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Source: *Epidemiology*, Vol. 3, No. 4 (Jul., 1992), pp. 319-336

Published by: Lippincott Williams & Wilkins

Stable URL: <http://www.jstor.org/stable/3702734>

Accessed: 20-04-2016 23:07 UTC

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G-Estimation of the Effect of Prophylaxis Therapy for *Pneumocystis carinii* Pneumonia on the Survival of AIDS Patients

James M. Robins,^{1,2} Donald Blevins,² Grant Ritter,² and Michael Wulfsohn²

AIDS Clinical Trial Group Randomized Trial 002 compared the effect of high-dose with low-dose 3-azido-3-deoxythymidine (AZT) on the survival of AIDS patients. Embedded within the trial was an essentially uncontrolled observational study of the effect of prophylaxis therapy for pneumocystis carinii pneumonia on survival. In this paper, we estimate the causal effect of prophylaxis therapy on survival by using the method of G-estimation to estimate the parameters of a structural nested failure time model (SNFTM). Our SNFTM relates a subject's observed time of death and observed prophylaxis history to the time the subject would have died if, possibly contrary to fact, prophylaxis therapy had been withheld. We find that, under our assumptions, the data are

consistent with prophylaxis therapy increasing survival by 16% or decreasing survival by 18% at the $\alpha = 0.05$ level.

The analytic approach proposed in this paper will be necessary to control bias in any epidemiologic study in which there exists a time-dependent risk factor for death, such as pneumocystis carinii pneumonia history, that (A1) influences subsequent exposure to the agent under study, for example, prophylaxis therapy, and (A2) is itself influenced by past exposure to the study agent. Conditions A1 and A2 will be true whenever there exists a time-dependent risk factor that is simultaneously a confounder and an intermediate variable. (Epidemiology 1992;3:319-336)

Keywords: counterfactuals, causality, longitudinal data, epidemiologic methods, survival analysis, semiparametric methods, structural models, confounding, intermediate variables.

This paper describes new methods for the estimation, from observational data, of the causal effect of a time-dependent treatment or exposure on survival in the presence of time-dependent covariates that may be simultaneously confounders and intermediate variables.¹⁻⁸

To illustrate our methods, we shall estimate the effect of prophylaxis therapy for pneumocystis carinii pneumonia (PCP) on the survival of AIDS patients in AIDS Clinical Trial Group Trial 002. PCP is an opportunistic infection that afflicts AIDS patients. Patients may suffer repeated bouts of PCP, and it can be fatal. Prophylaxis might prolong survival by preventing further episodes of PCP. AIDS Clinical Trial Group

Trial 002 was a randomized trial comparing the effect of high- vs low-dose AZT (3-azido-3-deoxythymidine) on the survival of AIDS patients.⁹ Embedded within this trial was an essentially uncontrolled observational study of the effect of prophylaxis therapy for PCP on survival. The potential benefits of prophylactic treatment for PCP became known from other data sources during the course of Trial 002. Therefore, beginning in August 1987 (9 months after enrollment in the trial began, and 3 months before enrollment was closed), prophylaxis for subsequent PCP was allowed after one postrandomization bout of PCP. In April 1988, it was decided that prophylaxis could be given to any study subject without regard to the subject's PCP history. A number of different medications were used for prophylaxis, including aerosolized pentamidine, oral pentamidine, dapsone, and Fansidar. Except for these general guidelines, the decision whether and/or when to administer prophylaxis to a particular patient was left up to the treating physicians.

Our approach is based on the estimation of parameters of a new class of causal models, the structural nested failure time models (SNFTM), using a class of estimators referred to as the G-estimators.¹⁻³ An analysis using G-estimation generalizes and improves upon

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This work was supported in part by Grants K04-ES00180, 5-P30-ES00002, and R01-ES03405 from the National Institute of Environmental Health Sciences.

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analyses based on the G-computation algorithm and the G-null test previously described by Robins¹⁻⁷ and Robins and Greenland.⁸

The usual approach to the estimation of the effect of a time-varying treatment or exposure on survival is to model the hazard of failure at t as a function of past treatment history using a time-dependent Cox proportional hazards model.¹⁰ In Section 1, we will show that, in contrast to the methods introduced in this paper, the usual approach may be biased, whether or not one further adjusts for past confounder history in the analysis, when (A1) there exists a time-dependent risk factor for or predictor of the event of interest that also predicts subsequent treatment; and (A2) past treatment history predicts subsequent risk factor level.

Conditions A1 and A2 will be true whenever there are time-dependent covariates that are simultaneously confounders and intermediate variables. We now give four examples of studies in which Conditions A1 and A2 will be true.

In individuals with AIDS, the development of recurrent PCP is both an independent risk factor for death and a predictor of subsequent prophylaxis therapy for PCP, since the development of recurrent PCP is a major indication for prophylaxis therapy. In addition, prophylaxis may affect the future occurrence of PCP, so that both Conditions A1 and A2 are true. As a second example, some physicians withdraw women from exogenous estrogens at the time they develop an elevated blood cholesterol. Therefore, in a study of the effect of postmenopausal estrogen on cardiac mortality, the time-dependent cardiac risk factor "cholesterol" is a predictor of subsequent exposure. Furthermore, past estrogen treatment influences subsequent cholesterol levels. As a third example, in observational studies of the efficacy of cervical cancer screening on mortality, women who have had operative removal of their cervix owing to invasive disease are no longer at risk for further screening (that is, exposure) but are at increased risk for death. Therefore, the covariate "operative removal of the cervix" is an independent risk factor for death and a predictor of subsequent exposure. Furthermore, past screening can prevent the need for operative removal of the cervix by allowing early removal of superficial lesions in the preinvasive stage. As a final epidemiologic example, in occupational mortality studies, unhealthy workers who terminate employment early are at increased risk of death compared with other workers and receive no further exposure to the chemical agent under study. Therefore, the time-dependent covariate "employment status at time t " is an independent risk factor for death and a predi-

ctor of exposure to the study agent. In addition, previous exposure to the study agent may lead to early termination of employment if the agent causes a disabling illness.

We shall refer to these covariates as time-dependent confounders. It may be important to analyze the data from any of the above studies using the methods introduced in this paper.

1. Bias of Standard Methods

All standard methods (for example, Cox regression or Poisson regression) that predict the mortality rate at time t using a summary of prophylaxis history up to t will produce biased estimates of the causal effect of prophylaxis when there is a time-dependent covariate, past PCP history, that is simultaneously a confounder and an intermediate variable (whether or not one adjusts for the covariate in the analysis). This bias pertains to any summary measure of prophylaxis treatment including cumulative treatment, average treatment intensity, duration of treatment, etc.

To see why, consider a group of AIDS patients assigned to the low-dose AZT treatment arm in Trial 002 who are alive and at risk 10 months from time of enrollment, dichotomized into those who developed PCP at 8 months and those who are free of PCP at 8 months. (We ignore, for the sake of this argument, patients who developed PCP before 8 months.) PCP status at 8 months will be a confounder for the causal effect of prophylaxis treatment in the interval from 8 to 10 months if those individuals developing PCP at 8 months are at higher risk of dying at 10 months and are more likely to receive prophylaxis therapy between months 8 and 10. Note that the development of PCP at 8 months (even if successfully treated) will be an independent risk factor for death at 10 months if the further debilitation caused by the bout of PCP at 8 months increases the probability of death at 10 months. Indeed, a time-dependent Cox analysis shows that subjects who developed an episode of recurrent (that is, postrandomization) PCP 2 or more months before time t were $1\frac{1}{2}$ times as likely to die at t as those who had not developed recurrent PCP. In addition, a Cox analysis, using initiation of prophylaxis therapy as the failure time variable, showed that those with a past history of recurrent PCP were twice as likely to be placed on prophylaxis at time t than those without a history of recurrent PCP. This condition reflects the fact that recurrent PCP is a medical indication for the initiation of prophylaxis.

On the other hand, PCP status at 8 months will be an intermediate variable on the causal pathway from

prophylaxis therapy in the interval (0,8) months to the prevention of death at month 10 when (1) prophylaxis therapy in the interval (0,8) prevents the development of PCP at 8 months, and (2) PCP at 8 months is an independent risk factor for death at 10 months.

It follows that we must control for the confounder "PCP status at month 8" to estimate the causal effect of prophylaxis in the interval (8,10). On the other hand, we must not control for the intermediate variable "PCP status at month 8" to estimate the total (that is, overall) causal effect of prophylaxis therapy in the interval (0,8) on survival. If, however, we summarize prophylaxis history over the interval (0,10) in terms of cumulative dosage, average dose intensity, or time since the initiation of prophylaxis therapy, these requirements cannot be met, since we lose the ability to separate out prophylaxis in the interval (0,8) from prophylaxis in the interval (8,10). The G-estimation procedure introduced in this paper is specifically designed to control for confounding by intermediate variables by never lumping treatments received at different times.

One might expect, on the basis of the above discussion, that we could at least validly test the null hypothesis of no causal effect of treatment on mortality using a standard time-dependent Cox analysis that adjusts for past PCP history, since, when the null hypothesis of no prophylaxis effect is true, there is no causal pathway from prophylaxis therapy to death, and thus PCP cannot be an intermediate variable. In fact, as shown in Appendix 1, even this supposition is incorrect when Conditions A1 and A2 are true.

2. G-Estimation: A New Method of Analysis Based on SNFTMs

2a. THE ASSUMPTION OF NO UNMEASURED CONFOUNDERS

One cannot validly estimate the causal effect of a treatment from observational data in the presence of unmeasured confounding factors. Hence, we shall assume that there are no unmeasured confounders. We need, however, to define formally what it means to have no unmeasured confounders in a study with a time-varying treatment. To do so, we define the following counterfactual variables.

Let $T_{p^{-},i}$ be the death time of subject i if, possibly contrary to fact, prophylaxis was withheld at all times. Let $T_{p^{+},i}$ represent subject i 's death time if continuous prophylactic therapy was begun at start of follow-up. Time is measured as time from start of follow-up, that is, time from enrollment in Trial 002. These variables

are called counterfactual variables since they represent outcomes under circumstances that may not have actually occurred. See Rubin,¹¹ Holland,¹² Greenland and Robins,¹³ Robins,¹⁻⁷ and Robins and Greenland⁸ for discussion of the utility of counterfactual variables in causal inference. $T_{p^{+},i} - T_{p^{-},i}$ is the increase in subject i 's life due to continuous prophylactic therapy. Thus, the population average of $T_{p^{+},i}$ minus the population average of $T_{p^{-},i}$ is the increase in life expectancy that would result from continuous prophylaxis therapy, which will be our causal parameter of interest.

Definition

There is no unmeasured confounding for treatment (prophylaxis therapy) if, at each time t , among a subset of subjects with the same treatment and measured covariate history up to t , the probability of treatment at t does not further depend on either $T_{p^{+},i}$ or $T_{p^{-},i}$.

Since physicians tend to initiate prophylaxis in subjects who have had recurrent bouts of PCP, and recurrent PCP signifies poor prognosis patients (that is, patients with small values of $T_{p^{-},i}$), it follows that our assumption of no unmeasured confounders would be false if we had neglected to measure PCP history. We suppose throughout that once prophylaxis for PCP is initiated, a subject remains on prophylaxis thereafter. We have made this assumption because, in the available database, there is essentially no information about termination of prophylaxis. Our assumption of no unmeasured confounding factors then states that we have available, at each time t , data on the history of all time-independent and time-dependent covariates that simultaneously (a) predict $T_{p^{-},i}$ and (b) predict which study subjects will initiate prophylaxis at t . It is a primary goal of epidemiologists conducting an observational study to collect data on a sufficient number of covariates to ensure that the assumption of no unmeasured confounders will be true. We shall assume that this goal has been realized while recognizing that, in practice, this would never be precisely true and may, on occasion, not even be approximately true.

2b. A TEST OF THE NULL HYPOTHESIS OF NO TREATMENT EFFECT

Before considering estimation of the increase in life expectancy due to prophylaxis therapy, we shall develop a test of the sharp null hypothesis of no causal effect of prophylaxis on survival. That is, the hypothesis that

$$T_i = T_{p^{-},i} = T_{p^{+},i} \quad \text{for all subjects } i. \quad (1)$$

Define $\bar{L}_i(t)$ to be subject i 's recorded history of time-

dependent covariates up to t . (Overbars will be used to denote histories of time-dependent covariates.) For the moment, suppose that $\bar{L}_i(t)$ simply records a subject's PCP history before t . Let $\lambda_p[t|\bar{L}_i(t), T_{p^{-},i}]$ be the probability of initiating prophylaxis therapy on day t among subjects alive at t who have yet to begin prophylaxis therapy given both past covariate history $\bar{L}_i(t)$ and baseline failure time $T_{p^{-},i}$. We shall regard time to initiation of prophylaxis therapy as a "failure" time outcome variable. Then $\lambda_p[t|\bar{L}_i(t), T_{p^{-},i}]$ is, by definition, the hazard rate for initiating prophylaxis on day t given $T_{p^{-},i}$ and $\bar{L}_i(t)$. Our assumption of "no unmeasured confounders" implies that

$$\lambda_p[t|\bar{L}_i(t), T_{p^{-},i}] = \lambda_p[t|\bar{L}_i(t)], \quad (2)$$

since Eq 2 says that, given covariate history up to t , the probability of initiating prophylaxis at t does not further depend on $T_{p^{-},i}$.

Together, the null hypothesis (Eq 1) and the assumption of no unmeasured confounders (Eq 2) imply that, given covariate history up to t , the probability of initiating prophylaxis at t does not further depend on the observed failure time T_i , that is,

$$\lambda_p[t|\bar{L}_i(t), T_i] = \lambda_p[t|\bar{L}_i(t)]. \quad (3)$$

Thus, under the assumption of no unmeasured confounders, a test of Eq 3 is a test of the sharp null hypothesis. Since Eq 3, in contrast to Eq 2, depends only on the observed data, Eq 3 can be tested using standard statistical methods. We shall test Eq 3 using a Cox proportional hazards model that regards time to prophylaxis as the outcome failure time variable and treats a subject's observed death time T_i as a time-independent covariate in the model! Specifically, suppose that the probability of initiating prophylaxis at t depends on past PCP history $\bar{L}_i(t)$ only through the total number of bouts of PCP before t . We can then obtain an asymptotically distribution-free test of Eq 3 [and, thus, of the null hypothesis (Eq 1)] by performing a score test of the hypothesis $\alpha^* = 0$ in the stratified Cox model:

$$\lambda_p[t|\bar{L}_i(t), T_i] = \lambda_{0,s}(t)\exp(\alpha^*T_i), \quad (4)$$

where s is a time-dependent stratum indicator such that a subject is in stratum s at time t if he has had exactly s bouts of PCP up to t , and $\lambda_{0,s}(t)$ is a stratum-specific nuisance hazard for prophylaxis. Note that unless α^* equals 0, Eq 4 will depend on T_i , contradicting the hypothesis of Eq 3. The score test of $\alpha^* = 0$ in Eq 4 is a standard Mantel test for trend based on time-matched "case-control" data when (1) we regard a subject who initiates prophylaxis at time t as becoming

a "case" at t ; (2) we select, as the case's matched controls, subjects alive and without prophylaxis by t who have had the same number of bouts of PCP as the case before t ; and (3) we use each subject's observed death time, T_i , as the "exposure" variable in a matched (that is, stratified) Mantel test for trend. This test can be shown to be asymptotically equivalent to a member of the class of q -G-null tests described by one of us in Ref 1. In practice, one would wish to include in $\bar{L}_i(t)$ additional potential confounding variables. Specifically, we shall let $\bar{L}_i(t)$ include the following components: R = treatment arm indicator; C = end of follow-up date (October 25, 1989) minus date of randomization; $\bar{PCP}(t)$ = PCP history up to t ; $\bar{T4}(t)$ = T4-count history up to t ; $\bar{AZT}(t)$ = AZT treatment history up to t . [We have temporarily suppressed the dependence on the subject in our notation.] C is a subject's potential censoring time since, in our dataset, follow-up ended on October 25, 1989. $\bar{AZT}(t)$ is a subject's actual history of AZT treatment through t recorded on the drug history form available in the Trial 002 database. $\bar{T4}(t)$ is the history of a subject's T4 (or equivalently, CD4) lymphocyte count history recorded on a hematology form. To test Eq 3, we assume that we have a correctly specified Cox model for prophylaxis given by

$$\begin{aligned} \lambda_p[t|\bar{L}_i(t), T] = & \lambda_0(t)\exp[\alpha_1^*R + \alpha_2^*C + \alpha_3^*\bar{PCP}_1(t) \\ & + \alpha_4^*\bar{PCP}_2(t) + \alpha_5^*\bar{AZT}(t) + \alpha_6^*\bar{T4}_{<20}(t) + \alpha_7^*T], \end{aligned} \quad (5)$$

where $\bar{PCP}_1(t)$ takes the value 1 if the subject has had one or more postrandomization episodes of PCP before t and zero otherwise, $\bar{PCP}_2(t)$ takes the value 1 if the subject has had two or more episodes of postrandomization PCP before t and zero otherwise, $\bar{AZT}(t)$ takes the value 1 if the subject is no longer receiving AZT at time t (usually due to toxicity) and is zero otherwise, $\bar{T4}_{<20}(t)$ takes the value 1 if a subject's T4-count at t is less than 20 and zero otherwise, T is observed death time, $(\alpha_1^*, \dots, \alpha_7^*)$ are unknown parameters, and $\lambda_0(t)$ is an unspecified nuisance hazard function for prophylaxis.

If Eq 3 is true, the Cox model (Eq 5) cannot be a function of T . But Eq 5 will be independent of T if and only if $\alpha_7^* = 0$. Thus, a test of $\alpha_7^* = 0$ is a test of the null hypothesis (Eq 1). We shall use the Cox partial likelihood score test of the hypothesis $\alpha_7^* = 0$. To perform this test, one first estimates the parameters of Eq 5 with α_7^* set to zero. The resulting estimates of $(\alpha_1^*, \dots, \alpha_6^*)$ and their standard errors, based on maximization of the Cox partial likelihood, are given in Table 1. [To save computing time in the estimation of α^* , we randomly selected (at most) 30 noncases from

TABLE 1. Fit of Cox Model⁵

Covariate	$\hat{\alpha}$	Standard Error of $\hat{\alpha}$
R	-0.019	0.11
C	-0.0026	0.0005
I _{PCP1}	0.699	0.130
I _{PCP2}	0.754	0.203
I _{AZT}	0.327	0.123
I _{T4<20}	-0.373	0.127

each risk set to serve as the case's matched controls.] The indicators for past bouts of PCP and the indicator for discontinued AZT treatment are positive predictors, and the potential censoring date C is a negative predictor for the initiation of prophylaxis. These results are not surprising, since previous bouts of post-randomization PCP serve as a medical indication for physicians to initiate prophylaxis. Furthermore, physicians might feel that a subject needs prophylaxis if AZT therapy has had to be discontinued. In addition, since prophylaxis therapy was not allowed until August 1987, it is plausible that subjects randomized at later calendar dates (that is, subjects with small values of C) will be more likely to receive prophylaxis soon after randomization. It is unclear why subjects with low T4-counts were less likely to receive prophylaxis. After controlling for the other covariates in $\bar{L}(t)$, the treatment arm does not significantly predict the initiation of prophylaxis. The P-value of our score test of the hypothesis $\alpha_7^* = 0$ is 0.87. This test was originally called a "smooth estimated propensity G-test" in Ref 1, but it will simply be called a "G-test" in this paper.

2c. ESTIMATION OF THE TREATMENT EFFECT

We shall use SNFTMs to estimate the treatment effect. One simple SNFTM assumes that, under continuous prophylaxis therapy, a subject's life is expanded or contracted by the factor $e^{-\beta_p^*}$, where β_p^* is an unknown parameter that we will later estimate. That is,

$$T_{p^-,i} e^{-\beta_p^*} = T_{p^+,i}.$$

In particular, if $\beta_p^* < 0$, then $T_{p^-,i} < T_{p^+,i}$, and prophylactic therapy is beneficial. If $\beta_p^* = 0$, then $T_{p^-,i} = T_{p^+,i}$, and there is no effect of prophylaxis on survival. Finally, if $\beta_p^* > 0$, then prophylaxis decreases survival. We note that the expansion factor $e^{-\beta_p^*}$ is related to our parameter of public health interest. Specifically, $(T_{p^+,i} - T_{p^-,i})/T_{p^-,i} = e^{-\beta_p^*} - 1$ is the fractional increase in life expectancy due to continuous prophylactic therapy.

We next extend our causal model to incorporate other counterfactual prophylaxis histories. Let $T_{p=(v),i}$

represent subject i's death time if prophylaxis therapy were to begin at time v after enrollment and continued thereafter. If, in the absence of prophylaxis, a subject would die before v, then $T_{p=(v),i}$ equals $T_{p^-,i}$. Note that we can write $T_{p^+,i}$ as $T_{p=(0),i}$ and $T_{p^-,i}$ as $T_{p=(\infty),i}$. In our extended causal model, $e^{-\beta_p^*}$ is the factor by which a subject's remaining life ($T_{p^-,i} - v$) is expanded or contracted by initiating prophylaxis therapy at time v. That is, for each v,

$$e^{-\beta_p^*}(T_{p^-,i} - v) = (T_{p=(v),i} - v) \quad \text{if } T_{p=(v),i} > v \quad (6a)$$

$$T_{p^-,i} = T_{p=(v),i} \quad \text{otherwise.} \quad (6b)$$

When we substitute v = 0 into Eq 6a, we recover our previous SNFTM linking $T_{p^+,i}$ and $T_{p^-,i}$.

Let P_i be the time, if any, when subject i was observed to initiate prophylaxis in the actual study. Then a subject's observed death time T_i must be $T_{p=(v),i}$ with $v = P_i$ and thus, by Eq 6a, $e^{-\beta_p^*}(T_{p^-,i} - P_i) = (T_i - P_i)$. On the other hand, if a subject never initiates prophylaxis, his observed death time T_i obviously equals $T_{p^-,i}$. Thus, on solving for $T_{p^-,i}$, the SNFTM (Eq 6) implies that $T_{p^-,i}$ is linked to the observed death time and prophylaxis history by

$$T_{p^-,i} = P_i + (T_i - P_i)e^{\beta_p^*} \quad \text{if } P_i < T_i, \quad (7a)$$

and

$$T_{p^-,i} = T_i \quad \text{otherwise.} \quad (7b)$$

Define the new variable $T_i(\beta_p)$ by the right-hand side of Eq 7a and Eq 7b with β_p substituted for β_p^* . Note, $T_i(0) = T_i$ and $T_i(\beta_p) = T_{p^-,i}$. Furthermore, for each value of β_p , we can compute $T_i(\beta_p)$ based on a subject's observed data (T_i, P_i).

In Section 2b, we obtained a G-test of the sharp null hypothesis (Eq 1) [that is, the hypothesis that β_p^* equals 0] under the assumption (Eq 2) of no unmeasured confounders by performing a score test of the hypothesis $\alpha_7^* = 0$ in the Cox model Eq 5 or, if $\bar{L}_i(t)$ can be summarized by a discrete covariate, performing a Mantel trend test of the hypothesis $\alpha^* = 0$ in the Cox model Eq 4. By exactly the same logic, we can obtain a G-test of the hypothesis that true causal parameter β_p^* equals some particular non-zero value β_p , say $\beta_p = -0.05$, by performing a score test of the hypothesis $\alpha_7^* = 0$ in the Cox model

$$\begin{aligned} \lambda_p[t | \bar{L}(t), T] = & \lambda_0(t) \exp[\alpha_1^* R + \alpha_2^* C + \alpha_3^* I_{PCP1}(t) \\ & + \alpha_4^* I_{PCP2}(t) + \alpha_5^* I_{AZT}(t) + \alpha_6^* I_{T4<20}(t) + \alpha_7^* T(\beta_p)] \end{aligned} \quad (8)$$

or, if $\bar{L}_i(t)$ is summarized by a discrete covariate, by performing a Mantel trend test (that is, a Cox score

test) of the hypothesis $\alpha^* = 0$ in the Cox model

$$\lambda_p[t | \bar{L}(t), T(\beta_p)] = \lambda_{0,s}(t) \exp[\alpha^* T(\beta_p)] \quad (9)$$

This follows because if the value β_p that we are testing is the true causal parameter β_p^* , then $T_i(\beta_p) = T_{p^{-},i}$, which, by our assumption (Eq 2) of no unmeasured confounders, must have coefficient 0 in a correctly specified Cox model for $\lambda_p[t | \bar{L}_i(t), T_{p^{-},i}]$.

Thus, separately for each of the 41 values of β_p in the set $\{-1, -0.95, \dots, -0.05, 0.0, 0.05, \dots, 1\}$, we (a) computed the variable $T_i(\beta_p)$ and (b) performed a Cox partial likelihood score test of the hypothesis $\alpha_7^* = 0$ in the model (Eq 8). A large-sample 95% confidence interval for β_p^* consists of those β_p values for which the score test of the hypothesis $\alpha_7^* = 0$ fails to reject at a 5% level. Using the above approach, we obtained the 95% confidence interval of $(-0.15, 0.20)$ for β_p^* . Interpolating, we found that the score test would be 0 at $\beta_p = 0.025$, which we can use as a point estimate $\hat{\beta}_p$ of β_p^* . We shall call $\hat{\beta}_p$ a G-estimate of β_p^* .^{1,2} In Appendix 2, we show that $\hat{\beta}_p$ is asymptotically normal and unbiased as an estimator of β_p^* under our assumptions. Note, for each of the 41 variables $T_i(\beta_p)$, the score test of $\alpha_7^* = 0$ can be obtained without refitting the Cox model (Eq 8).

For each of the 41 test values of β_p , the G-estimation procedure tests the hypothesis that a particular value of β_p , say -0.05 , is the unknown parameter β_p^* that quantifies the causal effect of prophylaxis on survival. Conceptually, the G-estimation procedure checks, at each successive time t , for an association between the prophylaxis treatment received at time t and the hypothesized value $T_i(\beta_p)$ of the true but unknown baseline failure time $T_{p^{-},i}$, (a) after adjusting for confounder history before t , but (b) without adjusting for the "posttreatment" variables "covariate and prophylaxis history subsequent to t ." If, after adjustment for past confounder history, $T_i(\beta_p)$ fails to significantly predict which subjects initiate prophylaxis at each t , then we cannot rule out the possibility that the test value β_p is the true but unknown β_p^* . We thus place the test value β_p in our confidence interval for β_p^* . By separately examining the prophylaxis treatment received at each successive time t , the G-estimation procedure succeeds in controlling confounding by intermediate variables.

It is important to note that the G-analysis adjusts for both (a) the covariate history $\bar{L}(t)$ up to t , and (b) the treatment (that is, prophylaxis) history before t , since the "risk sets at t " in the Cox analysis of the model (Eq 8) are restricted to subjects who have not received prophylaxis before t . It is essential to the validity of the G-estimation procedure that treatment

history before t be regarded as a potential confounding factor for the effect of treatment received at t .

In describing the G-estimation procedure, we acted as if we could compute $T_i(\beta_p)$ for all study subjects. In fact, 130 of the 562 patients in Trial 002 were censored by (that is, were alive at) end of follow-up. Therefore, $T_i(\beta_p)$ could not be computed for these 130 subjects, since their death time T_i was not observed. The results reported above are actually based on the censored data methods described later.

3. Summary and Further Considerations

Under the assumptions that, in Randomized Trial 002, (a) our causal model (Eq 6) for the effect of prophylaxis on survival is correct; (b) our assumption (Eq 2) of no unmeasured confounders is true; (c) the specification (Eq 8) of our Cox model is correct; and (d) the recorded prophylaxis data are accurate, then we obtain a valid 95% confidence of $(-0.15, 0.20)$ for the parameter β_p^* measuring the effect of prophylaxis survival which implies a 95% confidence interval for the fractional change in life expectancy $e^{-\beta_p^*} - 1$ of $(-0.18, 0.16)$. Our results concerning the prophylaxis effect raise the question of whether treatment with prophylaxis for PCP actually increases the survival of AIDS patients.

We briefly consider how to make our inferences more robust to our Assumptions a-c. We first consider Assumptions b and c. To increase robustness to our assumption (Eq 2) of no unmeasured confounders, we could measure more time-independent and time-dependent potential confounders and include them in $\bar{L}(t)$. To increase robustness to the specification of our Cox model (Eq 8), we could add more covariates to the model. For example, when we added the logarithm of C and the total number of PCP episodes before t to the model (Eq 8), the resulting confidence interval for β_p^* remained $(-0.15, 0.20)$. Adding more covariates always implies less bias and, as discussed in Appendix 2, somewhat surprisingly, never decreases and may often increase the asymptotic efficiency with which β_p^* is estimated, although one must limit the total number of covariates in our Cox model (Eq 8) to be less than some small fraction of the number of subjects who received prophylaxis. Nonetheless, subject to this limitation, in the interest of both decreased bias and increased efficiency, the use of richly parameterized Cox models (Eq 8) should be encouraged.

We briefly discuss another approach to increasing the efficiency with which β_p^* is estimated. It follows from Assumption b (Eq 2) that we could also obtain a valid confidence interval for β_p^* if, instead of using

$\alpha_7^*T(\beta_p)$ in Eq 8, we used $\alpha_7^*g[T(\beta_p)]$ for any function $g(\cdot)$. For example, the choice $g[T(\beta_p)] = \ln[T(\beta_p)]$ yielded a confidence interval of $(-0.20, 0.15)$. Indeed, we could add α_7^* times any function $g(\cdot)$ of $T(\beta_p)$ and $\bar{L}(t)$. In Appendix 2, we give the optimal function $g(\cdot)$ and note that the estimate of β_p^* based on this optimal function is semiparametric efficient.¹⁴ That is, it is the most efficient possible estimate of β_p^* under the sole assumptions that the causal model (Eq 6), the assumption (Eq 2) of no unmeasured confounders, and the Cox model (Eq 8) are true.

We estimated the causal effect of prophylaxis on time to death by fitting a proportional hazards model for prophylaxis conditional on confounding variables $\bar{L}(t)$ and $T(\beta_p)$, where $T(\beta_p)$ represents the hypothesized failure time had prophylaxis been withheld. Our approach is an extension of the propensity score method of Rosenbaum and Rubin,¹⁵ Rosenbaum,¹⁶ and Robins *et al*¹⁷ to time-dependent treatments and covariates.

We have only considered a very simple SNFTM model (Eq 6) for the causal effect of prophylaxis on survival to try to make our main ideas transparent. In Appendix 2, we discuss SNFTM models in much greater generality. As we discuss in Appendix 2, to increase robustness to our causal model for prophylaxis, we could add interactions of prophylaxis with observed time-dependent and time-independent factors. For example, we could have replaced Eq 7a by

$$T_{p^-,i} = P_i + (T_i - P_i)e^{\beta_{p,1}^* + \beta_{p,2}^*I[PCP(P_i)] + \beta_{p,3}^*R_i} \quad (10)$$

where $I[PCP(P_i)] = 1$ if a postrandomization PCP episode occurs by P_i and is 0 otherwise. Under this model, the magnitude of the prophylaxis effect on survival can depend both on the treatment arm R and on past PCP history. Furthermore, we note that even this model (Eq 10) assumes no interaction with unmeasured factors. For example, according to Eq 10, if two subjects i and j have identical observed failure times, treatment arm assignment, prophylaxis, and PCP histories, they would have had an identical failure time $T_{p^-,i}$ if prophylaxis had always been withheld. In certain settings, this no interaction assumption might be considered biologically implausible. The general class of SNFTMs discussed in Appendix 2 allows the magnitude of the treatment effect to depend on unmeasured factors.

In Appendix 2, we show that the assumption of no unmeasured confounders alone implies that, given a sufficiently large dataset, we could nonparametrically estimate, using Robins' G-computation algorithm, population averages of $T_{p^+,i}$ and $T_{p^-,i}$ and thus the increase in life expectancy due to continuous therapy. Any nonparametric estimate of the population average

of $T_{p^+,i}$ must, however, be based solely on data from subjects who initiated prophylaxis at the time of enrollment. Since less than 20 subjects did so, in practice, we require SNFTMs to estimate accurately the population average of $T_{p^+,i}$.

We have only considered estimation of the effect of prophylaxis therapy on survival. In Appendix 2, methods for estimating the effect of prophylaxis therapy on (a) the development of subsequent PCP and (b) the evolution of CD4-counts over time, with death treated as a competing risk, are developed. In addition, we have as yet only considered estimating the overall effect of prophylaxis therapy on survival. If prophylaxis therapy increases the likelihood that a subject will cease taking AZT, it may be of greater interest to estimate the direct effect of prophylaxis on survival. Methods for estimating direct effects are discussed in Appendix 2.

We have focused attention on estimating the fractional increase in life expectancy $e^{-\beta_p^*} - 1$ due to continuous prophylaxis therapy. In much of the epidemiologic literature, rate ratios (RR) rather than fractional changes in life expectancy are the objects of estimation.¹⁸ Although Greenland and Robins¹⁹ and Robins and Greenland^{20,21} have argued that measures of change in life expectancy are often of greater public health interest than rate ratio measures, nonetheless, because of general interest in rate ratios, we now characterize the relation between the causal parameter β_p^* and the causal rate ratio parameter.

THE CAUSAL RATE RATIO

We define the causal rate ratio at t , causal $RR(t)$, to be the population mortality rate at t had all study subjects received prophylaxis therapy from the start of follow-up divided by the population mortality rate at t had prophylaxis been withheld from all study subjects. We caution the reader that this definition differs from that given previously by Robins and Greenland.²⁰ Mathematically, the causal $RR(t)$ is the ratio of the hazard rate at t of the random variable $T_{p^+,i}$ to that of the random variable $T_{p^-,i}$. If the population distribution of death times $T_{p^-,i}$ in the absence of prophylaxis is exponential with constant hazard λ , then, under our causal model of Eq 6, causal $RR(t) = \exp(\beta_p^*)$. If the distribution of $T_{p^-,i}$ is Weibull with hazard λt^θ , the causal $RR(t) = \exp[(\theta + 1)\beta_p^*]$.¹⁸

In the absence of censoring, the distribution of death times $T_{p^-,i}$ can be estimated by the empirical distribution of the $T_i(\hat{\beta}_p)$, when $\hat{\beta}_p$ is the G-estimator defined previously. If the empirical distribution of $T_i(\hat{\beta}_p)$ is consistent with a Weibull distribution, the Weibull

parameter θ can be estimated using maximum likelihood applied to the "data" $T_i(\hat{\beta}_p)$ for the n study subjects.

Finally, in the spirit of Greenland and Robins,¹³ Robins,⁴⁻⁷ Robins and Morgenstern,²² and Holland,²³ we can define conditions for confounding for the causal $RR(t)$. To do so, define the observable rate ratio, $obs\ RR(t)$, to be the expected mortality rate at t among those study subjects who actually received continuous prophylaxis therapy from the start of follow-up divided by the expected mortality rate at t for subjects who actually received no prophylaxis before t . The $obs\ RR(t)$ can be unbiasedly estimated using a correctly specified time-dependent Cox proportional hazards model for death that does not adjust for potential confounding factors such as PCP history.

We shall say there is no confounding for the causal $RR(t)$ if causal $RR(t) = obs\ RR(t)$. We can view confounding as a type of selection bias. That is, the mortality rate at t of those subjects who, in the actual study, had not received prophylaxis therapy before t is less than the mortality rate that would have been observed had all subjects been untreated before t , since, in the actual study, subjects at higher risk of death developed recurrent PCP and, as a consequence, received prophylaxis therapy before t .

Under the assumption (Eq 2) of no unmeasured confounders, a sufficient condition for there to be no confounding for the causal $RR(t)$ is that either: (a) $\bar{L}(t)$ is not an independent predictor of subsequent treatment, that is,

$$\lambda_p[t | \bar{L}(t)] = \lambda_p(t),$$

or (b) $\bar{L}(t)$ is not an independent risk factor for death, that is,

$$\lambda_T[t | \bar{L}(t), \overline{Proph}(t)] = \lambda_T[t | \overline{Proph}(t)],$$

where $\lambda_T(t)$ is the actual hazard rate for death (that is, the mortality rate) at t , and $\overline{Proph}(t)$ is prophylaxis history up to t .^{2,4,7}

Next, define the adjusted rate ratio at t , adj $RR(t)$, to be the expected mortality rate at t among a subset of subjects with a common observed covariate history $\bar{L}(t)$ before t who, in the actual study, received continuous prophylaxis up to t , divided by the expected mortality rate at t among subjects with the same common covariate history but who actually received no prophylaxis before t . The adj $RR(t)$ may depend on the covariate history. The adj $RR(t)$ can be unbiasedly estimated using a correctly specified time-dependent Cox model for death that either stratifies on or adjusts for the time-dependent covariates in $\bar{L}(t)$. If the adj $RR(t)$ equals the causal $RR(t)$, we say there is no

"confounding for the causal rate ratio after stratifying on confounder history."

Under the assumption (Eq 2) of no unmeasured confounders, sufficient conditions for there to be no confounding for the causal $RR(t)$ after stratifying on confounder history are, for each time t : (a) $\bar{L}(t)$ is not an independent risk factor for death, or (b) the adj $RR(t)$ equals 1 for each covariate history $\bar{L}(t)$, and treatment history before t is not an independent predictor of subsequent covariate status, that is,

$$pr[L(t^+) | \bar{L}(t), \overline{Proph}(t)] = pr[L(t^+) | \bar{L}(t)] \quad (11)$$

where t^+ is a time immediately subsequent to t .^{2,4} When Condition b holds, the causal $RR(t) = 1$. We note that even when, for all t and $\bar{L}(t)$, the adj $RR(t)$ is a constant different from 1, and Eq 11 holds, the adj $RR(t)$ need not equal causal $RR(t)$. Furthermore, the causal $RR(t)$ may be 1 for all t and Eq 11 may hold, and yet the adj $RR(t)$ may differ from 1 for some t and $\bar{L}(t)$.

In the four studies described in the introduction, none of the above sufficient conditions for lack of confounding is met, and, thus, there will be confounding for the causal $RR(t)$ whether or not one stratifies on the confounder history $\bar{L}(t)$.

CENSORING

We have heretofore ignored censoring in our theoretical development, although, as mentioned above, the numerical results that we have presented have actually used the censored data methods we now develop. Our models require a novel treatment of censoring.¹ In this section, to keep matters simple, we present only the specific censored data test and estimators used to obtain the numerical results above. Generalizations are discussed in Appendix 2. We define the potential censoring time C_i to be the difference between the end of follow-up date, October 29, 1989, and the subject's calendar date of randomization. We assumed that all subjects not known to be dead by that date were alive. Note that C_i is known for all subjects, even those who died before the end of follow-up. The observable random variables are then $[C_i, X_i = \min(T_i, C_i), \Delta_i, P_i^\dagger = \min(P_i, X_i), \sigma_i^\dagger, \bar{L}_i(X_i)]$, where (a) $\Delta_i = 1$ if $X_i = T_i$ and $\Delta_i = 0$ otherwise; (b) $\sigma_i^\dagger = 1$ if $P_i^\dagger = \min(P_i, X_i)$ is the date of initiation of prophylaxis and is zero otherwise; $\bar{L}_i(X_i)$ is the history up to X_i of the time-dependent and independent covariates listed previously and thus includes C_i . That is, we observe the minimum X_i of time to death and time to end of follow-up as well as the minimum P_i^\dagger of time to initiation of prophylaxis and X_i .

The key to our approach is to define a variable $X_i(\beta_p)$

that (a) in contrast to both T_i and $T_i(\beta_p)$, is observed for all subjects, including those censored, but (b), like $T_i(\beta_p^*)$, satisfies

$$\lambda_p[t | \bar{L}(t), X(\beta_p^*)] = \lambda_p[t | \bar{L}(t)] \quad (12)$$

where $\lambda_p(t)$ is the hazard for initiation of prophylaxis at t . We then estimate β_p^* by G-estimation as before, except with $X(\beta_p)$ replacing $T(\beta_p)$. Our definition of $X_i(\beta_p)$ will depend on the sign of β_p . Specifically, define $X_i(\beta_p)$ to be

$$\begin{aligned} \min[C_i, T_i(\beta_p)] & \text{ if } \beta_p \geq 0 \\ \min[e^{\beta_p} C_i, T_i(\beta_p)] & \text{ if } \beta_p < 0 \end{aligned} \quad (13)$$

Since C is a component of $\bar{L}(t)$ and $X(\beta_p)$ is a function of the random variables C and $T(\beta_p)$, it follows that our assumption (Eq 2) of no unmeasured confounders implies that Eq 12 holds. Furthermore, $X_i(\beta_p)$ is observed for all subjects i , since, by Eq 13, if $T_i > C_i$, (a) $X_i(\beta_p) = C_i$ if $\beta_p \geq 0$ and (b) $X_i(\beta_p) = e^{\beta_p} C_i$ if $\beta_p < 0$, but C_i is always observed.

Acknowledgments

We are indebted to Margaret Fischl for making available the data from AIDS Clinical Trial Group Trial 002. Kyle Steenland, Steve Mark, and Sander Greenland provided helpful suggestions.

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Appendix 1

In this Appendix, we show that even if both prophylaxis therapy for PCP and PCP itself have no causal effect on the survival of any subject, a Cox regression analysis that uses death as the failure time variable and adjusts for PCP history may falsely suggest that prophylaxis for PCP is harmful.

Specifically, we shall suppose that all episodes of PCP are immediately and successfully treated with a new intravenous medication, so that PCP causes neither death nor increased debilitation. Furthermore, we will assume that prophylaxis therapy, even though it prevents PCP in some patients, has no effect on survival. In particular, suppose that 300 subjects receive prophylaxis by 4 months, and 300 subjects never

receive prophylaxis. In both groups of 300, suppose 100 individuals are "poor prognosis" subjects who are destined to die at 10 months, 100 are moderate prognosis subjects destined to die at 20 months, and 100 are good prognosis subjects destined to die at 30 months. We suppose that neither prophylaxis *per se* nor PCP has any effect on survival. Prophylaxis, however, prevents the development of PCP in moderate prognosis patients. Indeed, for simplicity, suppose that all moderate prognosis patients would develop PCP at 8 months without prophylaxis, whereas none would develop PCP if given prophylaxis. In contrast, we assume that all poor prognosis and no good prognosis patients would develop PCP, regardless of prophylaxis therapy. Under these assumptions, the data would be as shown in Table A1. Inspecting Table A1, we observe that, within the stratum defined by the presence of PCP at 8 months, the mortality rate at 10 months is greater in those who received prophylaxis than in those who did not. Similarly, in the stratum defined by the absence of PCP, the mortality rate at 20 months is greater in those who received prophylaxis than in those who did not. Thus, a Cox analysis that adjusts for (or stratifies on) past PCP history would falsely suggest that prophylaxis has had an adverse effect on survival.

As discussed in the section on the causal rate ratio, this bias is attributable to the fact that, in Table A1, (a) prophylaxis by 4 months is a (protective) risk factor for subsequent PCP, and (b) PCP is an independent (noncausal) risk factor for death, since (1) the death rate at 10 months is greater in those with PCP than in those without PCP among subjects receiving prophylaxis, and (2) the death rate at both 10 and 20 months is greater in those with PCP than in those without PCP among subjects without prophylaxis. Thus, the adj RR(t) based on the Cox analysis exceeds the causal RR(t) of 1.0. Note, by construction, PCP is not a causal risk factor for death. Furthermore, PCP is not an intermediate variable on the causal pathway from prophylaxis treatment to death since, by construction, there is no such causal pathway.

Appendix 2

Technical Appendix

A2.1. Notation

Data on the covariates $L_i(t)$ and prophylaxis treatment were recorded at most once per day. We shall assume the recorded covariate process jumps at and only at times k , $k = (0, 1, 2, \dots)$,

days from enrollment, and the recorded treatment (prophylaxis) process, say $A_i(t)$, only jumps at time k^+ where k^+ is a time just after k . Let $L_{k,i}$ be subject i 's recorded value of $L_i(t)$ at k . Let $A_{k,i}$ be subject i 's (prophylaxis) treatment in $(k, k+1]$ so, by convention, $A_{k,i}$ follows $L_{k,i}$. $L_{0,i}$ is the value of all pre-enrollment time-dependent and time-independent covariates. Then $\bar{L}_{k,i} = (L_{0,i}, \dots, L_{k,i})$ and $\bar{A}_{k-1,i} = (A_{0,i}, \dots, A_{k-1,i})$ are the L -history and treatment history through day k . Define $\bar{L}(t) = \{\bar{L}_i(u); 0 \leq u \leq t\}$. Let $\text{int}(t)$ be the largest integer k less than or equal to t so that $\bar{L}(t) = \bar{L}_{\text{int}(t),i}$ because L -history only jumps at times k . We suppose realizations $a_{k,i}$ and $\ell_{k,i}$ of $A_{k,i}$ and $L_{k,i}$ lie in sets A_k and L_k of feasible a_k and ℓ_k values. Let \bar{A}_k and \bar{L}_k be the set of all vectors (a_0, a_1, \dots, a_k) and $(\ell_0, \ell_1, \dots, \ell_k)$ with $a_m \in A_m$, $\ell_m \in L_m$, $0 \leq m \leq k$. We shall adopt the convention that m and k will denote nonnegative integers, and if $\bar{\ell}_m$ and $\bar{\ell}_k$ are used in the same expression with $k < m$, $\bar{\ell}_k$ is the initial segment of $\bar{\ell}_m$. Similarly, if $k < t$, $\bar{\ell}_k$ is the initial segment of $\bar{\ell}(t)$. Finally, $\bar{\ell} = \bar{\ell}(\infty)$ is a covariate history defined on $[0, \infty)$. Similar remarks apply to $\bar{a}_m, \bar{a}_k, \bar{a}(t)$ and \bar{a} . In the next several sections, we briefly review results obtained in Ref 24, as we shall need them later. For convenience, define $\bar{A}_{-1,i}$ and $\bar{L}_{-1,i}$ to be zero.

A2.2. The Assumption of No Unmeasured Confounders

Our assumption of no unmeasured confounders is now that

$$T_{p=(v),i} \perp \!\!\! \perp \bar{A}_{k,i} | \bar{L}_{k,i}, \bar{A}_{k-1,i}, T_i > k \quad \text{for all } k, v, \quad (\text{A2.1})$$

where $A \perp \!\!\! \perp B | C$ means A is independent of B given C , and $T_{p=(v),i}$ is defined in Section 2c.

A2.3. A Baseline Rank-Preserving Structural Failure Time Model (RPSFTM)

A baseline RPSFTM assumes that $T_{p^-,i} = T_{p=(\infty),i}$ is linked to independent and identically distributed observables $\{T_i, \bar{L}_i(T_i), \bar{A}_i(T_i)\}$ by

$$T_{p^-,i} = h(T_i, \bar{L}_i(T_i), \bar{A}_i(T_i), \psi_0), \quad (\text{A2.2})$$

where $\psi_0 \in R^v$ is an unknown vector of parameters to be estimated, and $h(\cdot, \cdot, \cdot, \cdot)$ is a known smooth function, satisfying (1) monotonicity: $h(t, \bar{L}_i(t), \bar{A}_i(t), \psi) > h(u, \bar{L}_i(u), \bar{A}_i(u), \psi)$ if $t > u$; (2) identity: $h(t, \bar{L}_i(t), \bar{A}_i(t), \psi) = t$ if $\bar{A}_i(t)$ is identically zero on $(0, t)$; and (3) $h(t, \bar{L}_i(t), \bar{A}_i(t), 0) = t$ so that $\psi_0 = 0$ represents the null hypothesis of no causal effect of treatment on time to failure. A baseline RPSFTM is equivalent to the strong version of the accelerated failure time model originally proposed by Cox and Oakes.²⁵ As an example, the model

TABLE A1. A Hypothetical Study

PCP at 8 Months			No PCP		
	Time to Death (Months)			Time to Death (Months)	
	10	20	30	10	20
Prophylaxis by 4 months	100*	0	0	Prophylaxis by 4 months	0
No prophylaxis	100*	100†	0	No prophylaxis	100†

* Poor prognosis patients.

† Moderate prognosis subjects.

‡ Good prognosis subjects.

Eq 7 fit in the text is

$$T_{p^{-},i} = \int_0^{T_i} \exp\{\psi_0 A_i(u)\} du \quad (A2.3)$$

with $\psi_0 = \beta_p^*$.

A2.4. The Likelihood Function

Following the development in Ref 24, to write the likelihood as a function of ψ , we define $H_i(\psi) = h(T_i, \bar{L}_i(T_i), \bar{A}_i(T_i), \psi)$ so that, by Eq A2.2, $T_{p^{-},i} = H_i(\psi_0)$. Since the map from $\{T_i, \bar{L}_i(T_i), \bar{A}_i(T_i)\}$ to $\{H_i(\psi), \bar{L}_i(T_i), \bar{A}_i(T_i)\}$ is one to one with strictly positive Jacobian determinant $\partial H_i(\psi)/\partial T_i$, we have

$$\begin{aligned} & f_{\{T_i, \bar{L}_i(T_i), \bar{A}_i(T_i)\}}\{T_i, \bar{L}_i(T_i), \bar{A}_i(T_i)\} \\ &= \left\{ \frac{\partial H_i(\psi)}{\partial T_i} \right\} f_{\{H_i(\psi), \bar{L}_i(T_i), \bar{A}_i(T_i)\}}\{H_i(\psi), \bar{L}_i(T_i), \bar{A}_i(T_i)\}. \end{aligned} \quad (A2.4)$$

Then, by a decomposition into a product of conditional probabilities, the right-hand side of Eq A2.4 can be written:

$$\begin{aligned} & \left[\frac{\partial H_i(\psi)}{\partial T_i} \right] f_{\{H_i(\psi)\}} \prod_{m=0}^{m=\text{int}(T_i)} f_{\{\bar{L}_{m,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i(\psi), T_i > m\}} \\ & \cdot f_{\{A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, H_i(\psi), T_i > m\}} \end{aligned}$$

which, for $\psi = \psi_0$, can be written:

$$\begin{aligned} & \left[\frac{\partial H_i(\psi_0)}{\partial T_i} \right] f_{\{H_i(\psi_0)\}} \prod_{m=0}^{m=\text{int}(T_i)} f_{\{\bar{L}_{m,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i(\psi_0), T_i > m\}} \\ & \cdot \prod_{m=0}^{m=\text{int}(T_i)} f_{\{A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m\}}, \end{aligned} \quad (A2.5)$$

since Eqs A2.1 and A2.2 together imply

$$\begin{aligned} & f_{\{A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, H_i(\psi_0), T_i > m\}} \\ &= f_{\{A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m\}}. \end{aligned} \quad (A2.6)$$

Remark: $f_{\{\bar{L}_{m,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i(\psi), T_i > m\}} = f_{\{\bar{L}_{m,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i(\psi)\}}$ since the random variable $I\{T_i > m\}$ is a deterministic function of $\{\bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i(\psi)\}$.

The condition A2.6 is the sole restriction on the joint distribution of the observables implied by Eqs A2.1 and A2.2. Thus, we can specify a fully parametric model for the distribution of $\{T_i, \bar{L}_i(T_i), \bar{A}_i(T_i)\}$ by specifying parametric models $f_{\{\bar{L}_{m,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i(\psi_0), T_i > m; \theta_0\}}$, $f_{\{H_i(\psi_0); \theta_0\}}$, and $f_{\{A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m; \alpha_0\}}$. Since the baseline failure time $H_i(\psi_0)$ is not directly observed, it would be difficult for an investigator to specify a parametric model for $f_{\{\bar{L}_{m,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i(\psi_0), T_i > m\}}$. In contrast, an investigator might be much more secure specifying a parametric or semiparametric model for the densities $f_{\{A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m\}}$.

A2.5. Semiparametric G-Estimation of ψ_0

Suppose $A_{m,i}$ is dichotomous taking values zero or one. If the logistic model (Eq A2.8) for $f_{\{A_{m,i} = 1 | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m\}}$ is correctly specified, an asymptotic α -level G-test of the hypothesis $\psi = \psi_0$ is obtained by performing any standard likelihood-based test (for example, a score test) of the hypothesis $\theta = 0$ based on the likelihood of the extended

logistic model,

$$\mathcal{L}(\alpha, \theta, \psi) = \prod_{i=1}^n \mathcal{L}_i(\alpha, \theta, \psi), \quad \text{where}$$

$$\mathcal{L}_i(\alpha, \theta, \psi) = \prod_{m=0}^{\text{int}(T_i)} \mathcal{L}_{m,i}(\alpha, \theta, \psi), \quad (A2.7)$$

$\mathcal{L}_{m,i}(\alpha, \theta, \psi) = [P_{m,i}(\alpha, \theta, \psi)]^{A_{m,i}} [1 - P_{m,i}(\alpha, \theta, \psi)]^{1 - A_{m,i}}; P_{m,i}(\alpha, \theta, \psi) = D_{m,i}(\alpha, \theta, \psi)/(1 + D_{m,i}(\alpha, \theta, \psi)); D_{m,i}(\alpha, \theta, \psi) = \exp[\alpha' W_{m,i} + \theta' G_{m,i}\{H_i(\psi)\}]; \alpha' R^p$ and $\theta' R^v$ are unknown parameters; $W_{m,i}$ is a p -dimensional function of m , $\bar{L}_{m,i}, \bar{A}_{m-1,i}; G_{m,i}\{H_i(\psi)\} = g(H_i(\psi), \bar{A}_{m-1,i}, \bar{L}_{m,i}) \epsilon R^v$, $g(\cdot, \cdot, \cdot)$ is a fixed function, for example, if $v = 1$, $g(H_i(\psi), \bar{A}_{m-1,i}, \bar{L}_{m,i})$ might equal $H_i(\psi)$ or $\log\{H_i(\psi)\} A_{m-1,i}; G_{m,i}\{H_i(\psi)\}$ is treated as a fixed known covariate in the logistic likelihood $\mathcal{L}(\alpha, \theta, \psi)$, and

$$f_{\{A_{m,i} = 1 | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m\}} = P_{m,i}(\alpha_0, 0, \psi_0). \quad (A2.8)$$

More precisely, let $\tilde{\alpha}$ maximize $\mathcal{L}(\alpha, 0, \psi)$. Note, $\tilde{\alpha}$ does not depend on ψ . Define $S_\theta(\alpha, \theta, \psi) = \partial \log \mathcal{L}(\alpha, \theta, \psi) / \partial \theta$, $S_\theta(\psi) = S_\theta(\alpha_0, 0, \psi)$, $S_\alpha(\alpha, \theta, \psi) = \partial \log \mathcal{L}(\alpha, \theta, \psi) / \partial \alpha$, $S(\alpha, \theta, \psi) = \{S'_\alpha(\alpha, \theta, \psi), S'_\theta(\alpha, \theta, \psi)\}', I(\alpha, \theta, \psi) = -\partial S(\alpha, \theta, \psi) / \partial(\alpha, \theta)',$ and $I(\psi) = I(\tilde{\alpha}, 0, \psi)$. For any square $p + v$ dimensional square matrix a , write:

$$a = \begin{pmatrix} a_{\alpha\alpha} & a_{\theta\alpha} \\ a_{\alpha\theta} & a_{\theta\theta} \end{pmatrix},$$

where $a_{\alpha\alpha}$ and $a_{\theta\theta}$ are square matrices of dimension p and v , respectively. Define $a^{\theta\theta} = (a^{-1})_{\theta\theta} = \{a_{\theta\theta} - a_{\alpha\theta} a_{\alpha\alpha}^{-1} a_{\theta\alpha}\}^{-1}$. Note, $\hat{I}_{\alpha\alpha} = \hat{I}_{\alpha\alpha}(\psi)$ does not depend on ψ . Also, $S_\theta(\psi)$ does not depend on the model (Eq A2.8) for $f_{\{A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}\}}$. Robins²⁴ shows that the score statistic

$$S_\theta(\tilde{\alpha}, 0, \psi) \hat{I}^{\theta\theta}(\psi) S_\theta(\tilde{\alpha}, 0, \psi)$$

is asymptotically distributed χ^2 when $\psi = \psi_0$ since Eqs A2.6 and A2.8 imply that $\mathcal{L}_{m,i}(\alpha, \theta, \psi_0)$ is a correctly specified model for $f_{\{A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, H_i(\psi_0)\}}$ with true values α_0 and $\theta_0 = 0$ and, thus, $\mathcal{L}(\alpha, \theta, \psi_0)$ is a specified partial likelihood. Furthermore, under regularity conditions, $S_\theta(\tilde{\alpha}, 0, \psi) = 0$ will have a solution $\tilde{\psi}$ such that $n^{1/2}(\tilde{\psi} - \psi_0)$ is asymptotically normal with mean 0 and asymptotic variance $B(\hat{I}^{\theta\theta})^{-1}B'$ which can be consistently estimated by $n\hat{B}(\hat{I}^{\theta\theta})^{-1}\hat{B}'$ where $\hat{I}^{\theta\theta} = \hat{I}^{\theta\theta}(\tilde{\psi})$, $\hat{B}^{-1} = n^{-1}\partial S_\theta(\tilde{\alpha}, 0, \tilde{\psi})/\partial\psi'$, and $i^{\theta\theta}$ and B are the probability limits of $n^{-1}\hat{I}^{\theta\theta}$ and \hat{B} .²⁴

We can also estimate ψ_0 using conditional logistic regression. Indeed if, in Model A2.8, we allow a different main effect for each day m of the roughly 700 days of follow-up, as in Eq 8 in the text, we should use conditional rather than unconditional logistic regression.²⁵

Hence let $\mathcal{L}(\alpha, \theta, \psi) = \prod_{m=0}^\infty \mathcal{L}_m(\alpha, \theta, \psi)$, where

$$\mathcal{L}_m(\alpha, \theta, \psi) = \frac{\prod_{j: A_{m,j}=1} D_{m,j}(\alpha, \theta, \psi)}{\sum_{r \in s(m, d_m)} \left[\prod_{j \in r} D_{m,j}(\alpha, \theta, \psi) \right]} \quad \text{if } d_m > 0, \quad (A2.9)$$

$\mathcal{L}_m(\alpha, \theta, \psi) = 1$ otherwise, $s(m, d_m)$ is the set of all selections of $d_m = \sum_{i=1}^n A_{m,i}$ subjects from the risk set $\{j; T_j > m\}$, r is an element of $s(m, d_m)$, and j is a subject in r . If d_m is 1, the denominator of Eq A2.9 is $\sum_{j: T_j > m} D_{m,j}(\alpha, \theta, \psi)$. $\mathcal{L}(\alpha, \theta, \psi)$ is the Cox partial likelihood. Thus, the partial likelihood score test $S_{\mathcal{L}}(\tilde{\alpha}^c, 0, \psi) \hat{I}^{\theta\theta,c}(\psi) S_{\mathcal{L}}(\tilde{\alpha}^c, 0, \psi)$ is asymptotically χ^2 when $\psi =$

ψ_0 , and $\tilde{\psi}^c$ solving $S_{\theta}(\tilde{\alpha}^c, 0, \psi) = 0$ has asymptotic mean ψ_0 and variance that can be estimated by $\hat{B}^c(\hat{I}^{\theta, c})^{-1}\hat{B}^{c'}$. Here S_{θ} , \hat{B}^c , and \hat{I}^c refer to derivatives of $\log \mathcal{L}(\alpha, \theta, \psi)$, and $\tilde{\alpha}^c$ maximizes $\mathcal{L}(\alpha, \theta, \psi)$ when θ is set to zero. Furthermore, \hat{B}^c and \hat{B} converge to the same quantity $B = B^c$ and $i^{\theta, c} \geq i^{\theta}$ so that $\tilde{\psi}$ is at least as efficient as $\tilde{\psi}$. Eq A2.9 can be used as a basis for inference concerning ψ_0 even when the treatment process $A_i(t)$ can jump at any time t , provided that we let m index the observed jump times.

A2.6. Nondichotomous Treatment

We now allow $A_{m,i}$ to be continuous, ordinal, or discrete. Given a correctly specified model

$$\begin{aligned} f(A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m) \\ = f(A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m; \alpha_0) \end{aligned} \quad (\text{A2.10})$$

where $\alpha_0 \in R^p$ is an unknown parameter, and where for each $\alpha \in R^p$, $f(A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m; \alpha)$ is a density with respect to a measure μ , Robins²⁴ shows that the previous results hold if we define

$$\mathcal{L}_{m,i}(\alpha, \theta, \psi) = \frac{\exp[\theta' Q_{m,i}(A_{m,i}, H_i(\psi))]}{\int f(a_m | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m; \alpha)} \cdot \exp[\theta' Q_{m,i}(a_m, H_i(\psi))] d\mu(a_m), \quad (\text{A2.11})$$

$\theta \in R^v$ and $Q_{m,i}(A_{m,i}, H_i(\psi)) \equiv q(A_{m,i}, H_i(\psi), \bar{A}_{m-1,i}, \bar{L}_{m,i}) \epsilon R^v$ where $q(\cdot, \cdot, \cdot, \cdot)$ is a fixed function. If $A_{m,i}$ is dichotomous, Eq A2.10 is the logistic model A2.8, and we set $Q_{m,i}(A_{m,i}, H_i(\psi)) \equiv [G_{m,i}(H_i(\psi))] A_{m,i}$, then it is easy to calculate that Eq A2.11 equals $\mathcal{L}_{m,i}(\alpha, \theta, \psi)$ as defined in Section A2.5.

A2.7. Efficiency Properties of $\tilde{\psi}$

In Ref 24, it is shown that, for a fixed function q , rather than having the usual trade-off between bias and efficiency, increasing the number of covariates and parameters in a sequence of correctly specified models Eq A2.10 for $f(A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m)$ never decreases and often increases the efficiency with which ψ_0 is estimated. One can prove, however, that for a fixed function q , the quantity $B \mathcal{F}^*$ is less than or equal to the asymptotic variance of any estimator $\tilde{\psi}$ or $\tilde{\psi}^c$ based on any correctly specified model Eq A2.10 where

$$\begin{aligned} \mathcal{F} = E \left[\sum_{m=0}^{\text{int}(T_i)} \text{var}\{Q_{m,i} \right. \\ \left. - E(Q_{m,i} | \bar{L}_{m,i}, \bar{A}_{m,i}, T_i > m) | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m\} \right], \end{aligned}$$

$Q_{m,i} \equiv Q_{m,i}(A_{m,i}, H_i(\psi_0))$, and for matrices X and Y , $X \leq Y$ means $Y - X$ is non-negative definite.² The bound is sharp.² Furthermore, the asymptotic variance of $\tilde{\psi}$ does not depend on the Model A2.10 if and only if $E[Q_{m,i} | \bar{L}_{m,i}, \bar{A}_{m,i}, T_i > m]$ does not depend on $A_{m,i}$.²

To study the dependence of the asymptotic variance of $\tilde{\psi}$ on the choice of the function q , we shall write $\tilde{\psi}$ as $\tilde{\psi}(q)$. We prove in Ref 2 that there exists a function q_{opt} such that $\text{var}[n^{1/2}(\tilde{\psi}(q_{\text{opt}}) - \psi_0)]$ does not depend on the model Eq A2.10 and attains the semiparametric variance bound for ψ_0

under the sole restriction Eq A2.6. That is, there exists no regular estimator of ψ_0 with asymptotic variance less than of $\tilde{\psi}(q_{\text{opt}})$ that is guaranteed to be asymptotically normal and unbiased whatever be the densities $f(A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m)$, $f(H_i(\psi_0))$, and $f(L_{m,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i(\psi_0), T_i > m)$. Furthermore, the semiparametric variance bound under the sole restriction Eq A2.6 is the same as that under the joint restriction that both Eq A2.6 holds, and the density $f(A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m)$ satisfies Eq A2.10. Specifically, $q_{\text{opt}}(A_{m,i}, H_i(\psi_0), \bar{A}_{m-1,i}, \bar{L}_{m,i}) = E[S_{\psi}(\psi_0, H_i(\psi_0), \bar{L}_i(T_i), \bar{A}_i(T_i)) | \bar{L}_{m,i}, \bar{A}_{m-1,i}, H_i(\psi_0), T_i > m] - E[S_{\psi}(\psi_0, H_i(\psi_0), \bar{L}_i(T_i), \bar{A}_i(T_i)) | \bar{L}_{m,i}, \bar{A}_{m-1,i}, H_i(\psi_0), T_i > m]$ where $S_{\psi}(\psi, H_i(\psi), \bar{L}_i(T_i), \bar{A}_i(T_i))$ is the score for ψ for a single observation obtained by replacing ψ_0 by ψ in Eq A2.5 and then differentiating the natural logarithm of Eq A2.5 with respect to ψ . The function $q_{\text{opt}}(A_{m,i}, H_i(\psi_0), \bar{A}_{m-1,i}, \bar{L}_{m,i})$ is obtained by replacing $H_i(\psi_0)$ by $H_i(\psi)$ in $q_{\text{opt}}(A_{m,i}, H_i(\psi_0), \bar{A}_{m-1,i}, \bar{L}_{m,i})$. The estimator $\tilde{\psi}(q_{\text{opt}})$ is not feasible since q_{opt} depends on the unknown joint distribution of $\{T_i, \bar{L}_i(T_i), \bar{A}_i(T_i)\}$.

A2.8. Censoring by End of Follow-up

Let C_i the known potential censoring time defined as the difference between the end of follow-up date and the i^{th} individual's date of entry into the study, be the only form of censoring. Since C_i is known, we can and do include it in each $\bar{L}_{m,i}$. We observe $\{X_i = \min(T_i, C_i), \bar{L}_i(X_i), \bar{A}_i(X_i), \Delta_i = I[T_i < C_i]\}$. First suppose $A_{m,i} \in \{0, 1\}$ and the baseline RPSFTM Eq A2.3 holds. As discussed in Ref 24, since Eq A2.6 implies that any function of $(H_i(\psi_0), \bar{L}_{m,i}, \bar{A}_{m-1,i})$ will be independent of $A_{m,i}$ given $(\bar{L}_{m,i}, \bar{A}_{m-1,i})$, we define an observable random variable $X_{m,i}(\psi)$ that is a function of $(H_i(\psi), \bar{L}_{m,i}, \bar{A}_{m-1,i})$ to be used as a basis for inference concerning ψ_0 . Specifically, $X_{m,i}(\psi) \equiv \min\{H_i(\psi), C_{m,i}(\psi)\}$ where:

$$\begin{aligned} C_{m,i}(\psi) \equiv C_i - m \\ + \int_0^m \exp\{\psi A_i(t)\} dt \quad \text{if } \psi \geq 0 \end{aligned} \quad (\text{A2.12a})$$

$$\begin{aligned} C_{m,i}(\psi) \equiv \{\exp(\psi)\}(C_i - m) \\ + \int_0^m \exp\{\psi A_i(t)\} dt \quad \text{if } \psi < 0 \end{aligned} \quad (\text{A2.12b})$$

$X_{m,i}(\psi)$ is an observable since $T_i > C_i$ implies $H_i(\psi) > C_{m,i}(\psi)$. Let $\Delta_{m,i}(\psi) \equiv I\{H_i(\psi) < C_{m,i}(\psi)\}$. Then,

$$\{\Delta_{m,i}(\psi_0), X_{m,i}(\psi_0)\} \sqcup A_{m,i} | \bar{L}_{m,i}, \bar{A}_{m-1,i}, T_i > m \quad (\text{A2.13})$$

Let $\mathcal{L}(\alpha, \theta, \psi)$ and $\mathcal{L}^c(\alpha, \theta, \psi)$ be as defined previously except with $Q_{m,i}(A_{m,i}, X_{m,i}(\psi), \Delta_{m,i}(\psi))$ substituted for $Q_{m,i}(A_{m,i}, H_i(\psi))$. Since $S_{\theta}(\tilde{\alpha}, 0, \psi)$ may now be discontinuous in ψ , define ψ to be a solution to $o_p(1) = n^{-1}S_{\theta}(\tilde{\alpha}, 0, \psi)S_{\theta}(\tilde{\alpha}, 0, \psi)$. This implies that $\tilde{\psi}$ locally minimizes $S_{\theta}(\tilde{\alpha}, 0, \psi)S_{\theta}(\tilde{\alpha}, 0, \psi)$ in a neighborhood of ψ_0 . Then the asymptotic properties of $\tilde{\psi}$ are as discussed previously when B^{-1} is redefined to be the $v \times v$ matrix of "numerical" partial derivatives of $n^{-1}S_{\theta}(\tilde{\alpha}, 0, \psi)$ with respect to ψ' evaluated at $\tilde{\psi}$ based on a step size proportional to $n^{-1/2}$. That is, with c_1, \dots, c_v fixed constants and e_k the $v \times 1$ vector with k^{th} element 1 and remaining elements zero, \hat{B}^{-1} has $(j, k)^{\text{th}}$ element

$$\frac{n^{-1}[S_{\theta}(\tilde{\alpha}, 0, \tilde{\psi} + c_k e_k n^{-1/2}) - S_{\theta}(\tilde{\alpha}, 0, \tilde{\psi} - c_k e_k n^{-1/2})]}{2c_k n^{-1/2}},$$

when S_θ is the j^{th} element of S_θ .²⁶ This relation follows from the fact that Eq A2.13 implies that, under regularity conditions, for $|\psi - \psi_0| = O(n^{-1/2})$,

$$\begin{aligned} n^{-1/2}S_\theta(\hat{\alpha}, 0, \psi) &= n^{-1/2}S_\theta(\hat{\alpha}, 0, \psi_0) \\ &\quad + B^{-1}n^{1/2}(\psi - \psi_0) + o_p(1), \end{aligned} \quad (\text{A2.14})$$

where $B^{-1} = \partial E[n^{-1}S_\theta(\alpha_0, 0, \psi)]/\partial\psi'|_{\psi=\psi_0}$. Analogous results apply to $\tilde{\psi}^c$ solving $o_p(1) = n^{-1}S_\theta(\hat{\alpha}, 0, \psi)/S_\theta(\hat{\alpha}, 0, \psi)$.

The above results remain true in the general case in which $A_{m,i}$ is nondichotomous, and the general baseline RPSFTM (Eq A2.2) holds if we redefine $C_{m,i}(\psi) \equiv \min\{h(C_i, \bar{L}(C_i), \bar{a}(C_i); \psi), (\bar{L}(C_i), \bar{a}(C_i)) \in LA_{m,i}(C_i)\}$, and $LA_{m,i}(C_i)$ is a set of $(\bar{L}(C_i), \bar{a}(C_i))$ histories satisfying $\frac{1}{n} = \text{pr}[\bar{L}(C_i), \bar{A}(C_i) \in LA_{m,i}(C_i) | C_i = C_i, T_j > C_i, \bar{L}_j(m) = \bar{L}_i(m), \bar{A}_i(m) = A_i(m)]$. We suppose that there exists σ such that $C_{m,i}(\psi) > \sigma > 0$ for all m, i , and ψ in a neighborhood of ψ_0 . Eq A2.12 and Eq 13 are special cases. There will be efficiency advantages to choosing $LA_{m,i}(C_i)$ to be the smallest such set. In that case, $C_{m,i}(\psi)$ is the earliest potential censoring time on the ψ -time scale for any subject censored at C_i with history $(\bar{L}_{m,i}, \bar{A}_{m-1,i})$ through time m . Further calculation shows that the asymptotic variances of $\tilde{\psi}(q)$ and $\tilde{\psi}^c(q)$ are minimized by choosing q to be $q_{\text{opt}}^{\text{mod}}$ where $q_{\text{opt}}^{\text{mod}}$ is as defined like q_{opt} in Section A2.7 except that it is modified so that, in the conditioning events, $H_i(\psi_0)$ is now replaced by $(X_{m,i}(\psi_0), \Delta_{m,i}(\psi_0))$. Estimators that are more efficient than even $\tilde{\psi}^c(q_{\text{opt}}^{\text{mod}})$ are discussed in Ref 27.

A2.9. Nonparametric Identification

In this section, we will show that the assumption of no unmeasured confounders is sufficient to identify the survival curves of the counterfactual random variables $T_{p=(v),i}$ without specifying a baseline RPSFTM Eq A2.2. In fact, we will obtain identification for a much larger class of counterfactual variables.

We define a *feasible treatment regime* G to be a function $G(t_k, \bar{L}_k)$ that assigned to each possible t_k and $\bar{L}_k \in \bar{A}_k$, a treatment rate $a_k \in A_k$. An example of a feasible regime is “take a dosage a_k of 1,000 milligrams of prophylaxis daily in the interval $(k, k+1]$ if the subject has had an episode of PCP by time k . Otherwise, take no prophylaxis in that interval.” Let G be the set of all feasible regimes. Note, G depends on the covariates recorded in ℓ_k . Given the function $G(t_k, \bar{L}_k)$ of two arguments (t_k, \bar{L}_k) , we define the function $G(\bar{L}_k)$ of one argument by the relation $G(\bar{L}_k) = \{G(t_m, \bar{L}_m); 0 \leq m \leq k\}$. Since there is a one to one relation between the functions $G(t_k, \bar{L}_k)$ and $G(\bar{L}_k)$, we shall identify the regime G with both functions.

For each subject i and each regime G , we shall assume that there exists $T_{i,G}$ representing the time to death that would be observed if, possibly contrary to fact, subject i had followed a treatment history consistent with regime G . Note that the counterfactual variables $T_{i,G}$ include the variables $T_{p=(v),i}$ discussed in the text. We shall make the following consistency assumption that formalizes the idea that a subject’s survival through t depends only on treatment received before t .

Consistency Assumption: For any regime G and time k for which $G(\bar{L}_{k,i}) = \bar{A}_{k,i}$, we assume $T_{i,G} \geq t \Leftrightarrow T_i \geq t$, for $t \in (k, k+1]$.

We shall assume that the observed and counterfactual data

$(t_i, \bar{L}_i(t_i), \bar{a}_i(t_i), \{t_{i,G}; G \in G\})$ are realizations of independent and identically distributed random vectors $(T_i, \bar{L}_i(T_i), \bar{A}_i(T_i), \{T_{i,G}; G \in G\})$. Therefore, for notational convenience, we shall often drop the subscript i when referring to these random variables. $\text{pr}[T_G > t]$ is the treatment regime-specific counterfactual survival curve for regime G . We shall suppose that, for all k , the density $f_{\bar{A}_k, \bar{L}_k}(\bar{a}_k, \bar{L}_k | T > k) \neq 0$ for all $\bar{a}_k \in \bar{A}_k, \bar{L}_k \in \bar{L}_k$ whenever $f(\bar{a}_{k-1}, \bar{L}_k | T > k) \neq 0$. Until Section A2.15, we assume the distribution of $T_G, G \in G$, is proper, that is, without mass at infinity. We could generalize our assumption of no unmeasured confounders to: for all m and $G \in G$

$$A_m \sqcup T_G | \bar{L}_m, \bar{A}_{m-1}, T > m.$$

In fact, we shall only require the somewhat weaker assumption that for all m, G ,

$$A_m \sqcup T_G | \bar{L}_m, G(\bar{L}_{m-1}), T > m. \quad (\text{A2.15})$$

Eq A2.15 has been called the assumption of weak randomization in Ref 1 or the assumption of randomization with respect to death in Ref 5.

Theorem 1: Under Assumption A2.15 and the consistency assumption, $\text{pr}[T_G > t]$ is identified. Specifically,

$$\begin{aligned} \text{pr}[T_G > t] &= \int \int \cdots \int \left\{ \text{pr}[T > t | T > \text{int}(t), \ell_{\text{int}(t)}, G(\ell_{\text{int}(t)})] \right. \\ &\quad \cdot \prod_{m=1}^{\text{int}(t)} \text{pr}[T > m | T > m-1, \ell_{m-1}, G(\ell_{m-1})] \\ &\quad \left. \cdot \prod_{m=0}^{\text{int}(t)} dF[\ell_m | T > m, \ell_{m-1}, G(\ell_{m-1})] \right\}. \end{aligned} \quad (\text{A2.16})$$

Furthermore, for $0 \leq k+1 < t$, $\text{pr}[T_G > t | \bar{L}_k = \bar{L}_k, \bar{A}_k = G(\bar{L}_k), T > k]$ is as given by Eq A2.16, except that both products now begin at $m = k+1$ rather than at $m = 1$ and $m = 0$.

In Eq A2.16, $dF[\ell_m | T > m, \bar{L}_{m-1}, G(\bar{L}_{m-1})]$ refers to the conditional density of L_m given $\bar{L}_{m-1} = \bar{L}_{m-1}, T > m, \bar{A}_{m-1} = G(\bar{L}_{m-1})$. Similarly, $\text{pr}[T > m+1 | T > m, \bar{L}_{m-1}, G(\bar{L}_{m-1})]$ is the probability that $T > m+1$ given $\bar{L}_{m-1} = \bar{L}_{m-1}, T > m, \bar{A}_{m-1} = G(\bar{L}_{m-1})$. Eq A2.16 is the G -computation algorithm formula.

Proof: See proof of Theorem A.1 in Ref 3, Theorem A.1 in Ref 7, or Theorem AD.1 in Ref 5.

If there is censoring by end of follow-up, the quantities $\text{pr}[T_G > t | C]$ for $t \leq C$ [rather than $\text{pr}[T_G > t]$] are identified where C is as defined in Section A2.8. $\text{pr}[T_G > t | C]$ is given by Eq A2.16 with C added to each conditioning event. [Since C is included in each $\bar{L}_m, m \geq 0$, this inclusion is redundant except for the $dF(\ell_0)$ term.]

A2.10. Structural Nested Failure Time Models

Owing to sparse data, nonparametric estimation of $\text{pr}[T_G > t]$ based on the nonparametric estimation of the probabilities in Eq A2.16 is not practical, and we must therefore make modeling assumptions. Our goal in this section is to develop models that, when Eq A2.15 holds,

- (1) in contrast to the baseline RPSFTM Eq A2.2, do not unrealistically assume that $T_{p^-,i}$ is a deterministic function of $(T_i, \bar{L}_i(T_i), \bar{A}_i(T_i))$;
- (2) if correctly specified, allow for consistent estimation of (a) $\text{pr}[T_G > t]$ in the absence of censoring, or (b), with censoring, $\text{pr}[T_G > t | C]$, for $t \leq C$ for all $G \in G$;

- (3) even, under misspecification, allow for an asymptotically normal α -level test of the G-null hypothesis

$$\text{pr}[T_G > t] = \text{pr}[T > t] \text{ for all } G \in \mathbf{G} \quad (\text{A2.17})$$

provided that we have a correctly specified model for $f[A_m | \bar{L}_m, \bar{A}_{m-1}, T > m]$, and

- (4) there exists a (possibly vector-valued) parameter, say ψ_0 , such that $\psi_0 = 0$ if and only if the G-null hypothesis holds.

The most straightforward approach to the estimation of $\text{pr}(T_G > t)$ is to specify parametric or semiparametric models for the conditional probabilities on the right-hand side of Eq A2.16 as in Refs 4 and 6. Unfortunately, as discussed in Refs 1, 2, 4, and 6, this approach fails to satisfy Goals 3 and 4. Thus, the alternative approach based on SNFTMs described below is necessary.

Given any treatment history $\bar{a} = (a_0, a_1, \dots)$ on $(0, \infty)$, let $G = (\bar{a})$ be the regime defined by $G(\bar{l}_k) = \bar{a}_k$ for all \bar{l}_k , and let $T_{G=(\bar{a})}$ be the corresponding counterfactual variable. Also, given \bar{a} as above, adopt the convention that $(\bar{a}_m, 0)$ will be the history $\bar{a}^{(1)}$ on $(0, \infty)$ characterized by $a_k^{(1)} = a_k$ if $k \leq m$ and $a_k^{(1)} = 0$ if $k > m$. Thus, $T_{G=(0)} = T_{p-} = T_{p=(\infty)}$.

For $t > m$, define the blip function $\gamma(t, \bar{l}_m, \bar{a}_m)$ by the relation

$$\begin{aligned} \text{pr}[T_{G=(\bar{a}_m, 0)} > t | \bar{l}_m, \bar{a}_m, T > m] \\ &= \text{pr}[T_{G=(\bar{a}_{m-1}, 0)} > \gamma(t, \bar{l}_m, \bar{a}_m) | \bar{l}_m, \bar{a}_m, T > m]. \end{aligned} \quad (\text{A2.18})$$

To clarify the meaning of the function $\gamma(t, \bar{l}_m, \bar{a}_m)$, consider the subset with observed history $(\bar{l}_m, \bar{a}_m, T > m)$. The function $\gamma(t, \bar{l}_m, \bar{a}_m)$ is a measure of the magnitude of the causal effect of a final brief "blip" of treatment a_m in the interval $(t_m, t_{m+1}]$ on the survival experience of this subset, in the sense that it maps percentiles of the random variable $T_{G=(\bar{a}_m, 0)}$ into those of the random variable $T_{G=(\bar{a}_{m-1}, 0)}$. We assume that the random variables, $T_{G=(\bar{a}_m, 0)}$ and $T_{G=(\bar{a}_{m-1}, 0)}$, conditional on (\bar{l}_m, \bar{a}_m) have a density on (m, ∞) that is continuous almost everywhere. Thus, it follows from its definition that $\gamma(t, \bar{l}_m, \bar{a}_m)$ is well defined and satisfies (a) $\gamma(t, \bar{l}_m, \bar{a}_m) > m$; (b) $\gamma(t, \bar{l}_m, \bar{a}_m) = t$ if $a_m = 0$; and (c) $\gamma(t, \bar{l}_m, \bar{a}_m)$ is increasing in t ; and (d) the derivative of $\gamma(t, \bar{l}_m, \bar{a}_m)$ with respect to t is continuous almost everywhere.

Note, by Eq A2.18, conditional on $(\bar{l}_m, \bar{A}_m, T > m)$, the random variable $\gamma(T_{G=(\bar{a}_m, 0)}, \bar{l}_m, \bar{A}_m)$ has the same distribution as $T_{G=(\bar{a}_{m-1}, 0)}$. If, conditional on $(\bar{l}_m, \bar{A}_m, T > m)$, these two random variables are equal with probability one, we say there is local rank preservation. Local rank preservation is a strong, untestable assumption that would rarely be expected to hold.

For $t \leq T$, define $H_{\text{int}(t)}(t) \equiv h_{\text{int}(t)}(t, \bar{l}(t), \bar{A}(t))$ to be $\gamma(t, \bar{l}_{\text{int}(t)}, \bar{A}_{\text{int}(t)})$ and, for $0 \leq m < \text{int}(t)$, define $H_m(t) \equiv h_m(t, \bar{l}(t), \bar{A}(t))$ to be $\gamma(H_{m+1}(t), \bar{l}_m, \bar{A}_m)$. Define $H(t) \equiv h(t, \bar{l}(t), \bar{A}(t))$ to be $H_0(t)$. Let $H \equiv H(T)$ and $H_m \equiv H_m(T)$. Note, if we have local rank preservation, $H_m = T_{G=(\bar{a}_{m-1}, 0)}$ for $T > m$, H is $T_{G=(0)} \equiv T_{p-}$, and, therefore

$$\begin{aligned} \text{pr}[H_m > t | \bar{l}_m, \bar{A}_m, T > m] \\ &= \text{pr}[T_{G=(\bar{a}_{m-1}, 0)} > t | \bar{l}_m, \bar{A}_m, T > m]. \end{aligned} \quad (\text{A2.19})$$

In fact, in Ref 27 we prove that, even without local rank preservation,

Theorem 2: The consistency assumption implies Eq A2.19. In particular, $\text{pr}[H > t] = \text{pr}[T_{G=(0)} > t]$.

It follows from Theorems 1 and 2, and the fact that H is a deterministic function of $(H_m, \bar{l}_m, \bar{A}_{m-1})$, that

Corollary 1: If Eq A2.15 and the consistency assumption hold, then $\gamma(t, \bar{l}_m, \bar{a}_m)$ is identified, $H_m \sqcup A_m | \bar{l}_m, \bar{A}_{m-1}, T > m$ and

$$H \sqcup A_m | \bar{l}_m, \bar{A}_{m-1}, T > m \quad (\text{A2.20})$$

In Refs 1 and 2, we prove:

Theorem 3: If Eq A2.15 and the consistency assumption hold, then

- (a) the G-null hypothesis (Eq A2.17) holds if and only if $\gamma(t, \bar{l}_m, \bar{a}_m) = t$ for all m and t , $t > m$;
- (b) the following Monte Carlo algorithm produces independent realizations $t_{v, "G"}$ of a random variable $T_{v, "G"}$ whose distribution is that of T_G . Define the function $\rho(x, \bar{l}_m, \bar{a}_m)$ recursively for all \bar{l}_m, \bar{a}_m and $x \in (0, \infty)$ as follows. $\rho(x, \bar{l}_0, \bar{a}_0) = \gamma^{-1}(x, \bar{l}_0, \bar{a}_0)$ where $\gamma^{-1}(u, \bar{l}_k, \bar{a}_k) \equiv t$ if $\gamma(t, \bar{l}_k, \bar{a}_k) = u$. For $1 \leq k \leq m$, $\rho(x, \bar{l}_k, \bar{a}_k) = \gamma^{-1}(\rho(x, \bar{l}_{k-1}, \bar{a}_{k-1}), \bar{l}_k, \bar{a}_k)$ if $\rho(x, \bar{l}_{k-1}, \bar{a}_{k-1}) \geq k$; and $\rho(x, \bar{l}_k, \bar{a}_k) = \rho(x, \bar{l}_{k-1}, \bar{a}_{k-1})$ otherwise. We call $\rho(x, \bar{l}_m, \bar{a}_m)$ the recursive blip-up function. Let $\rho(x, \bar{l}, \bar{a}) = \lim_{m \rightarrow \infty} \rho(x, \bar{l}_m, \bar{a}_m)$ if the limit exists and $\rho(x, \bar{l}, \bar{a}) = \infty$, otherwise. Then, given a regime G ,

Step 1: Set $v = 1$

Step 2: Draw h_v from $f_{H|C}(h)$

Step 3: Draw $\ell_{0,v}$ from $f[\ell_0 | h_v]$

Step 4: Set $m = 1$

Step 5: If $\rho[h_v, \bar{l}_{m-1,v}, G(\bar{l}_{m-1,v})] \leq m$, set $t_{v, "G"} = \rho[h_v, \bar{l}_{m-1,v}, G(\bar{l}_{m-1,v})]$, increment v by 1, and return to Step 2. If $\rho[h_v, \bar{l}_{m-1,v}, G(\bar{l}_{m-1,v})] > m$, draw $\ell_{m,v}$ from $f[\ell_m | \bar{l}_{m-1,v}, G(\bar{l}_{m-1,v}), h_v, T > m]$, increment m by 1, and return to Step 5.

In the presence of censoring, we would be interested in sampling from the conditional distribution of T_G given $C = c$. To do so, draw h_v from $f_{H|C}(h | c)$ and $\ell_{0,v}$ from $f[\ell_0 | h_v, c]$ in Steps 2 and 3.

If $\gamma(t, \bar{l}_m, \bar{a}_m)$ does not depend on \bar{l}_m , then $T_{G=(\bar{a}_m)}$ has the same distribution as $\rho(H, \bar{a}) \equiv \rho(H, \bar{l}, \bar{a})$. Note, if $\rho(x, \bar{a}) < \infty$, $\rho(x, \bar{a}) = \rho(x, \bar{l}_{m^*-1}, \bar{a}_{m^*-1}) \equiv \rho(x, \bar{a}_{m^*-1})$ where m^* is the integer solving $m^* - 1 < \rho(x, \bar{a}_{m^*-1}) \leq m^*$.

A heuristic explanation of the above Monte Carlo algorithm is as follows. If a "simulated subject" v with baseline time h_v manages to survive to time m under regime G , we randomly draw $\ell_{m,v}$ and then use the recursive blip-up function ρ to determine whether subject v has survived to time $m + 1$ under regime G or whether the subject has died at a time $t_{v, "G"}$ in the interval $(m, m + 1]$. This explanation is heuristic in that it (unnecessarily) assumes rank preservation. **Definition:** The superpopulation follows a SNFTM or blip model $\gamma^*(t, \bar{l}_m, \bar{a}_m, \psi)$ if $\gamma(t, \bar{l}_m, \bar{a}_m) = \gamma^*(t, \bar{l}_m, \bar{a}_m, \psi_0)$ where (1) $\gamma^*(\cdot, \dots, \cdot)$ is a known function; (2) ψ_0 is a finite vector of unknown parameters to be estimated taking values in R^v ; (3) for each value of $\psi \in R^v$, $\gamma^*(t, \bar{l}_m, \bar{a}_m, \psi)$ satisfies the Conditions a-d following Eq A2.18 that were satisfied by $\gamma(t, \bar{l}_m, \bar{a}_m)$; (4) $\partial \gamma^*(t, \bar{l}_m, \bar{a}_m, \psi) / \partial \psi'$ and $\partial^2 \gamma^*(t, \bar{l}_m, \bar{a}_m, \psi) / \partial \psi' \partial t$ are continuous for all ψ and almost all $t \in (m, \infty)$; and (5) $\gamma^*(t, \bar{l}_m, \bar{a}_m, \psi) = t$ if $\psi = 0$.

Let $H(t, \psi) \equiv h(t, \bar{l}(t), \bar{A}(t), \psi)$ be defined like $H(t) \equiv h(t, \bar{l}(t), \bar{A}(t))$ except with $\gamma^*(t, \bar{l}_m, \bar{a}_m, \psi)$ replacing $\gamma(t, \bar{l}_m, \bar{a}_m)$. Redefine $H(\psi) \equiv H(T, \psi)$ so that $H(\psi_0) = H$. Note, $H(\psi)$ satisfies the Conditions a-d following Eq A2.2. Eq A2.2,

however, would only be expected to be true if there is local rank preservation so that $H(\psi_0) = T_p$. That is, in general, a SNFTM will be a baseline RPSFTM only if there is local rank preservation. Even without local rank preservation, by Theorem 2, $\text{pr}[H(\psi_0) > t] = \text{pr}[T_p > t]$. Furthermore, by Eq A2.20, Eq A2.6 holds. Eq A2.6 is the only independent restriction on the joint distribution of the observables implied by the SNFTM and Eq A2.15, and thus semiparametric G-estimation of ψ_0 can proceed exactly as in Section A2.8. (In this sense, the assumption of local rank preservation is unnecessary.) In addition, it follows from Theorem 3a that, under Eq A2.15, $\psi_0 = 0$ if and only if the G-null hypothesis (Eq A2.17) holds. Hence, by specifying a SNFTM and estimating ψ_0 by G-estimation, we have satisfied Modeling Goals 1, 3, and 4 above. To fulfill Goal 2 in the presence of censoring, we proceed as follows.

Estimation Algorithm for the Law of T_G given C:

- Compute a G-estimate $\tilde{\psi}$ of the parameter ψ_0 of a SNFTM as in Section A2.8.
- Specify parametric models $f[\ell_{m,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i, T_i > m, C_i; \phi]$ and $f_H(h | C_i; \eta)$ depending on ϕ and η .
- Define $(\hat{\phi}, \hat{\eta})$ to be the (ϕ, η) that maximize the censored data likelihood given $\tilde{\psi}$:

$$\prod_{i=1}^n \left[\left\{ [\partial H_i(\tilde{\psi}) / \partial T_i] f_H(H_i(\tilde{\psi}) | C_i; \eta) \right. \right. \\ \cdot \prod_{m=0}^{\text{int}(T_i)} f[L_{m,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i(\tilde{\psi}), T_i \\ \left. \left. > m, C_i; \phi \right\}^{\Delta_i} \times \left\{ \int_{H_i(X_i, \tilde{\psi})}^{\infty} dh f_H(h | C_i; \eta) \right. \right. \\ \cdot \prod_{m=0}^{\text{int}(X_i)} f[L_{m,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, h, T_i > m, C_i; \phi] \left. \right\}^{1-\Delta_i} \right].$$

- Implement the Monte Carlo algorithm in Step b of Theorem 3 as modified for censoring except draw h_v from $f_H(h | C; \eta)$; draw $\ell_{m,v}$ from $f[\ell_m | \bar{L}_{m-1,v}, G(\bar{L}_{m-1,v}), h_v, C, T > m; \phi]$; replace $\gamma^{-1}(u, \bar{L}_k, \bar{a}_k)$ with $\gamma^{*-1}(u, \bar{L}_k, \bar{a}_k, \psi)$ in defining $\rho(h, \bar{L}_k, \bar{a}_k)$ where $\gamma^{*-1}(u, \bar{L}_k, \bar{a}_k, \psi) = t \Leftrightarrow \gamma^*(t, \bar{L}_k, \bar{a}_k, \psi) = u$. We have:

Theorem 4: If Eq A2.15 and the consistency assumption hold, and if the SNFTM model and the parametric models in Step b above are correctly specified, then the distribution of the realizations from the Monte Carlo algorithm in Step d above will converge to the conditional distribution of T_G given $C = c$.

$$\begin{aligned} \gamma^*(t, \bar{L}_m, \bar{a}_m, \psi_0) &= (t - m) \exp(\psi_{0,1} a_m + \psi_{0,2} a_m \ell_m) + m \\ &\quad \text{if } t < m + 1 \\ \gamma^*(t, \bar{L}_m, \bar{a}_m, \psi_0) &= t + \exp(\psi_{0,1} a_m + \psi_{0,2} a_m \ell_m) - 1 \\ &\quad \text{if } t \geq m + 1 \end{aligned} \quad (\text{A2.21a})$$

where $\psi'_0 = (\psi_{0,1}, \psi_{0,2})$ and, for concreteness, suppose ℓ_m is the covariate "CD4-count at m ." Given (\bar{a}, \bar{L}) defined on $(0, \infty)$, write

$$x = \int_0^t \exp\{\psi_{0,1} a(u) + \psi_{0,2} a(u) \ell(u)\} du. \quad (\text{A2.21b})$$

Then, under Eq A2.21a, $h(t, \bar{L}_m, \bar{a}_m)$ equals x ; $\rho(x, \bar{L}_m, \bar{a}_m)$ equals t ; if $\psi_{0,2} = 0$, $\rho(x, \bar{a}_m) = \rho(x, \bar{L}_m, \bar{a}_m)$; and $\rho(x, \bar{L}_m, \bar{a}_m)$ equals t in Eq A2.21b when $a(u)$ is replaced by 0 for all $u > m + 1$.

Remark: Given a correctly specified SNFTM $\gamma^*(t, \bar{L}_m, \bar{a}_m, \psi)$, the true parameter ψ_0 can be consistently estimated under weaker assumptions than Eq A2.15. For example, suppose that $A_m = (A_m^{(1)}, A_m^{(2)})'$ with $A_m^{(1)}$ recording the prescribed treatment and $A_m^{(2)}$ the actual treatment in $(m, m + 1]$. One might then regard

$$A_m^{(1)} \sqcup T_G | \bar{L}_m, G(\bar{L}_{m-1}), T > m \quad (\text{A2.15}^*)$$

as true, but Eq A2.15 as false, if an independent predictor of T_G and actual treatment had not been included in \bar{L}_m . Under Eq A2.15*, an asymptotically normal and unbiased estimator $\tilde{\psi}^*$ of ψ_0 can be constructed as in Section A2.8, except that (i) parametric models for $f[A_m^{(1)} | \bar{L}_m, \bar{A}_{m-1}, T > m]$ replace models for $f[A_m | \bar{L}_m, \bar{A}_{m-1}, T > m]$ and (ii) $A_m^{(1)}$ replaces A_m as the first argument in the function $Q_m(A_m, X_m, \psi, \Delta_m(\psi))$. However, Theorems 1, 3, and 4 are no longer true when Eq A2.15 is replaced by Eq A2.15*. Hence, $\text{pr}[T_G > t | C]$ is no longer nonparametrically identified when Eq A2.15* is true but Eq A2.15 is false. Thus, even with large datasets, there will be limits to our ability to test whether the SNFTM $\gamma^*(t, \bar{L}_m, \bar{a}_m, \psi)$ is correctly specified.

A2.11. Adjustment for Censoring by Competing Risks and for Missing Data

Suppose that we wished to estimate the effect of prophylaxis therapy on the development of subsequent PCP with death treated as a competing risk. To do so, redefine, for the moment, T to be the actual time to the first postrandomization episode of PCP. Redefine T_G to be the time to the first postrandomization episode of PCP had regime G been followed and had all deaths occurring before the development of PCP been prevented. Let D be the random variable recording a subject's actual death time. D is observed if and only if $D < C$.

We assume that we have recorded data on a sufficient number of confounding factors so that censoring due to death is independent of T_G given $\bar{L}_i(t), \bar{A}_i(t)$, that is, for $G \in G$,

$$\lambda_D[t | \bar{L}_i(t), \bar{A}_i(t), T_i > t] = \lambda_D[t | \bar{L}_i(t), \bar{A}_i(t), T_i > t, T_G] \quad (\text{A2.22})$$

where $\lambda_D(t)$ is the mortality rate at t (that is, the hazard at t of the random variable D).

Remark 1: In Sections A2.1–A2.10, we frequently encounter expressions (for example, Eq A2.6) of the form $\text{pr}(V_m | B_m)$ indexed by a time m where either or both of the events V_m and B_m are well defined only for subjects alive at m . In such instances, it is to be understood that the event $D > m$ has been (implicitly) appended to the conditioning event B_m . Specifically, in this subsection, we shall assume the following. The event $D_i > m$ or $D > m$ (as appropriate) has been appended to the conditioning events in Eqs A2.6, A2.10, A2.15, A2.18, A2.19, and A2.20 and in the expressions for the conditional laws of ℓ_m or L_m given in Step 5 of Theorem 3b and in Steps b, c, and d of the estimation algorithm for the law of T_G given C . In Ref 2, we prove:

Theorem 5: Suppose Eq A2.22, Eq A2.15, and the consistency assumption hold, and a SNFTM $\gamma^*(t, \bar{L}_m, \bar{a}_m, \psi)$ is correctly

specified, then Eq A2.6,

$$\begin{aligned} \lambda_D[t | \bar{L}_i(t), \bar{A}_i(t), T_i > t] \\ = \lambda_D[t | \bar{L}_i(t), \bar{A}_i(t), T_i > t, H_i(\psi_0)], \end{aligned} \quad (\text{A2.23})$$

and Theorem 3 hold.

Results in Refs 27 and 28 imply:

Theorem 6: If Eqs A2.15, A2.10, and A2.22 hold, and we have a correctly specified Cox model for the hazard of death, that is

$$\lambda_D[t | \bar{L}_i(t), \bar{A}_i(t), T_i > t] = \lambda_D(t) \exp[\omega_0' V_i(t)] \quad (\text{A2.24})$$

where $V_i(t)$ is a vector-valued function of $(\bar{L}_i(t), \bar{A}_i(t))$ and ω_0 is an unknown parameter vector to be estimated, then, under regularity conditions, there exists a solution $\hat{\psi}^*$ to $n^{-1} S_{\theta}^*(\hat{\alpha}, 0, \psi)' S_{\theta}^*(\hat{\alpha}, 0, \psi) = o_p(1)$ such that $n^{1/2}(\hat{\psi}^* - \psi_0)$ is asymptotically normal with mean 0, where $S_{\theta}^*(\hat{\alpha}, 0, \psi)$ is defined like $S_{\theta}(\hat{\alpha}, 0, \psi)$ in Section A2.8, except that $Q_{m,i}(\mathbf{A}_{m,i}, X_{m,i}, \psi, \Delta_{m,i}(\psi))$ is replaced by $Q_{m,i}^*(\mathbf{A}_{m,i}, X_{m,i}, \psi, \Delta_{m,i}(\psi)) / \hat{K}_i(X_i)$ where X_i is now

$$\min(T_i, D_i, C_i), \tau_i = I\{X_i \neq D_i\}, \hat{K}_i(u)$$

$$\begin{aligned} &= \prod_{ij: X_j \leq u, \tau_j=0} \{1 - \hat{\lambda}(X_j) \exp[\hat{\omega}' V_i(X_j)]\}, \hat{\lambda}(X_i) \\ &= (1 - \tau_i) \left[\sum_{i=1}^n e^{\hat{\omega}' V_i(X_i)} I\{X_i \geq X_j\} \right]^{-1} \end{aligned}$$

is the Cox baseline hazard estimator, and $\hat{\omega}$ is the Cox maximum partial likelihood estimator of ω_0 . In fitting the Cox model (Eq A2.24), subjects are regarded as censored at the time that they develop postrandomization PCP. A regularity condition for this result is that the limit $K_i(X_i)$ of $\hat{K}_i(X_i)$ is bounded away from 0 with probability one, where $K_i(u) \equiv \exp[-\int_0^u \lambda_D[t | \bar{L}_i(t), \bar{A}_i(t), T_i > t] dt]$. The key step in the proof of Theorem 6 is the observation that, under Eqs A2.6, A2.10, and A2.23, $E[S_{\theta}^{**}(\alpha_0, 0, \psi_0)] = 0$ where $S^{**}(\alpha_0, 0, \psi_0)$ replaces $\hat{K}_i(X_i)$ by $K_i(X_i)$ in $S^*(\alpha_0, 0, \psi_0)$. Finally, $\text{pr}(T_G > t | c)$ can still be estimated by the estimation algorithm for the law of T_G given C of Theorem 4 but with $\hat{\psi}^*$ replacing $\hat{\psi}$ and with Δ_i replaced by $\Delta_i \tau_i$ in Step c. A consistent estimator for the asymptotic variance of $\hat{\psi}^*$ is provided in Ref 27. Furthermore, in Ref 27, the function $Q_{m,i}$ that minimizes the asymptotic variance of $\hat{\psi}^*$ is derived.

Remark 2: To adjust for missing covariate and treatment data and loss to follow-up (as well as for death as a competing risk), redefine D_i to be the minimum of time to death and the first time m for which complete data on $L_{m,i}$ and $A_{m,i}$ are unavailable, and continue to add the event $D > m$ to each conditioning event B_m discussed in Remark 1. With D so redefined, if Eqs A2.10, A2.15, A2.22, and A2.23 remain true, the methods of this subsection can still be used to estimate ψ_0 and the law of T_G . Since the law of D will have a discrete component at each time m , straightforward modifications of Eq A2.23 and the definition and estimate of $K_i(X_i)$ that incorporate a "discrete" Cox model at each positive integer m are necessary.

Let T and T_G again represent death times as in earlier sections. For the remainder of this subsection, redefine D to be equal to the potential censoring time due to end of follow-up, where D is assumed to be continuous with support on $(0, c_{\max})$, and redefine C to be $c_{\max} - \epsilon$ for some small $\epsilon > 0$.

[Subtracting ϵ from c_{\max} is to guarantee that $K_i(X_i)$ is bounded away from zero.] Then Eq A2.23 represents an additional assumption concerning censoring by end of follow-up that provides additional information for estimating ψ_0 . Specifically, under the suppositions of Theorem 6, there will exist an estimator $\tilde{\psi}^*$ that is more efficient than the estimator $\tilde{\psi}^{(\text{mod})}$ of Section A2.8.²⁷

A2.12. Estimation of Direct Effects Using SNFTMs

Suppose subjects taking prophylaxis for PCP are less likely to take AZT than other subjects because of a concern that prophylaxis therapy may exacerbate AZT-related toxicities. In this case, the net (that is, overall) effect of prophylaxis on survival will underestimate its direct effect. In this section, we consider the estimation of the direct effect of prophylaxis. Heretofore, we have identified the treatment $A(t)$ with prophylaxis and included the AZT dose rate in $L(t)$. The parameters of our SNFTMs have been measures of the overall effect of prophylaxis. In this section, we redefine $A(t) = (A_P(t), A_Z(t))'$ with $A_P(t)$ and $A_Z(t)$, respectively, the prophylaxis and AZT dosage rate at t ; $L(t)$ will no longer include $A_Z(t)$. For simplicity, suppose $A_P(t)$ and $A_Z(t)$ are both dichotomous variables, and $A_P(t) = 1$ if a subject is taking prophylaxis therapy at t and $A_P(t) = 0$ otherwise, with $A_Z(t)$ similarly defined. Let G_1, G_2, G_3 , and G_4 represent, respectively, the regimes (1) always withhold AZT and prophylaxis; (2) always withhold AZT, always take prophylaxis; (3) always take AZT, always withhold prophylaxis; and (4) always take both AZT and prophylaxis. The contrasts (a) $C_{12}(t) = \text{pr}(T_{G_2} > t) - \text{pr}(T_{G_1} > t)$ and (b) $C_{34}(t) = \text{pr}(T_{G_3} > t) - \text{pr}(T_{G_4} > t)$ are, respectively, the direct effect of prophylaxis on survival with AZT (a) always withheld and (b) always taken. Suppose that we have a correctly specified SNFTM such that

$$\begin{aligned} \gamma(t, \bar{L}_m, \bar{a}_m) &= m + (t - m) \exp\{\psi_{0,1} a_{m,P} \\ &\quad + \psi_{0,2} a_{m,Z} + \psi_{0,3} a_{m,P} \bar{L}_m + \psi_{0,4} a_{m,Z} \bar{L}_m\} \end{aligned} \quad (\text{A2.25})$$

where $\bar{a}_m = (\bar{a}_{m,P}, \bar{a}_{m,Z})'$ and, for example, $a_{m,P}$ and \bar{L}_m are prophylaxis dose rate and CD4-count at m . If the assumption of no unmeasured confounders (Eq A2.15) holds, we can estimate $\text{pr}(T_G > t)$ and hence the contrasts $C_{12}(t)$ and $C_{34}(t)$ as in Section A2.10.

Furthermore, if $0 = \psi_{0,1} = \psi_{0,2} = \psi_{0,3} = \psi_{0,4}$, the G -null hypothesis holds by Theorem 3, and thus, $C_{12}(t) = C_{34}(t) = 0$ for all t . Suppose next that $\psi_{0,1} = \psi_{0,3} = \psi_{0,4} = 0$, but $\psi_{0,2} \neq 0$. It follows from Part c of Theorem 3 that $C_{12}(t) = C_{34}(t) = 0$ continues to hold.

More interestingly, suppose that

$$\psi_{0,1} = \psi_{0,3} = 0, \psi_{0,2} \neq 0, \psi_{0,4} \neq 0 \quad (\text{A2.26})$$

so that the blip function $\gamma(t, \bar{L}_m, \bar{a}_m)$ in Eq A2.25 still does not depend on prophylaxis history $\bar{a}_{m,P}$. One might wrongly suspect that if the blip function does not depend on prophylaxis history, then prophylaxis has no direct effect on survival. It is clear, however, from Part b of Theorem 3 that when Eqs A2.25 and A2.26 hold, although $C_{12}(t) = 0$ for all t , $C_{34}(t) \neq 0$ for some t , unless $f[L_{m-1,i} | \bar{L}_{m-1,i}, \bar{A}_{m-1,i}, H_i(\psi_0), T_i > m]$ does not depend on prophylaxis history $\bar{A}_{m-1,i,P}$ for all m .

It follows that, if we were particularly interested in testing the null hypothesis $C_{34}(t) = 0$ for all t , then, in specifying our blip function, we should redefine the baseline (that is, "zero") level of AZT to be when a subject is actively taking

AZT. That is, $A_Z(t) = 0$ if a subject is taking AZT at t and $A_Z(t) = 1$ otherwise. If our redefined blip function does not depend on prophylaxis history, then $C_{34}(t)$ will be zero.

A2.13. Conditions for Confounding

To ensure that Assumption A2.15 holds, investigators are likely to record in $L(t)$ data on a large number of covariates. It may be of interest to reduce the dimensionality of the problem by finding a subset $L^{(1)}(t)$ of $L(t) = (L^{(1)}(t)', L^{(2)}(t)')'$ such that

$$A_m \sqcup T_G | \bar{L}_m^{(1)}, G(\bar{L}_{m-1}^{(1)}), T > m, \text{ for all } m, G \in \mathbf{G}^{(1)} \quad (\text{A2.27})$$

where $\mathbf{G}^{(1)} = \{G \in \mathbf{G}; G(\bar{L}_m) = G(\bar{L}_m^{(1)})\}$ does not depend on $\bar{L}_m^{(2)}$ so that, by Theorem 1, $\text{pr}[T_G > t]$ is identified for $G \in \mathbf{G}^{(1)}$ in the absence of data on $L^{(2)}(t)$. To do so, we use the following theorem. The proof of Part (a) is similar to that of Theorem A.2 and Corollary A.2 of Ref 7. Part (b) is proved in Ref 27.

Theorem 7: (a) If Eq A2.15 and the consistency assumption hold and either

$$A_m \sqcup \bar{L}_m^{(2)} | \bar{A}_{m-1}, \bar{L}_m^{(1)}, T > m, \quad (\text{A2.28})$$

or both

$$\lambda_T[t | \bar{A}(t), \bar{L}(t)] = \lambda_T[t | \bar{A}(t), \bar{L}^{(1)}(t)] \quad (\text{A2.29a})$$

and

$$L_m^{(1)} \sqcup \bar{L}_{m-1}^{(2)} | \bar{A}_{m-1}, \bar{L}_m^{(1)}, T > m, \quad (\text{A2.29b})$$

then Eq A2.27 holds and

$$H \sqcup A_m | \bar{L}_m^{(1)}, \bar{A}_{m-1}, T > m \quad (\text{A2.30})$$

(b) Furthermore, if Eqs A2.15, A2.29a, A2.29b, and the consistency assumption hold, then

$$H \sqcup \bar{L}_m^{(2)} | T > m, \bar{A}_m, \bar{L}_m^{(1)} \quad (\text{A2.31})$$

and $\gamma(t, \bar{L}_m, \bar{a}_m)$ does not depend on $\bar{L}_m^{(2)}$.

If Eq A2.28 or both Eqs A2.29a and A2.29b hold, we say that $L^{(2)}(t)$ is not a confounder for the causal effect of treatment on survival given $L^{(1)}(t)$. If Eq A2.29b is false, Eq A2.15 plus Eq A2.29a fail to imply that $\text{pr}[T_G > t]$ is identified in the absence of data on $L^{(2)}(t)$.

Theorem 7 can be used to show that, given Eq A2.15, if Eq A2.27 holds because Eq A2.28 is known *a priori*, a semiparametric efficient estimator of ψ_0 in the semiparametric model characterized by a SNFTM, Eqs A2.6, A2.10, and A2.28, uses data on $L^{(2)}(t)$ (if available) and does not depend on the known restriction Eq A2.28 even if it is known that $\gamma(t, \bar{L}_m, \bar{a}_m)$ does not depend on $\bar{L}_m^{(2)}$. In contrast, if instead Eqs A2.29a and A2.29b are known *a priori*, a semiparametric efficient estimator of ψ_0 will not depend on $L^{(2)}(t)$.

Write H as $H^{(a^0)}$ and define $H^{(a^0(l))}$ and $H^{(a)}$ just like $H^{(a^0)}$ except with $\gamma(t, \bar{L}_m^{(1)}, \bar{a}_m)$ and $\gamma(t, \bar{a}_m)$ replacing $\gamma(t, \bar{L}_m, \bar{a}_m)$ where (1) $\gamma(t, \bar{L}_m^{(1)}, \bar{a}_m)$ and (2) $\gamma(t, \bar{a}_m)$ are defined by Eq A2.18 but with (1) $\bar{L}_m^{(1)}$ replacing \bar{L}_m and (2) \bar{L}_m deleted. If $\gamma(t, \bar{L}_m, \bar{a}_m)$ does not depend on $\bar{L}_m^{(2)}$, $H^{(a^0)} = H^{(a^0(l))}$. It follows easily from Theorem 2, Theorem 7, and Corollary 1 that even if $H^{(a^0)} \neq H^{(a^0(l))}$, we have:

Theorem 8: Under the suppositions of Theorem 7a, $H^{(a^0(l))} \sqcup A_m | \bar{L}_m^{(1)}, \bar{A}_{m-1}, T > m$.

A2.14. Estimation in the Absence of Confounding and the Robins-Tsiatis Rank Estimator

If, for all m and \bar{a} defined on $(0, \infty)$, with \bar{a}_{m-1} the initial segment of \bar{a}

$$A_m \sqcup T_{G=(\bar{a})} | T > m, \bar{A}_{m-1} = \bar{a}_{m-1}, \quad (\text{A2.32})$$

we say there exists no confounding for the effect of treatment on survival. By specializing our previous results to this case, we can prove:

Theorem 9: If Eq A2.32 and the consistency assumption hold, (a) $\text{pr}[T_{G=(\bar{a})} > t] = \exp[- \int_0^t \lambda_T[u | \bar{a}(u)] du]$; (b) $H^{(a)} \equiv H^{(a)}(T)$ with $H^{(a)}(t) = S_0^{-1}\{S(t, \bar{A}(t))\}$ where $S(t, \bar{a}, t) = \exp\{- \int_0^t \lambda_T[u | \bar{a}(u)]\}$, $S_0(t) = S(t, \bar{a}, t = 0)$, and $S_0^{-1}(t) = u$ if $S_0(u) = t$; (c) $A_m \sqcup H^{(a)} | T > m, \bar{A}_{m-1}$; (d) $\lambda_{H^{(a)}}[u | \bar{A}| H^{(a), -1}(u)] = \lambda_{H^{(a)}}(u)$, where $H^{(a), -1}(u) = t$ if $H^{(a)}(t) = u$; (e)

$$\lambda_{H^{(a)}}[u | \bar{A}| H^{(a), -1}(u, \psi_0)] = \lambda_{H^{(a)}}(u), \quad (\text{A2.33})$$

if $H^{(a), -1}(u, \psi_0)$ is based on a correctly specified SNFTM $\gamma^*(t, \bar{a}_m; \psi)$ for $\gamma(t, \bar{a}_m)$ and hence $H^{(a), -1}(u, \psi_0) = H^{(a), -1}(u)$.

Part e of Theorem 9 allows us to relate the results obtained in Ref 24 and this paper to those obtained in Ref 29. Suppose, for the moment, that there is no censoring. Under the supposition of Theorem 9, semiparametric estimation of the parameter ψ_0 of $\gamma^*(t, \bar{a}_m, \psi_0)$ can be based on the class of rank estimators proposed by Robins and Tsiatis²⁹ without needing to model either $f[A_m | \bar{A}_{m-1}, T > m]$ or $f_{H^{(a)}}(h)$ since Eq A2.33 is precisely the accelerated time model defined by Eq 2.3 of Ref 29. However, (a) if Eq A2.32 is true because Eq A2.15 and $A_m \sqcup \bar{L}_m | T > m, \bar{A}_{m-1}$ are known to hold, and (b) $\gamma(t, \bar{L}_m, \bar{a}_m)$ is known to equal $\gamma(t, \bar{a}_m)$ so that $H^{(a^0)} = H^{(a)}$, then, although the optimal Robins-Tsiatis rank estimator is semiparametric efficient in the absence of data on $L(t)$, the semiparametric efficient estimator given data on $L(t)$ is $\tilde{\psi}(q_{opt})$ of Section A2.7. In contrast, if Eq A2.32 is true because it is known that $\lambda_T[t | \bar{A}(t), \bar{L}(t)] = \lambda_T[t | \bar{A}(t)]$, $\tilde{\psi}(q_{opt})$ is inefficient and the semiparametric efficient estimator of ψ_0 is the optimal Robins-Tsiatis estimator.

In the presence of censoring by C, the Robins-Tsiatis rank estimator will be consistent for ψ_0 in the presence of independent censoring, that is,

$$\lambda_T[u | \bar{a}(u), C > u] = \lambda_T[u | \bar{a}(u), C = t] = \lambda_T[u | \bar{a}(u)] \quad (\text{A2.34})$$

for $t \leq u$, since Eq A2.32 plus Eq A2.34 implies Eq 2.4 of Ref 29. Under Eqs A2.32 and A2.34, the Kaplan-Meier estimator applied to the data $\{H_i^{(a)}(\tilde{\psi}), \Delta_i\}$, $i = 1, \dots, n$ will provide a consistent estimator of $\text{pr}[H^{(a)} > t]$ and, thus, of $\text{pr}[T_{G=(0)} > t]$ if $\tilde{\psi}$ is consistent for ψ_0 .

A2.15. Curative Therapies, Biological Theories, and the Specification of Blip Functions

In this section, we continue to assume that $T_{G=(0)}$ has a proper distribution, that is, has no mass at infinity. In contrast, we shall allow T_G to have mass p at infinity. This would be appropriate if T and T_G represented death from AIDS (in the absence of competing causes of death) and regime G cured a fraction p of AIDS patients. As an example, consider the blip function

$$\gamma(t, \bar{L}_m, \bar{a}_m) = \exp(\psi_0 a_m)(t - m) + m \quad (\text{A2.35})$$

For $\bar{a} \equiv \{a(t) = d; 0 < t < \infty\}$, it is easy to show that $\rho(x, \bar{a}) =$

$\infty \Leftrightarrow x > \{\exp(-\psi_0 d) - 1\}^{-1}$. Hence, if Eq A2.15 holds, by Theorem 3c, $\text{pr}[T_{G=(\bar{a})} = \infty]$ equals $\text{pr}[T_{G=(0)} > \{\exp(-\psi_0 d) - 1\}^{-1}]$. In contrast, for the blip model (Eq A2.21a), $\rho(x, \bar{a})$ is always finite and thus cure is not possible, that is, $\text{pr}[T_{G=(\bar{a})} = \infty] = 0$. Thus, if an investigator's biological understanding suggests that a particular therapy, say PCP prophylaxis, cannot cure a patient of AIDS, it is important not to use a blip model such as Eq A2.35 to analyze the data. It is clear from the above discussion that it is less than straightforward to deduce the mathematical restrictions on a blip function implied by a particular biological theory. Robins (unpublished data) derives the restrictions placed by various biological theories on the form of the blip function $\gamma(t, \bar{l}_m, \bar{a}_m)$ by defining "instantaneous" or "continuous time" blip functions that model the effect of a truly instantaneous blip of treatment on survival. These instantaneous blip SNFTMs also allow the results in this Appendix to be extended to incorporate jumps in the treatment and covariates process in continuous time.

A2.16. Structural Nested Models for Non-Failure Time Outcomes

In this section, we briefly consider the estimation of the effect of treatment on the evolution of a continuous outcome variable Y_m such as CD4-count. Let \bar{Y}_M and $\bar{Y}_{M,G}$ be a subject's actual history and counterfactual history under regime G of a continuous component of Y_m of L_m in a study in which, for each subject, L_m was recorded at times $(0, 1, \dots, M)$. Assume that the consistency assumption

$$G(\bar{L}_{m-1}) = \bar{A}_{m-1} \text{ implies } \bar{Y}_m = \bar{Y}_{m,G} \quad (\text{A2.36})$$

holds.

For $\bar{x}_M \in R^{M+1}$, let $\gamma(\bar{x}_M, \bar{l}_m, \bar{a}_m)$ taking values in R^{M+1} be a function such that conditional on (\bar{L}_m, \bar{A}_m) , $\gamma(\bar{Y}_{M,G=(\bar{A}_m, 0)}, \bar{L}_m, \bar{A}_m)$ has the same distribution as $\bar{Y}_{M,G=(\bar{A}_{m-1}, 0)}$. If $\gamma(\bar{x}_M, \bar{l}_m, \bar{a}_m) = \bar{z}_M$, then, by the consistency assumption, $\bar{x}_m = \bar{z}_m$, and, if $a_m = 0$, $\bar{x}_M = \bar{z}_M$. For fixed \bar{l}_m, \bar{a}_m , $\gamma(\bar{x}_M, \bar{l}_m, \bar{a}_m)$ can and will always be chosen to be one to one with a strictly positive Jacobian determinant. Let H be the cumulative blip-down variable and $\rho(\bar{x}_M, \bar{l}_m, \bar{a}_m)$ be the recursive blip-up func-

tion redefined as follows. $H = H_0$ where $H_{M-1} = \gamma(\bar{Y}_M, \bar{L}_{M-1}, \bar{A}_{M-1})$, and $H_m = \gamma(H_{m+1}, \bar{L}_m, \bar{A}_m)$ for $0 \leq m < M - 1$. Let $H(\psi)$ be defined like H but based on a structural nested distribution model $\gamma^*(\bar{x}_M, \bar{l}_m, \bar{a}_m, \psi)$ with true value ψ_0 satisfying $\gamma^*(\bar{x}_M, \bar{l}_m, \bar{a}_m, \psi_0) = \gamma(\bar{x}_M, \bar{l}_m, \bar{a}_m)$. $\rho(\bar{x}_M, \bar{l}_0, \bar{a}_0) = \gamma^{-1}(\bar{x}_M, \bar{l}_0, \bar{a}_0)$ and $\rho(\bar{x}_M, \bar{l}_m, \bar{a}_m) = \gamma^{-1}\{\rho(\bar{x}_M, \bar{l}_{m-1}, \bar{a}_{m-1}), \bar{l}_m, \bar{a}_m\}$. $\rho(\bar{x}_M, \bar{l}, \bar{a})$ equals $\rho(\bar{x}_M, \bar{l}_{M-1}, \bar{a}_{M-1})$.

For the moment, assume that no death or loss to follow-up occurs, so T exceeds time M with probability one. It can be shown that H_m and $\bar{Y}_{M,G=(\bar{A}_{m-1}, 0)}$ have the same distribution given \bar{L}_m, \bar{A}_m . Furthermore, if the assumption (Eq A2.15) of no unmeasured confounders holds with $\bar{Y}_{M,G}$ in place of T_G , and then Theorems 3 and 4 hold with $\bar{Y}_{M,G}$ in place of T_G , $\bar{Y}_{M,v,G}$ in place of $t_{v,G}$ and Step 5 of Theorem 3b replaced by the following Step 5'.

Step 5': For $m = 1, \dots, M - 1$, recursively draw $\ell_{m,v}$ from $f[\ell_m | \bar{l}_{m-1,v}, G(\bar{l}_{m-1,v}), h_v, T > m]$; then, set $\bar{y}_{m,v,G}$ equal to $\rho[h_v, \bar{l}_{m-1,v}, G(\bar{l}_{m-1,v})]$; increment v by 1 and return to Step 2.

Note, $\bar{y}_{m,v}$ is a deterministic function of $(\bar{l}_{m-1,v}, G(\bar{l}_{m-1,v}), h_v)$, since it is the $m + 1^{\text{st}}$ component of $\rho[h_v, \bar{l}_{m-1,v}, G(\bar{l}_{m-1,v})]$. Thus, it will only be necessary to specify a model for the density of the components of ℓ_m other than y_m . Also, note that there is no censoring by C , so $\Delta = 1$ for all subjects.

Furthermore, to allow for loss to follow-up and missing treatment or covariate data, we can use the methods of Section A2.11 with D_i as defined in Remark 2 of that section.

Rather than specifying a model for the entire distribution transformation function $\gamma(\bar{x}_M, \bar{l}_m, \bar{a}_m)$, an investigator may find it easier to specify a model only for the effect of a brief blip of treatment on the mean of $\bar{Y}_{M,G=(\bar{A}_{m-1}, 0)}$, that is, a structural nested mean model $\gamma^{MN,*}(\bar{L}_m, \bar{A}_m, \psi)$ for $\gamma^{MN}(\bar{L}_m, \bar{A}_m) \equiv E[\bar{Y}_{M,G=(\bar{A}_m, 0)} - \bar{Y}_{M,G=(\bar{A}_{m-1}, 0)} | \bar{L}_m, \bar{A}_m]$. If so, one can estimate $E[\bar{Y}_{M,G}]$ for $G \in G$ using the methods described in Ref 3. The generalized estimating equation approach of Zeger and Liang³⁰ is not a competitor since, at best, it can only be used to estimate the quantities $E[Y_m | \bar{a}_{m-1}]$ and $E[Y_m | \bar{a}_{m-1}, \bar{l}_{m-1}]$, neither of which will equal the counterfactual means $E[Y_{m,G=(\bar{a}_{m-1}, 0)}]$ of causal interest when there exist time-dependent confounders.