time at which TB treatment is initiated. We excluded 1823 individuals who had missing data on one or more baseline covariates. Our analysis dataset therefore contains 4903 HIV/TB co-infected patients with TB therapy initiated. Among these patients, 3593 had observed cART initiation times within one year subsequent to the initiation of TB treatment, 52 were observed to start cART after one year of their TB treatment, and 449 were observed not to start cART. The remaining 809 patients were either administratively censored, lost to follow-up, or had died prior to the initiation of cART, all resulting in right censored exposure (cART initiation) times.

Baseline CD4 count is a key marker physicians use to decide cART initiation time. To be consistent with AMPATH guidelines, we divide baseline CD4 count into three groups: ≤ 50, $51 - 200$, and $201 - 350$. In estimating time-varying weights for cART initiation as described in section 3.4, at any given time, $\overline{L}(t)$ in model (14) includes binary marital status, binary indicator of post primary education, gender, clinic site (urban vs. rural), WHO stage (stage 1 or 2; stage 3 or 4; missing), baseline weight, most recently observed CD4 (time-varying), and baseline age. Higher-order terms of the variables were tested and were not statistically significant. We carry out our analysis with and without assuming informative censoring by C. When assuming informative censoring, we use the same covariates for the censoring model. Our results are similar under both assumptions. Bootstrap re-sampling with 1000 replicates is used to estimate standard errors of the optimal initiation times. The weights and optimal initiation times are computed for each sample of the 1000 replicates.

We use two versions of $h_1(a)$: one for those with CD4 ≤ 200 and the other for CD4

$\in (200, 350]$, and a common spline function $h_2(t-a)$ for the three CD4 groups. The baseline hazard $\lambda_\infty(t)$ was stratified on baseline CD4 count, allowing a distinct baseline hazard function for each stratum.

The plots of fitted $h_1(a)$ and $h_2(t-a)$ are shown in Figure 3. Key findings from the plots are as follows: (i) the first plot for $h_1(a)$ shows a sharp increase in log hazard when $a > 20$ weeks, suggesting that for patients with CD4 below 200, delay in treatment initiation beyond 20 weeks has a detrimental effect on survival. A minor U shape in the plot suggests that early initiation ($a < 10$ weeks) may slightly increase mortality hazard; (ii) the second plot for $h_1(a)$ suggests delay in treatment initiation for patients with CD4 $\in (200, 350]$ does not have noticeable effect on mortality hazard; (iii) the third plot for $h_2(t-a)$ shows that longer treatment duration time reduces mortality hazard for all CD4 subgroups. Selection of the optimal initiation time must balance earlier initiation and longer duration. Any potential negative effects associated with early initiation for CD4 ≤ 200 are clearly overwhelmed by the benefit gained from longer treatment duration.

We use the output of our model to estimate the optimal initiation times. Figure 4 shows one-year mortality as a function of cART initiation time, stratified by CD4 count subgroups. The 95% confidence bands are obtained by bootstrap re-sampling with 1000 replicates. The effect of early cART initiation is most pronounced for CD4 $\leq$ 50, and least noticeable for CD4 $\in (200, 350]$. The estimated optimal time and the corresponding 95% CI are .55 $(0, 7.53)$ for CD4 ≤ 50, .51 $(0, 8.00)$ for CD4 $\in (50, 200]$, and 4.83 $(0, 34.00)$ for CD4 $\in (200, 350]$.

Our results suggest cART should be initiated within 8 weeks of the initiation of TB therapy for AMPATH patients with CD4 counts lower than 200, and the optimal time should be at the start of TB therapy. For patients with CD4 $\in (200, 350]$, the optimal initiation time is about 5 weeks subsequent to the start of TB therapy, however the effect of early initiation is not as significant. Our results are consistent with AMPATH guidelines in treating HIV/TB co-infected patients, and are consistent with general findings of randomized control trials.

5 Summary and discussion

Determining the optimal cART initiation time for treating HIV/TB co-infected patients is important. Currently, RCTs and observational studies have been carried out to study the effect of initiation time only at a small number of time points during the course of TB treatment. We examine the effect of cART timing on continuous scale.

We use data from a large observational cohort to gain more detailed information about treatment effects in practical settings. We formulate a statistical model that captures separately both the causal effect of cART timing and duration on mortality rate. Our model is parameterized in terms of two highly flexible components using unspecified smooth functions of time, generating data-driven representations of the overall treatment effect. The observational data have rich information but pose complications for statistical analysis. We develop methods for fitting the model to complex observational data wherein initiation time is nonrandomly assigned, and both mortality and cART initiation time are subject to censoring. We further use the output of our model to generate the full distribution of potential outcomes corresponding to specific cART initiation times, and to derive CD4-specific optimal initiation times. Our results are consistent with general RCT findings and current AMPATH guidelines.

There are two potential sources of bias in our analysis. First, censoring by C could be associated with higher death rate. We assess this issue by assuming both informative and non-informative censoring mechanism, and carry out our analysis under both assumptions.

Our results under the two censoring mechanisms are similar. Second, we make sequential randomization assumption for the initiation of treatment. We are pursuing a sensitivity analysis as an extension to our analysis to assess the effect of violations of this assumption.

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Table 1: Treatment regimens and dosing frequency for new TB patients (WHO 2010).

Intensive Phase	Continuation phase	Comments
2 months of HRZE	4 months of HR	
2 months of HRZE	4 months of HRE	Applies only in countries with high levels of isoniazid resistance in new TB patients, and where results of isoniazid drug susceptibility testing in new patients are unavailable before the continuation phase begins

NB: H: Isoniazid; R: Rifampin; Z: Pyrazinamide; E: Ethambutol

Table 2: AMPATH guidelines for initiating ART in adults co-infected with HIV and TB. Timing of ART initiation is in relation to start of TB treatment.

Criteria at TB treatment initiation	Timing of ART
CD4 count ≤ 50 and/or presence of opportunistic infection	After 2 weeks
$50 <$ CD4 count ≤ 200	After 1 month
CD4 count > 200 or clinically stable	After 2 months

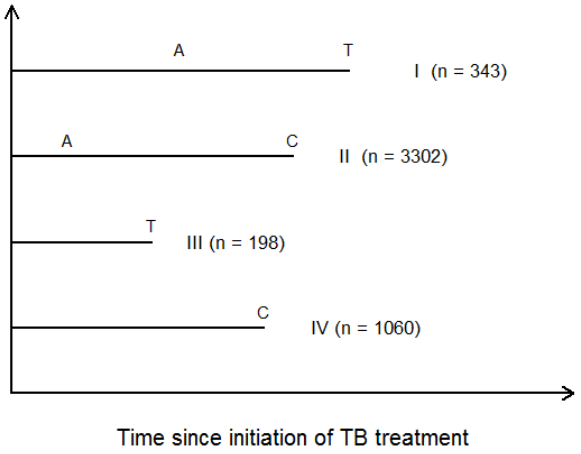
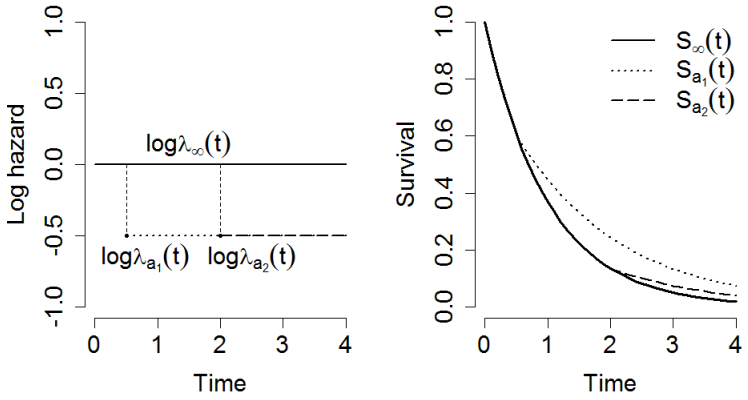
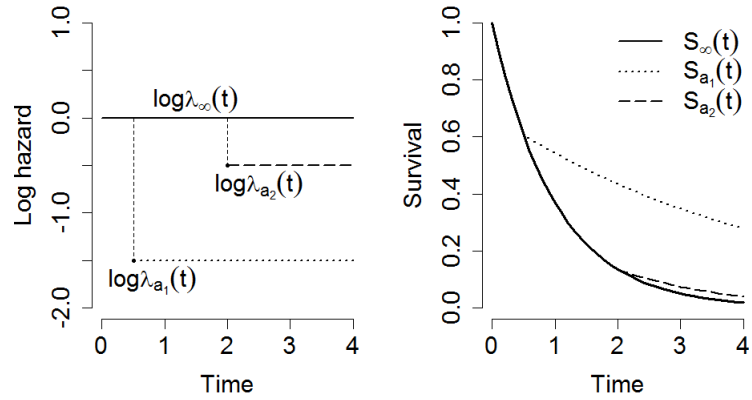


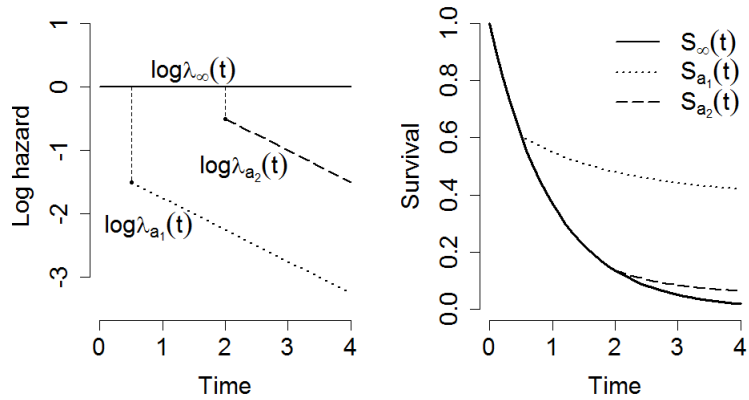
Figure 1: Patterns of observed information on cART initiation time A and death time T. Either or both may be right censored prior to 1 year at time C.



(a) $h_1(a_1) = h_1(a_2) = -.5;\ h_2(a) = 0$



(b) $h_1(a_1) = -1.5;\ h_1(a_2) = -.5;\ h_2(a) = 0$



(c) $h_1(a_1) = -1.5;\ h_1(a_2) = -.5;\ h_2(a) = -.5(t-a)$

Figure 2: Simple examples of the hazard models and corresponding survival models; Two initialization times are compared: $a_1 = .5;\ a_2 = 2$.

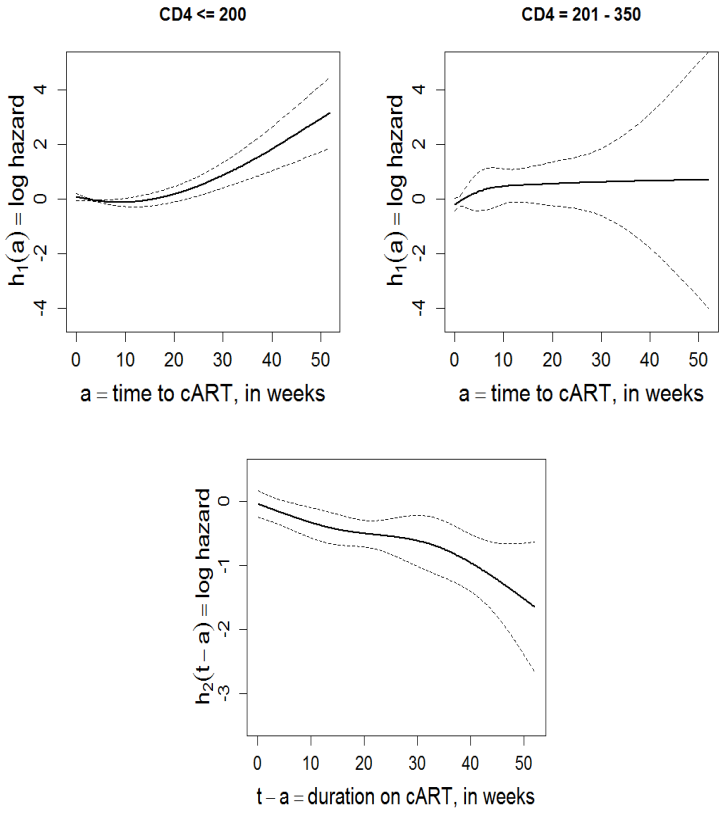


Figure 3: Fitted spline functions $h_1(a)$ and $h_2(t-a)$ in the equation (1) with $r(t,a) = \exp\left[I(a \leq t)\{h_1(a) + h_2(t-a)\}\right]$.

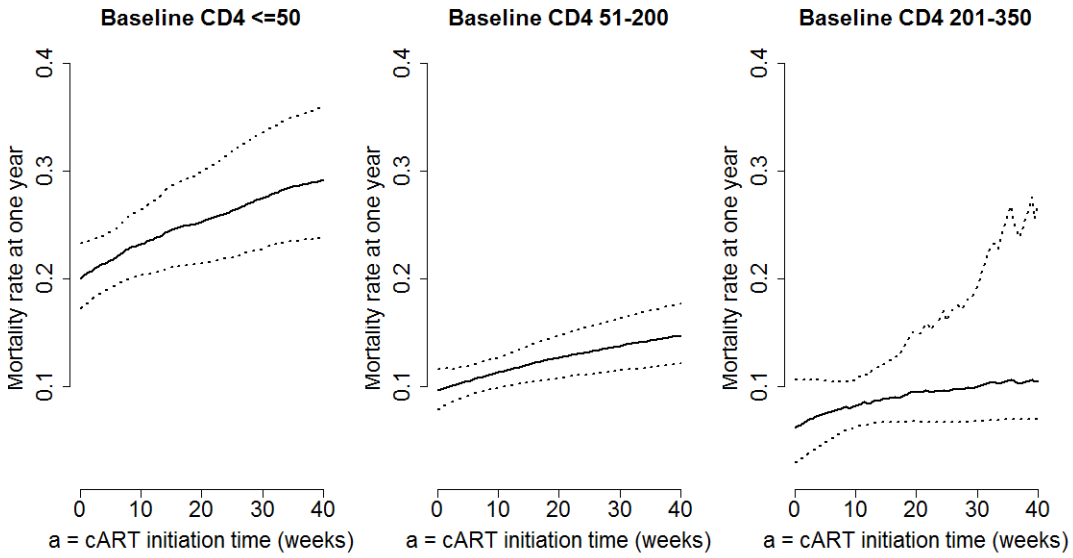


Figure 4: Causal effect of cART initiation: one-year mortality as a function of cART initiation time, stratified by baseline CD4 count.