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## Estimation and extrapolation of optimal treatment and testing strategies

3

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### SUMMARY

We review recent developments in the estimation of an optimal treatment strategy or regime from longitudinal data collected in an observational study. We also propose novel methods for using the data obtained from an observational database in one health-care system to determine the optimal treatment regime for biologically similar subjects in a second health-care system when, for cultural, logistical, and financial reasons, the two health-care systems differ (and will continue to differ) in the frequency of, and reasons for, both laboratory tests and physician visits. Finally, we propose a novel method for estimating the optimal timing of expensive and/or painful diagnostic or prognostic tests. Diagnostic or prognostic tests are only useful in so far as they help a physician to determine the optimal dosing strategy, by providing information on both the current health state and the prognosis of a patient because, in contrast to drug therapies, these tests have no direct causal effect on disease progression. Our new method explicitly incorporates this no direct effect restriction. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS: dynamic regime; causal inference; marginal structural model; value of information

### 1. INTRODUCTION

The goal of this paper is to describe the recent developments in the estimation of an optimal treatment strategy or regime from longitudinal data collected in an observational study. Estimation of the optimal time for an asymptomatic HIV-infected subject to start highly active retroviral therapy (HAART) will serve as a paradigmatic example. The following is a loose approximation

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to the current International Aids Society (IAS) ‘when to start’ recommendations:

- 1
- 3 • If plasma HIV RNA exceeds 150 000 copies/mL and CD4 decline has exceeded 100 cells/ $\mu$ L per year, start HAART when the CD4 first falls below 500.
- 5 • If HIV RNA is persistently low ( $<10\,000$  copies/mL) and CD4 decline is less than 50 cells/ $\mu$ L per year, start when the CD4 first falls below 200.
- Otherwise, start when the CD4 count first drops below 350.

7 The recommended strategy is an example of a deterministic dynamic treatment regime, that is, a sequential decision strategy in which the treatment to be given at time  $t$  is a deterministic function of the subject’s measured time-dependent covariate (and possibly treatment history) up to  $t$ .

9 Some of the biological considerations and empirical data on which the IAS recommendations were based are as follows. The current understanding of the biology of the effect of HAART on HIV infection is not sufficient to determine the optimal time to start therapy because early initiation of HAART has both risks and benefits; early initiation can prevent viral-induced decline of, and permanent damage to, the immune system, but also allows more time for drug resistance and side effects to develop. Thus, the ‘when to start’ question must be addressed with empirical data. Randomized trial data have shown that for asymptomatic subjects with CD4 count  $<200$ , it is better to initiate HAART than to delay further. However, current recommendations for subjects with CD4 counts exceeding 200, such as the above IAS recommendations, are based solely on the analyses of observational data. Unfortunately, we show in Section 2 that the appropriate use of observational data to determine ‘when to start’ poses a nontrivial methodologic challenge. Specifically, we provide a somewhat simplified description of one of the observational analyses [1] that formed the basis of the 2004 IAS recommendations and show that the published analysis has potential for severe bias.

15 In Section 3, we discuss assumptions under which it is possible to use observational data to estimate the optimal treatment regime in a class of prespecified, logistically feasible dynamic regimes and describe an analytic approach based on dynamic marginal structural models (MSMs), which recovers the optimal regime in the class. Dynamic MSMs were introduced by Orellana *et al.* [2] and independently by Van der Laan [3]. In Section 4 we give a more precise mathematical formulation of the problem, the identifying assumptions, and our analytic methodology.

17 In Section 5, we describe an alternative approach based on doubly robust  $g$ -estimation of optimal regime structural nested mean models (SNMMs) that can optimize over a much bigger class of candidate regimes than the class that can be optimized over when using dynamic MSMs. This method was introduced by Robins [4] as a generalization of a closely related approach by Murphy [5]. See Moodie *et al.* [6] for additional discussion.  $G$ -estimation of optimal regime SNMMs is a robust twist on the classic method of dynamic programming (backward induction) for sequential decision making under uncertainty. Because optimal regime SNMM methods generally optimize over a larger class of regimes than do dynamic MSM methods, the optimal treatment strategy estimated using an optimal regime SNMM should generally have a higher expected utility than the optimal strategy estimated with a dynamic MSM. However, the estimated optimal decision strategy based on optimal regime SNMMs may be such a complicated function of past covariate history that in many health-care settings, particularly those found in developing countries, it may be logistically difficult or impossible to implement. In that case, dynamic MSM would be preferable. An example of the complex estimated optimal regimes that could be produced by fitting an optimal regime SNMM would be the following: Begin HAART the first time that the following quantity

1 exceeds zero:

3  $17.2 - 4.1 \times \text{current CD4 count} - 3.2 \times \text{the rate of decline of CD4} + 5.6 \times \text{the square of the rate of}$   
 decline of CD4  $+ 2.1 \times \text{the current CD4 count} \times \text{the rate of decline CD4} - 4.6 \times \text{the rate of decline}$   
 of CD4  $\times \text{the square of the current HIV RNA}$ .

5 This regime would be logistically impossible to implement in settings where, because of poor  
 record keeping or fragmented patient care, complete data on past CD4-count measurements do not  
 7 exist.

9 In Section 6, we develop novel methods to use data obtained from an observational database in  
 one health-care system to determine the optimal treatment regime for biologically similar subjects  
 in a second health-care system when, for cultural, logistical, and financial reasons, the two health-  
 11 care systems differ (and will continue to differ) in the frequency of, and reasons for, laboratory tests  
 of diagnostic or prognostic value. In Section 7, we derive conditions under which the determination  
 13 of the optimal treatment regime remains possible even though the observation processes (i.e. visit  
 processes) in both health-care systems are nonignorable, provide a method of estimation under  
 15 these conditions, and discuss the substantive plausibility of the derived conditions.

17 In Section 6, we also develop a novel method to estimate the optimal timing of expensive and/or  
 painful diagnostic tests. Diagnostic tests, in contrast to drug therapies, have no direct causal effect  
 on disease progression. That is, tests are only useful in so far as they help a physician to determine  
 19 the optimal dosing strategy, by providing information on both the current health state and the  
 prognosis of a patient. Our new method explicitly incorporates this no direct effect restriction.

## 21 2. POTENTIAL BIASES IN OBSERVATIONAL ANALYSES

A greatly simplified version of the design and analysis reported in Palella *et al.* [1] can be described  
 23 as follows. Asymptomatic treatment-naïve HIV-infected subjects were enrolled on January 1, 1996  
 and their CD4 count was measured. Subjects with CD4 counts from 325 to 350 were enrolled and  
 25 followed until the minimum of time to death and clinical AIDS, with time measured as time since  
 enrollment. Subjects with CD4 count above 300 at the time of HAART initiation were designated  
 27 as group 1, and those with CD4 count below 200 at the time of HAART initiation were designated  
 as group 2. Subjects who either never started HAART or started it when their CD4 count was  
 29 between 200 and 300 were excluded from the analysis. Subjects in groups 1 and 2 were compared  
 using a time-independent Cox proportional hazards model with an indicator variable for the group  
 31 as the covariate and with time measured as time since enrollment.

Before we critique this approach, we begin by observing that it is better than a common  
 33 alternative approach in which time in the Cox model is not time since enrollment on January 1,  
 1996 but time since initiation of HAART. Under this alternative approach, the survival time of  
 35 those starting with CD4 > 300 (group 1) will be better than the survival time of those starting  
 when CD4 < 200 (group 2) even under the null hypothesis that HAART has no causal effect on  
 37 any subject's time to clinical AIDS or death. In fact, this is an instance of classic lead-time bias.  
 Clinical AIDS or death rarely occurs before the CD4 count drops below 200. The time it takes a  
 39 group 1 subject's CD4 count to fall from 300 to 200 is the lead time. We, therefore, see that a  
 recommendation based on this alternative analysis would incorrectly recommend to 'start HAART  
 41 when CD4 is above 300' when, indeed, HAART has no causal effect.

The approach based on time since enrollment also has the potential for severe bias when  
 43 prescribing trends' change with calendar time. To make clear why this is so, we consider an example

1 with extreme trends. Suppose that during 1996, no subject with a CD4 above 300 was treated with  
 3 HAART because physicians were worried about using a newly introduced treatment regimen on  
 5 patients who were doing reasonably well. However, all subjects with CD4 counts falling below  
 7 200 were treated. Suppose that during 1997 every subject with a CD4 below 350 was treated  
 9 with HAART because doctors had come to believe that HAART was beneficial for most patients.  
 11 Subjects who started HAART when their CD4 fell below 200 constitute a selected subgroup of  
 13 very sick subjects with rapid CD4-count decline. Many of these subjects would probably have  
 15 died before the end of 1996. In contrast, all subjects who started HAART when their CD4 count  
 17 was above 300 must have started during 1997 and, consequently, must have had (i) at least one  
 19 year of survival and (ii) a slow rate of CD4 decline, an indication of good health.

11 It follows that under the null hypothesis that HAART has no causal effect on any subject's time to  
 13 clinical AIDS or death, the survival time in group 1 will be better than the survival time in group 2  
 15 even under the null hypothesis that HAART has no causal effect on any subject's time to clinical  
 17 AIDS or death, so a recommendation based on this analysis will also incorrectly recommend to  
 19 'start HAART when CD4 is above 300'. The reason for this bias (which is sometimes referred to  
 as 'immortal person time' bias) is that starting treatment with a CD4 above 300 is a surrogate for  
 slowly declining counts and, in fact, for survival itself. In fact, the extreme prescribing trends of the  
 example are but an exaggeration of the actual prescribing trends in 1996–1997, so the possibility  
 of bias is real.

19 In fact, the approach based on time since enrollment can result in bias even in the absence of  
 21 prescribing trends. Because subjects who either never start therapy or start it between 200 and 300  
 23 are dropped from the analysis, a subject's group status is determined by events that occur after  
 start of follow-up and are prognostic for survival. Below we show how to eliminate this type of bias.

### 3. APPROPRIATE OBSERVATIONAL ANALYSES

#### 3.1. *A randomized clinical trial comparing two treatment strategies*

25 Suppose we wanted to compare two simple strategies or regimes: strategy 1: 'start HAART when  
 27 the CD4 count first falls below 500' *versus* strategy 2: 'start HAART when CD4 count first falls  
 29 below 200' among the subset of people who at the time of diagnosis have CD4 count above 500.  
 31 If we had the resources to conduct a randomized trial, we might proceed as follows. We enroll,  
 33 at the time of HIV diagnosis, asymptomatic HIV-infected subjects with CD4 counts greater than  
 35 500 at diagnosis with HIV. We do not give HAART while a subject's CD4 count is above 500. We  
 37 designate as start of follow-up (i.e time 0) the time when a subject's CD4 count first falls below  
 500 and at that time we randomize each subject to either 'start HAART when the CD4 count  
 first falls below 500' (group 1) or to 'start HAART when the CD4 count first falls below 200'  
 (group 2). We compare the survival of the two groups using a Cox proportional hazards model  
 for the minimum of time to clinical AIDS or death with an indicator variable for group as the  
 covariate and with time measured as time since start of follow-up (i.e. randomization). As such a  
 trial has not been conducted, we must rely on observational data.

#### 3.2. *Observational analogue of a randomized trial*

39 Our goal is to implement a design and analysis plan for observational data, which is the observa-  
 41 tional analogue of the above randomized trial. We follow an approach similar to the one described

1 in Hernán *et al.* [7]. As in the randomized trial, we find asymptomatic HIV-infected subjects with  
2 CD4 counts greater than 500 at the time of diagnosis. Suppose, for now, that, in our data, no  
3 subject with a CD4 count exceeding 500 initiates HAART. Then we designate as the subject's  
4 start of follow-up time (i.e. time 0) the time at which the subject's CD4 count first falls below  
5 500. Every subject who initiates HAART at time 0 is assigned to group 1. All subjects who do  
6 not start HAART at time 0 are assigned to group 2. The two groups are then compared using  
7 a time-independent Cox proportional hazards model with an indicator variable for group as a  
8 covariate and with time measured as time since start of follow-up. Because treatment was not  
9 randomized, we must also adjust for potential baseline confounding factors (measured at or before  
10 time 0) such as HIV RNA, calendar date of entry, pre-baseline rate of CD4-cell-count decline, and  
11 various higher-order interactions. We can adjust either by matching or stratifying on these baseline  
12 factors or by including them as covariates in the Cox model.

13 By definition, all group 1 subjects successfully follow the protocol 'start HAART when the  
14 CD4 count first falls below 200'. However, any group 2 patient who either (i) begins HAART at a  
15 time  $t$  at which his CD4 count still exceeds 200 or (ii) fails to start HAART at the first time that  
16 his CD4 count falls below 200 must be regarded as censored at time  $t$  because he has failed to  
17 follow the group 2 protocol we wish to test— 'start HAART when the CD4 count first falls below  
18 200'. In our experience, essentially all untreated subjects whose CD4 count falls below 200 are  
19 started on HAART, so only censoring for reason (i) remains an issue.

20 Now, in a Cox model analysis, censoring is ordinarily handled simply by excluding a subject  
21 censored at  $t$  from all risk sets subsequent to  $t$ . However, this standard approach is statistically valid  
22 only if, conditional on the baseline covariates in the model, censoring and failure (the minimum of  
23 time to clinical AIDS or death) are independent. However, as we now argue, censoring for reason  
24 (i) is dependent.

25 To understand why, consider all group 2 subjects with CD4 cell count still greater than  
26 200 cells/mL at time  $t$  after entry. Conditional on the baseline covariates, the subgroup who initi-  
27 ates HAART (and thus becomes censored) at  $t$  will have on average faster CD4-cell-count decline  
28 from 0 to  $t$  and higher HIV RNA at  $t$  than those who do not initiate HAART (and thus remain  
29 uncensored) at time  $t$ . This reflects the fact that physicians preferentially prescribe HAART to  
30 patients doing poorly. Thus, within any stratum of baseline covariates, individuals censored at  $t$   
31 will have worse prognosis than those who remain uncensored.

32 We conclude that a standard Cox analysis (which assumes independent censoring) will show  
33 the failure rate of the group 2 subjects artificially lowered compared with what would have been  
34 seen in the above ideal randomized trial in which all group 2 subjects wait until a CD4 of 200 to  
35 start. Thus, if in truth, it is better to start at 500 than at 200, a standard Cox analysis may fail to  
36 detect this fact due to selection bias.

37 We can try to correct for bias due to dependent censoring by inverse probability of censoring  
38 weighting (IPCW) of each subject in each risk set. That is, each group 2 subject in a risk set  
39 at time  $u$  who remains uncensored at  $u$  is given a weight equal to the inverse of the conditional  
40 probability of his having remained uncensored up to time  $u$ , given both his baseline covariates and  
41 his history up to  $u$  of post-baseline time-dependent prognostic covariates (such as HIV RNA and  
42 CD4 cell count). Specifically, suppose a group 2 subject at risk and uncensored at  $u$  with a CD4  
43 count falling linearly from 500 to 250 from 0 to  $u$  has a probability of  $\frac{1}{4}$  that he would not have  
44 started treatment by  $u$ . Then he counts for four people: himself and the three other similar people,  
45 i.e. with the same rate of CD4-count decline, who did start therapy. That is, his weight is 4 in the  
risk set at  $u$ . On the other hand, suppose that an uncensored subject with a CD4 falling from 500

1 to 300 from 0 to  $u$  has probability of  $\frac{1}{2}$  of having remained uncensored. Then, he counts for only  
2 persons with a similar CD4-count decline rate.

3 Formally, let  $C$  be the discrete random variable encoding time to censoring measured in weeks.  
4 Let  $\text{pr}[C \neq j | C > j - 1, \text{Past}(j)]$  be the discrete hazard of remaining uncensored at week  $j$  given all  
5 the past measured (time-dependent and baseline) covariate history  $\text{Past}(j)$ , where we include the  
6 indicator  $I(T > j)$  of survival in  $\text{Past}(j)$  (that is,  $I(T > j) = 1$  if the minimum  $T$  of time to AIDS  
7 or death exceeds  $j$  and is zero otherwise). Then, to estimate the parameters of the Cox model for  
8 failure, we compute the usual partial likelihood estimator except that for each subject in a risk set  
9 at time  $u$ , we multiply his contribution to the risk set by an estimate  $\widehat{W}(u)$  of

$$W(u) = 1 \bigg/ \prod_{j=1}^u \text{pr}[C \neq j | C > j - 1, \text{Past}(j)] \tag{1}$$

11 the inverse of the probability of having remained uncensored to time  $u$ . We refer to such a procedure  
12 as an IPCW-adjusted Cox analysis.

13 In our discussion, it will prove useful to have an alternative expression for the weight  
14  $W(u)$ . Let  $A(t) = 1$  if a subject has started HAART by week  $t$  and  $A(t) = 0$  otherwise.  
15 Let  $\bar{A}(k-1) = \{A(0), A(1), \dots, A(k-1)\}$  be treatment history through  $k-1$ . Then define  
16  $f[a(k) | \bar{a}(k-1), \text{past}(k)] = \text{pr}(A(k) = a(k) | \bar{A}(k-1) = \bar{a}(k-1), \text{Past}(k) = \text{past}(k))$ . Define

$$W(u) = 1 \bigg/ \prod_{k=1}^u f[A(k) | \bar{A}(k-1), \text{Past}(k)] \tag{2}$$

17 where, for any subject,  $f[A(k) | \bar{A}(k-1), \text{Past}(k)]$  is the density  $f[a(k) | \bar{a}(k-1), \text{past}(k)]$  evaluated  
18 at the subject's observed data. The denominator of  $W(u)$  is informally the probability that a subject  
19 had his observed HAART history through  $u$ . Note, by definition, if  $A(k-1) = 1$ , then  $A(k) = 1$  so  
20  $f[A(k) | \bar{A}(k-1), \text{Past}(k-1)] = 1$  unless past HAART history is identically 0, i.e.  $\bar{A}(k-1) = 0$ . For  
21 uncensored subjects in a risk set at  $u$ , this alternative definition of  $W(u)$  agrees with the previous  
22 definition. To see why, note that all group 1 subjects started HAART at time 0 so  $A(0) = 1$  and  
23 thus  $W(u) = 1$ . Further, by definition, any group 2 subject who is uncensored at  $u$  must have an  
24 observed HAART history that agrees with that specified by the regime 'start HAART when CD4  
25 count first falls below 200.' Thus, the probability that the subjects remained uncensored is precisely  
26 the probability that the subjects had their observed HAART history.

Suppose we specify the discrete time logistic model

$$\text{logit}\{\text{pr}(A(k) = 1 | \bar{A}(k-1) = 0, \text{Past}(k), I(T > k) = 1)\} = \alpha^T Q(k)$$

28 where  $Q(k)^T = (Q_1(k), Q_2(k), Q_3(k))$ ,  $Q_1(k)$  is HIV RNA at week  $k$ ,  $Q_2(k)$  is the lowest recorded  
29 CD4 count up to  $k$ , and  $Q_3(k)$  is the rate of CD4-count decline from 0 to  $k$ . Let

$$\widehat{W}(u) = 1 \bigg/ \prod_{k=1}^u f[A(k) | \bar{A}(k-1), \text{Past}(k); \widehat{\alpha}]$$

33 where  $\widehat{\alpha}$  is the partial maximum likelihood estimator (MLE) of  $\alpha$ . For uncensored subjects  
34 at risk at  $u$ ,  $\widehat{W}(u) = 1$  for all group 1 subjects since  $A(0) = 1$ , while for uncensored group 2  
35 subjects,  $f[A(k) | \bar{A}(k-1), \text{Past}(k); \widehat{\alpha}] = 1$  if  $A(k-1) = 1$ ,  $f[A(k) | \bar{A}(k-1), \text{Past}(k); \widehat{\alpha}] = e^{\widehat{\alpha}^T Q(k)} / \{1 +$   
36  $e^{\widehat{\alpha}^T Q(k)}\}$  if  $Q_2(k) < 200$  and  $A(k-1) = 0$  (since then  $A(k) = 1$ ), and  $f[A(k) | \bar{A}(k-1), \text{Past}(k); \widehat{\alpha}] =$   
37  $1 / \{1 + e^{\widehat{\alpha}^T Q(k)}\}$  if  $Q_2(k) \geq 200$  and  $A(k-1) = 0$  (since then  $A(k) = 0$ ).

1 This IPCW-adjusted Cox analysis produces valid inferences analogous to those that would be  
 3 found with our idealized randomized trial if (a) the Cox model for failure and the logistic model for  
 5 HAART initiation are correctly specified, (b) there is no residual confounding by any unmeasured  
 7 baseline covariates, and (c)  $\text{Past}(j)$  contains sufficient time-dependent and baseline covariates so  
 that censoring and failure are conditionally independent at each  $j$  within group 2. In contrast to  
 assumption (a), assumptions (b) and (c) are not empirically testable. Assumptions (b) and (c) can be  
 incorporated in the single assumption of no unmeasured confounders or sequential randomization  
 that specifies

$$9 \quad T_x \Pi A(t) | \bar{A}(t-1) = 0, \text{Past}(t), \quad t = 0, 1, \dots \quad (3)$$

for  $x = 200$  and  $500$ , where  $T_x$  is a subject's potential or counterfactual failure time had the subject  
 11 followed the dynamic regime in which HAART is initiated the first time the subject's measured  
 CD4 count falls below  $x$ . Here  $\text{Past}(0)$  are the baseline covariates.

13 Henceforth, we suppose that there exist subjects in our data set who begin HAART before  
 their CD4 count drops to 500. The preceding IPCW-adjusted Cox analysis can be easily modified  
 15 to account for this additional complication. Specifically, we proceed as above except with the  
 following modifications: (i) all subjects who initiate HAART with a CD4 count exceeding 500 are  
 17 excluded from the Cox model analysis comparing groups 1 and 2 and (ii) each subject included  
 in the Cox analysis who is in a risk set at  $u$  receives a weight  $\{\widehat{W}(u)\widehat{W}^*\}$ , where  $\widehat{W}(u)$  is as  
 19 previously defined and  $\widehat{W}^*$  is an estimate of the inverse  $W^*$  of the conditional probability that  
 a subject did not initiate therapy during the interval from time of diagnosis of infection with  
 21 HIV to the time his CD4 count was first observed to fall below 500. That is, if we let  $X_{500}$   
 denote the time a subject's CD4 count first fell below 500 with time measured as time since  
 23 HIV diagnosis,  $W^* = 1 / \prod_{t=1}^{X_{500}} f[A(t) | \bar{A}(t-1), \text{Past}(t)]$  if  $X_{500} \neq 0$  and  $W^* = 1$  if  $X_{500} = 0$ . As an  
 example, consider a subject who started HAART the first time his CD4 fell below 500 and so is  
 25 in group 1 with  $\widehat{W}(u) = 1$ . Suppose the subject's estimated probability of having started HAART  
 before his CD4 fell to 500 was  $\frac{1}{2}$ . Then  $\widehat{W}^* = 2$  and the subject is given a weight of 2 whenever  
 27 he contributes to a risk set.

In contrast with our IPCW analyses, if one were to add post-baseline CD4 count and HIV RNA  
 29 as a time-dependent covariate in the Cox model for failure (rather than using IPCW weights), bias  
 due to dependent censoring would not be eliminated; furthermore, new bias could be introduced  
 31 from regression adjustment for a post-baseline variable if that variable was affected by treatment  
 group. In summary, correction for dependent censoring can be accomplished by using post-baseline  
 33 time-dependent covariates, not as covariates in a time-dependent Cox model, but rather to estimate  
 the IPC weights for a time-independent Cox model.

35 *3.2.1. Data analysis.* Hernán *et al.* [7] conducted an analysis of the 2344 HIV-infected subjects  
 included in the French Hospital Database on HIV (FHDH) [8] who had their first CD4 cell  
 37 count measurement below 500 cells/mL between January 1, 1996 and June 30, 2004 while being  
 treatment-naive. They followed these subjects from their first CD4 cell count measurement below  
 39 500 cells/mL (baseline) until a diagnosis of AIDS, death, or June 2004, whichever occurred earlier.  
 Data on HAART use, as well as on time-dependent covariates (e.g. CD4 cell count), were recorded  
 41 throughout the follow-up. Groups 1 and 2 were defined as in the previous subsection except that  
 they followed subjects from entry into the FHDH cohort because time of diagnosis was often not  
 43 recorded in the database. There were 131 subjects in group 1 and 2217 in group 2. Six hundred and

1 fifty subjects in group 2 were censored from starting HAART when their CD4 count still exceeded  
200 and five were censored for failing to start HAART the first time their CD4 was below 200.

3 A Cox analysis found a hazard ratio of 0.9 (95 per cent confidence interval: 0.4, 1.8) comparing  
4 groups 1 and 2 with a standard Cox analysis that adjusted for baseline potential confounders but  
5 assumed independent censoring. In contrast an IPCW Cox analysis found a hazard ratio of 0.5  
6 (95 per cent confidence interval: 0.2, 1.1), so as expected on theoretical grounds, the standard Cox  
7 analysis underestimated the benefit of starting HAART at a CD4 of 500.

3.2.2. *Time since diagnosis as an alternative analytic time scale.* In the hypothetical randomized  
9 trial described at the beginning of this subsection, it makes no logical difference whether we  
10 randomize each subject to one of the two regimes—‘start HAART when the CD4 count first falls  
11 below 500’ (group 1) or to ‘start HAART when the CD4 count first falls below 200’ (group 2)  
12—at time of enrollment (i.e. time of diagnosis of HIV infection) *versus* at the time when the CD4  
13 count first falls below 500. Had we done the former, time since randomization would denote time  
14 since the diagnosis of HIV infection rather than time since a subject’s CD4 count first fell below  
15 500. It follows that had we compared the survival of the two groups using a Cox model for the  
16 minimum of time to clinical AIDS or death with an indicator variable for group as the covariate,  
17 an interaction between time and group, and with time measured as time since the diagnosis of HIV  
18 infection, the rate ratios of our Cox model would still have a valid causal interpretation. However,  
19 the rate ratios would have a different causal interpretation (and different magnitude) than the rate  
20 ratios in our earlier Cox model that used time since the CD4 count first fell below 500. We next  
21 describe the observational analogue of the Cox model analysis of our randomized trial with time  
22 now measured as time since HIV diagnosis.

23 Specifically in our observational analogue, we again restrict to subjects whose CD4 count  
24 exceeded 500 at time of diagnosis. However, baseline covariates would now be covariates recorded  
25 at the time of HIV diagnosis and the time in the Cox model would become time from diagnosis.  
26 Each subject would be placed in both groups 1 and 2 at time of diagnosis. We use a robust variance  
27 estimator and the Breslow estimator to handle the correlations and ties thereby induced. In each  
28 treatment group, we censor a subject the first time they fail to follow the group-specific regime.  
29 Among uncensored subjects in a risk set at time  $u$ , we weight each subject by  $\bar{W}(u)$  calculated  
30 as earlier, except that  $u$  now indicates time since diagnosis. Subjects in group 1 are now subject  
31 to censoring. In particular, group 1 subjects are censored if they start HAART when their CD4 is  
32 above 500 or fail to start HAART when their CD4 first drops below 500. For concreteness and  
33 without loss of generality, in the remainder of this paper we will assume that time is measured as  
34 time from diagnosis of HIV infection.

### 35 3.3. *Choosing the optimal regime among more than two regimes*

In this subsection we consider two important issues we have yet to address. First, in practice we  
37 want to choose between more than two candidate regimes. For example, if we wish to find the  
38 optimal CD4 count  $x$  at which to start HAART, we would want to compare all  $x$ ’s in the candidate  
39 set  $\{500, 499, \dots, 200\}$  rather than just two dynamic regimes.

40 Second, to determine which  $x$  is optimal, we need a well-defined numerical measure to rank  
41 regimes. For example, one might wish to choose  $x$  to maximize the expected ‘years (or quality-  
42 adjusted years) of life’. We refer to the random variable  $Y$  whose expectation we wish to maximize  
43 as a (subject-specific) utility function. Our goal is then to find the regime  $x$  that maximizes expected

1 utility. Expected years (or quality-adjusted years) of life lived measures have a much more natural  
 3 and useful public health and policy interpretation than the hazard ratio measure that is typically  
 reported after fitting a Cox model.

However ‘years (or quality-adjusted years) of life’ cannot be assessed when follow-up of the  
 cohort is not to extinction but rather only to a fixed administrative end-of-follow-up date  $K + 1$   
 weeks from start of a subject’s follow-up. Our methods can be easily extended to settings in which  
 the potential length of follow-up varies with the subject, but, for simplicity, we do not do so in  
 this paper. Clearly, among survivors at the administrative end of follow-up, the healthier ones  
 (according to an agreed on measure of current health) have a greater post-study expected survival  
 (and thus warrant a higher utility  $Y$ ) than the less healthy survivors and a much greater expected  
 survival (and thus warrant a much higher utility) than the nonsurvivors who died just before  $K + 1$ .  
 For example, in the context of the FHDH data, a possible choice of utility  $Y$  would be

$$Y = \text{time to death if death occurred before } K + 1$$

$$Y = K + 3 \quad \text{if alive with clinical AIDS at } K + 1$$

$$Y = K + 4 \frac{\text{CD4}}{500} \quad \text{if alive without clinical AIDS at } K + 1$$

Henceforth, we assume that some agreement has been reached on the choice of utility  $Y$  so data  
 5 on  $Y$  is available for all subjects, if as we assume throughout, there is no drop-out.

To formalize the problem, we let  $Y_x$  be a subject’s potential or counterfactual utility had the  
 7 subject followed the dynamic regime in which HAART *is to be* initiated the first time the subject’s  
 measured CD4 count falls below  $x$ . Our goal is to find  $x_{\text{opt}} \in \{500, 499, \dots, 201\}$  for which the  
 9 expected utility  $E(Y_x)$  is a maximum. We first show how to design and analyze a randomized trial  
 to determine  $x_{\text{opt}}$ . We then consider how to mimic the trial using observational data. Throughout  
 11 we will assume that there exists a unique  $x_{\text{opt}}$ .

3.3.1. *A randomized trial.* Consider a randomized clinical trial (RCT) with full compliance with  $X$ ,  
 13 taking values in  $\{500, 499, \dots, 201\}$ , the random variable recording the assigned dynamic regime.  
 Because  $X$  was randomly assigned, it is independent of the counterfactuals  $Y_x$ . Under the consistency  
 15 assumption that states that if  $X = x$  then  $Y = Y_x$ , the observed utility  $Y$  is indeed a function  
 of the set of counterfactuals  $\{Y_x; x = 500, 499, \dots, 201\}$  and the treatment assignment  $X$ . Suppose  
 17 the data on each subject are  $(Y, X)$ . Then the average  $\widehat{E}[Y|X = x]$  of  $Y$  among subjects randomized  
 to regime  $x$  is an unbiased estimator of  $E[Y_x]$ . [This follows from the fact that (i)  $\widehat{E}[Y|X = x]$  is  
 19 unbiased for  $E[Y|X = x]$  and (ii)  $E[Y|X = x] = E[Y_x|X = x] = E[Y_x]$  by consistency and random-  
 ization.] Thus, the natural estimate of  $x_{\text{opt}}$  is the value of  $x$  for which  $\widehat{E}[Y|X = x]$  is a maximum.  
 21 However, even if, say, 900 subjects are enrolled in the trial, the number of subjects randomized  
 to treatment arm  $x$  must be three or less for the majority of the 300 treatment arms. For these  
 23 arms,  $\widehat{E}[Y|X = x]$  will be highly variable. As a consequence, the natural estimator of  $x_{\text{opt}}$  will  
 be so variable as to be useless. Thus, even in a randomized trial, to obtain a reasonably efficient  
 25 estimator of  $x_{\text{opt}}$ , it is necessary to use our prior biological knowledge that  $E[Y_x]$  is a smooth  
 function of  $x$ . One, among many, possible approaches to exploiting this smoothness is to assume  
 27 that  $E[Y_x]$  is a flexible polynomial, for example, a polynomial of degree 5. If we assume

$$E[Y_x] = \beta_0 + \sum_{k=1}^5 \beta_k x^k$$

1 then, by  $E[Y_x] = E[Y|X=x]$ , we have that the estimator  $\hat{\beta}$  of  $\beta = (\beta_0, \dots, \beta_5)$  obtained from fitting  
 2 by ordinary least squares (OLS) the regression model  $Y = \beta_0 + \sum_{k=1}^5 \beta_k X^k + \varepsilon$  to the observed data  
 3  $(Y_i, X_i), i = 1, \dots, n$ , on the  $n$  study subjects is unbiased for  $\beta = (\beta_0, \dots, \beta_5)^T$ . It follows that an  
 4 unbiased estimator of  $\hat{E}[Y_x]$  is  $\hat{\beta}_0 + \sum_{k=1}^5 \hat{\beta}_k x^k$ . We then use the first year calculus to find the  
 5 value  $\hat{x}_{\text{opt}}$  of  $x$  at which the fitted polynomial  $\hat{E}[Y_x] = \hat{\beta}_0 + \sum_{k=1}^5 \hat{\beta}_k x^k$  obtains its maximum on the  
 6 closed interval  $[201, 500]$ . Of course, the  $\hat{x}_{\text{opt}}$  one obtains in this manner will not generally be an  
 7 integer, but can always be rounded off to the closest integer in  $\{500, 499, \dots, 201\}$ . For simplicity,  
 8 we assume that the maximum is attained at a unique  $\hat{x}_{\text{opt}}$ .

9 The quintic model for  $E[Y_x]$  will, of course, not be exactly correct. If incorrect, the estimator  
 $\hat{x}_{\text{opt}}$  will be biased as an estimator of the true  $x_{\text{opt}}$ . Using a higher-degree polynomial will decrease  
 11 bias but increase variance. Elsewhere we plan to study how to use cross-validation to select the  
 12 degree of the flexible polynomial.

13 By including interactions with the measured pretreatment variables  $V$ , such as gender, ethnicity,  
 14 HIV risk group (e.g. IV drug users versus homosexual contact), and genetic profile (single  
 15 nucleotide polymorphisms), we can allow for the fact that the optimal treatment regime in our  
 16 candidate set may differ depending on a subject's measured pretreatment variables  $V$ .

17 For instance, consider the model  $E[Y_x|V] = \beta_0 + \sum_{k=1}^5 \beta_k x^k + \eta_0^T V + \sum_{k=1}^5 \eta_k^T V x^k$ . Let  $(\hat{\beta}, \hat{\eta})$   
 18 be the OLS estimates from the fit of  $Y = \beta_0 + \sum_{k=1}^5 \beta_k X^k + \eta_0^T V + \sum_{k=1}^5 \eta_k^T V X^k + \varepsilon$  to the observed  
 19 data  $(Y_i, X_i, V_i), i = 1, \dots, n$ . The optimal CD4 count  $x_{\text{opt}}(V)$  at which a subject with baseline  
 20 covariates  $V$  should start is given by the value  $x_{\text{opt}}(V)$  that maximizes  $E[Y_x|V]$ , over all allow-  
 21 able  $x$ , which is also the  $x(V)$  that maximizes  $E[Y_x|V] - E[Y_{x_0}|V]$  at any fixed value  $x_0$ . Choosing  
 $x_0 = 0, x_{\text{opt}}(V)$  maximizes  $\sum_{k=1}^5 \beta_k x^k + \sum_{k=1}^5 \eta_k^T V x^k = \sum_{k=1}^5 (\beta_k + \eta_k^T V) x^k$ . Thus, our estimate  
 23  $\hat{x}_{\text{opt}}(V)$  of  $x_{\text{opt}}(V)$ , which for ease of reference below we call the RCT estimator of  $x_{\text{opt}}(V)$ , is  
 given by the (assumed unique) value  $x(V)$  that maximizes  $\sum_{k=1}^5 (\hat{\beta}_k + \hat{\eta}_k^T V) x^k$  for the given  $V$ .

25 3.3.2. *An observational study and dynamic MSMs.* To understand how to mimic the above random-  
 26 ized trial, we require the following observations. Suppose data on when, if ever, a subject began  
 27 HAART and data on successive CD4 counts are available. Suppose no subject has two CD4  
 28 measurements in the same week. Consider a subject who started HAART at a CD4 cell count  
 29 of 250 in week  $t$  whose lowest prior CD4 count was 300. Then this subject's observed data are  
 30 consistent with having followed regime  $x$  for  $x = 251, 252, \dots, 300$ . In fact, the subject followed  
 31 all of these regimes. Next consider a subject who never started therapy and whose lowest CD4  
 32 count was 225. Then this subject followed regimes  $x$  for  $x = 201, 202, \dots, 225$ . Finally, consider  
 33 a subject who started antiretroviral therapy at a CD4 cell count of 250 in week  $t$  whose lowest  
 34 previous CD4 count was 250 or less. Then this subject failed to follow any regime in the set  
 35  $\{500, 499, \dots, 201\}$ .

We are now ready to describe our procedure. Time will be in weeks since enrollment in the cohort.  
 37 As we did for the RCT, we assume the model  $E[Y_x|V] = \beta_0 + \sum_{k=1}^5 \beta_k x^k + \eta_0^T V + \sum_{k=1}^5 \eta_k^T V x^k$ .  
 Let  $\Gamma_i$  be the number of regimes in the set  $\{500, 499, \dots, 201\}$  followed by subject  $i$ . We create  
 39 an artificial data set of size  $\Gamma = \sum_{i=1}^n \Gamma_i$ , with each subject  $i$ , for  $i = 1, \dots, n$ , contributing  $\Gamma_i$   
 40 observations  $(Y_i, V_i, X_{i1}), (Y_i, V_i, X_{i2}), \dots, (Y_i, V_i, X_{i\Gamma_i})$ , where the  $X_{ik}, k = 1, \dots, \Gamma_i$ , denote the  
 41 regimes followed by subject  $i$ .

Our estimator of  $(\beta, \eta)$  is computed as the weighted least-squares estimator  $(\hat{\beta}, \hat{\eta})$  from the fit  
 43 of the regression model  $Y = \beta_0 + \sum_{k=1}^5 \beta_k X^k + \eta_0^T V + \sum_{k=1}^5 \eta_k^T V X^k + \varepsilon$  to the artificial data set of

1 size  $\Gamma$ , pretending all observations in the artificial data set are independent and weighting each  
 2 artificial observation  $(Y_i, V_i, X_{ik})$  with the weights  $\widehat{W}_i(K)$ , i.e. the earlier weight  $\widehat{W}_i(u)$  with  $u$  set  
 3 to the last time  $K$  that one could start therapy before administrative end of follow-up at  $K+1$ .  
 4 As in our RCT,  $\widehat{x}_{\text{opt}}(V)$  is given by the value  $x(V)$  that maximizes  $\sum_{k=1}^5 (\widehat{\beta}_k + \widehat{\eta}_k^T V)x^k$ . Our  
 5 observational estimator  $\widehat{x}_{\text{opt}}(V)$  of  $x_{\text{opt}}(V)$  will be consistent if (i) our assumption of no unmeasured  
 6 confounders holds for all  $x \in \{500, 499, \dots, 201\}$ , i.e. equation (3) with  $Y_x$  replacing  $T_x$ , (ii) the  
 7 model  $E[Y_x|V] - E[Y_0|V] = \sum_{k=1}^5 (\beta_k + \eta_k^T V)x^k$  is correct for all  $x \in \{500, 499, \dots, 201\}$ , (iii) the  
 8 model for treatment initiation used to obtain  $\widehat{W}(K)$  is correct, and (iv)  $V$  is the vector of all  
 9 baseline covariates  $\text{Past}(0)$  needed to ensure no unmeasured confounding.

10 We stress that condition (ii) implies that our estimate  $\widehat{x}_{\text{opt}}(V)$  is consistent even if the model  
 11  $E[Y_0|V] = \beta_0 + \eta_0^T V$  for the main effect of  $V$  is wrong. The remark in Section 4.3 provides an  
 explanation.

For logistical reasons, we may only be interested in  $x_{\text{opt}}(V)$  when  $V$  is a strict subset of the set  
 $\text{Past}(0)$  of baseline potential confounders. Fortunately, if we redefine

$$W(u) = 1 \bigg/ \prod_{k=0}^u f[A(k)|\bar{A}(k-1), \text{Past}(k)]$$

$$\widehat{W}(u) = 1 \bigg/ \prod_{k=0}^u f[A(k)|\bar{A}(k-1), \text{Past}(k); \widehat{\alpha}]$$

13 to include time 0 in the denominator, the above estimate of  $\widehat{x}_{\text{opt}}(V)$  remains consistent when (iv)  
 14 is replaced by ‘ $V$  is a subset of  $\text{Past}(0)$ ’, as the redefined estimated weight  $\widehat{W}(u)$  serves to control  
 15 confounding by variables included in  $\text{Past}(0)$  but not in  $V$ .

16 Finally, as discussed further in Section 4.3, we can use dynamic MSMs to optimize a more  
 17 complex class of candidate regimes in both randomized and observational studies. For example,  
 we might consider the class of regimes:

- 18 • if current HIV RNA is greater than  $z$ , start HAART if the current CD4 count is less than  $x$ ,
- 19 • if current HIV RNA is not greater than  $z$ , start HAART if the current CD4 count is less  
 20 than  $q$ ,

21 and use methods similar to those just described to jointly estimate the three numbers  $(z_{\text{opt}},$   
 22  $x_{\text{opt}}, q_{\text{opt}})$ .

## 4. A FORMALIZATION

### 25 4.1. The data

26 We consider a study of the effect of a time-dependent dichotomous exposure  $A(t)$  on a utility  
 27 function  $Y$ . The terms exposure and treatment will be used synonymously and interchangeably. We  
 28 assume a fixed study population, i.e. a closed cohort with a well-defined, known start of follow-up  
 29 date for each subject. Time  $t$  will refer to time in weeks since start of follow-up, which we also  
 30 refer to as time since baseline. We only consider the estimation of the effect of exposures occurring  
 31 at or after the start of follow-up because the estimation of the effects of pre-baseline exposures  
 is not possible without making strong untestable assumptions. Subjects change exposure only at

1 the beginning of a week so  $A(t)$  is recorded at fixed times  $t=0, 1, \dots, K$  weeks from baseline.  
 2 Covariates  $L(t)$  are recorded at times  $t=0, 1, \dots, K, K+1$ . Data on  $L(t)$  become available prior  
 3 to the determination of  $A(t)$  but after  $A(t-1)$ . Baseline covariates  $L(0)$  refer to all covariates,  
 4 including pre-baseline exposure, that occur prior to the baseline exposure  $A(0)$ . We use overbars  
 5 to denote history, i.e. the exposure history through time (i.e. week)  $t$  is  $\bar{A}(t) = \{A(0), A(1), \dots, A(t)\}$ .  
 6 We denote a subject's total exposure and covariate history by  $\bar{A} = \bar{A}(K)$  and  $\bar{L} = \bar{L}(K+1)$ . We let  
 7  $\bar{O} = \bar{O}(K+1) = (\bar{A}, \bar{L})$ . Utility  $Y$  is formally defined as  $Y = y(\bar{A}, \bar{L})$  with  $y(\cdot, \cdot)$  being a known  
 8 function. We use capital letters to denote random variables, scriptic letters to denote their sample  
 9 space (i.e. the set of possible realizations), and lower case letters to denote elements of the sample  
 10 space.

#### 11 4.2. Treatment regimes and counterfactuals

12 Let  $\bar{a} = \bar{a}(K) = \{a(0), a(1), \dots, a(K)\}$  be an element of the sample space  $\bar{\mathcal{A}}$  of  $\bar{A}$ . For simplicity, we  
 13 take  $\bar{\mathcal{A}}$  to be a finite set. Let  $\bar{L}_{\bar{a}}(m) = \{L(0), L_{a(0)}(1), \dots, L_{\bar{a}(m-1)}(m)\}$  be a subject's counterfactual  
 14  $L$ -history through  $m$  under the regime  $\bar{a}$ . Note that  $\bar{L}_{\bar{a}}(m)$  only depends on  $\bar{a}$  through  $\bar{a}(m-1)$ ,  
 15 as the future treatments cannot determine past responses. Define  $\bar{L}_{\bar{a}} = \bar{L}_{\bar{a}}(K+1)$  to be a subject's  
 16 complete counterfactual  $L$ -history under regime  $\bar{a}$ . Let  $\bar{L}_{\bar{\mathcal{A}}} = \{\bar{L}_{\bar{a}}; \bar{a} \in \bar{\mathcal{A}}\}$ . A realization  $\bar{l}_{\bar{\mathcal{A}}} =$   
 17  $\{\bar{l}_{\bar{a}}; \bar{a} \in \bar{\mathcal{A}}\}$  of  $\bar{L}_{\bar{\mathcal{A}}}$  is a set of covariate histories indexed by the elements  $\bar{a}$  of  $\bar{\mathcal{A}}$ . This notation  
 18 implicitly includes the assumption that a subject's counterfactual responses do not depend on the  
 19 treatments given to other subjects.

We make the following assumption linking the counterfactual data and the observed data:

20 *Consistency assumption (C):*  $\bar{L}(m) = \bar{L}_{\bar{A}(m-1)}(m)$ .

21 This assumption implies that  $\bar{O} = (\bar{A}, \bar{L})$  equals  $(\bar{A}, \bar{L}_{\bar{A}})$ . That is, if  $\bar{A} = \bar{a}$ , a subject's observed  
 22  $\bar{L}$  is obtained by selecting from  $\bar{L}_{\bar{\mathcal{A}}}$  the element  $\bar{L}_{\bar{a}}$ .

23 So far we have only considered static regimes  $\bar{a}$ . To characterize the optimal treatment strategy,  
 24 it is usually necessary to consider dynamic regimes as well.

25 We use  $g$  to denote a general regime. A nonrandom regime  $g$  is a treatment strategy or rule in  
 26 which the treatment prescribed by  $g$  at time  $t$  depends in a deterministic manner on the evolution  
 27 of a subject's measured time-dependent covariates  $\bar{L}(t)$  and, possibly, treatments  $\bar{A}(t-1)$  up to  $t$ .  
 28 An example would be the dynamic regime 'take the treatment methotrexate at week  $t$  if and only  
 29 if the neutrophil count has been greater than 1000 for three consecutive weeks and the patient  
 30 was not on treatment at week  $t-1$ '. Mathematically, a nonrandom regime  $g$  is a collection of  
 31 functions  $\bar{d} = \{d_k[\bar{a}(k-1), \bar{l}(k)]; k=0, \dots, K\}$  with a range of  $d_k$  contained in the sample space  
 32  $\mathcal{A}(k)$  of  $A(k)$  and such that  $d_k[\bar{a}(k-1), \bar{l}(k)]$  specifies the treatment to be taken at  $k$  for a subject  
 33 with past history  $[\bar{a}(k-1), \bar{l}(k)]$ . In our methotrexate example,  $d_k[\bar{a}(k-1), \bar{l}(k)]$  is 1 if a subject's  
 34  $a(k-1)$  is zero and his  $\bar{l}(k)$  implies that his neutrophil count has been greater than 1000 at weeks  
 35  $k, k-1, k-2$  (so  $k$  must be at least 2); otherwise  $d_k[\bar{a}(k-1), \bar{l}(k)]$  is 0. We write either  $g_{\bar{d}}$  or  $g = \bar{d}$   
 36 to indicate the dependence on the functions  $\bar{d}$ . Earlier we considered the nonrandom regime  $\bar{d}_x$ :  
 37 begin antiretroviral therapy the first time  $t$  the measured CD4 count falls below  $x$ . This regime has  
 38  $d_{x,k}[\bar{a}(k-1), \bar{l}(k)] = 1$  if minimum CD4 count through  $k$  is less than  $x$  and is 0 otherwise. If, for  
 39 all  $k$ 's,  $d_k[\bar{a}(k-1), \bar{l}(k)]$  is a constant  $a(k)$  that does not depend on  $(\bar{a}(k-1), \bar{l}(k))$ , the regime  $\bar{d}$   
 40 is said to be nondynamic or static and is written as  $g = \bar{a}$ .

41 The regime  $\bar{d}$  is naturally associated with counterfactual random variables  $(\bar{A}_{\bar{d}}, \bar{L}_{\bar{d}})$  that repre-  
 42 sent a subject's treatment and covariate history when following the regime. Specifically we regard

1  $\bar{d}$  as defining a mapping  $\bar{d}: \bar{L}_{\mathcal{A}} \mapsto d(\bar{L}_{\mathcal{A}}) \equiv (\bar{A}_{\bar{d}}, \bar{L}_{\bar{d}})$  defined recursively as follows:  $L_{\bar{d}}(0) =$   
 2  $L(0)$ ,  $A_{\bar{d}}(0) = d_0[L_{\bar{d}}(0)]$ . For  $m = 1, \dots, K + 1$ ,  $L_{\bar{d}}(m) = L_{\bar{A}_{\bar{d}}(m-1)}(m)$ ,  $A_{\bar{d}}(m) = d_m[\bar{A}_{\bar{d}}(m-1),$   
 3  $L_{\bar{A}_{\bar{d}}(m-1)}(m)]$  except  $A_{\bar{d}}(K + 1)$  is left undefined. Furthermore,  $Y_{\bar{d}} = y(\bar{A}_{\bar{d}}, \bar{L}_{\bar{d}})$ .

4 In addition to the preceding consistency assumption, we make the following SR assumption and  
 5 positivity assumption.

6 *Sequential randomization (SR) assumption:* For each  $k$ ,  $A(k)$  is independent of  $\bar{L}_{\mathcal{A}}$  given  $(\bar{A}(k -$   
 7  $1), \bar{L}(k))$ . Equivalently,

$$f(\bar{A}|\bar{L}_{\mathcal{A}}) = \prod_{k=0}^K f[A(k)|\bar{A}(k-1), \bar{L}_{\bar{A}}(k)] = \prod_{k=0}^K f[A(k)|\bar{A}(k-1), \bar{L}(k)]$$

9 where the last equality follows from assumption C.

10 *Positivity assumption (PO):*  $f\{a(k)|\bar{A}(k-1), \bar{L}(k)\} > 0$  with probability one for all  $a(k) \in \mathcal{A}(k)$ .

### 11 4.3. Dynamic and general MSMs

12 To help understand the general formulation of dynamic and general MSMs it will be helpful  
 13 to introduce them in connection with the example discussed in earlier sections on determining  
 14 the optimal CD4 level at which to start treating HIV-positive subjects with HAART. Henceforth,  
 15 consider an observational study of subjects with CD4 counts exceeding 500 at time of diagnosis  
 16 of HIV infection. Subjects return to the clinic weekly to have various clinical and laboratory  
 17 measurements made. Let  $L(t)$  be the vector of measurements made at week  $t$  including CD4 cell  
 18 count. We let  $A(t)$  denote the indicator of whether HAART has been initiated at week  $t$  or before.  
 19 Let  $Y$  be a utility known at the end of follow-up at  $K + 1$ , higher values of which are preferable.  
 20 Let  $\bar{d}_x$  denote the dynamic regime ‘begin antiretroviral therapy the first time  $t$  the measured CD4  
 21 count falls below  $x$ ,’ where  $x \in \mathcal{X}\{201, \dots, 500\}$ . The model

$$E[Y_{\bar{d}_x} | V] = h(x, V, \psi^*) \tag{4}$$

23 where

$$h(x, V, \psi) = h_1(x, V, \psi_1) + h_2(V, \psi_0) \quad \text{with } h_1(x, V, 0) = 0 \tag{5}$$

25 is an example of a dynamic regime MSM for the conditional counterfactual mean of  $Y$ , given  
 26 a subset  $V$  of the baseline covariates  $L(0)$ . Note that the value  $\psi_1^* = 0$  is equivalent to the null  
 27 hypothesis that all regimes in  $\{\bar{d}_x; x \in \mathcal{X}\}$  have the same mean, given  $V$ .

28 In Section 3.3, we chose  $\psi_1 = \{\beta_1, \dots, \beta_5, \eta_1^T, \dots, \eta_5^T\}^T$ ,  $\psi_0 = (\beta_0, \eta_0^T)^T$ ,  $h_1(x, V, \psi_1) =$   
 29  $\sum_{k=1}^5 (\beta_k + \eta_k^T V) x^k$ , and  $h_2(V, \psi_0) = \beta_0 + \eta_0^T V$ . More generally, suppose  $h(x, V, \psi) = (r(x, V)^T,$   
 30  $r^*(V)^T) \psi$  for some known functions  $r(x, V)$  and  $r^*(V)$ . Let  $\Gamma_i$  be the number of regimes  
 31 followed by subject  $i$  and create an artificial data set of size  $\Gamma = \sum_{i=1}^N \Gamma_i$ , with each subject  $i$ , for  
 32  $i = 1, \dots, N$ , contributing  $\Gamma_i$  artificial observations  $(Y_i, V_i, X_{i1}), (Y_i, V_i, X_{i2}), \dots, (Y_i, V_i, X_{i\Gamma_i})$ ,  
 33 where  $X_{ik}, k = 1, \dots, \Gamma_i$ , denote the regimes followed by subject  $i$ . Formally, to follow a regime  $x$   
 34 means that one’s observed treatment  $\bar{A}$  is equal to the treatment  $\bar{A}_{\bar{d}_x}$  the subject would have  
 35 had under the regime  $\bar{d}_x$ . To estimate  $\psi$  we fit by weighted least squares with an independence  
 36 working covariance matrix, the regression model

$$E[Y|X, V] = h(X, V, \psi) = (r(X, V)^T, r^*(V)^T) \psi \tag{6}$$

1 to the artificial data set weighting each artificial observation  $(Y_i, V_i, X_{ik})$  by  $\widehat{S}\widehat{W}_{ik} = \widehat{W}_i q^*(X_{ik}, V_i)$ ,  
 2 where  $\widehat{W} = \prod_{k=0}^K 1/f[A(k)|\bar{A}(k-1), \bar{L}(k); \widehat{\alpha}]$  and  $q^*(\cdot, \cdot)$  is a user-supplied (possibly data-  
 3 dependent) function. Different choices of  $q^*$  impact the efficiency with which  $\psi$  (and hence the  
 4 optimal  $x$ ) is estimated; however, all choices yield consistent estimators of  $\psi$ . [In our earlier  
 5 discussion, we implicitly chose  $q^*(\cdot, \cdot)$  to be the constant 1 so  $\widehat{S}\widehat{W}_{ik}$  equalled  $\widehat{W}_i$  as previously  
 6 defined.] The optimal treatment regime in the class  $\{\bar{d}_x; x \in \mathcal{X}\}$  for a subject with  $V = v$  is  
 7 estimated as the value of  $x$  that maximizes  $h(x, v, \widehat{\psi})$  or, equivalently,  $h_1(x, v, \widehat{\psi}_1)$  over  $x \in \mathcal{X}$   
 8 for  $v$  fixed.

9 Orellana *et al.* [2] showed that  $\widehat{\psi}$  based on the artificial data set converges to the parameter  
 $\psi^*$  of our dynamic MSM under the assumptions SR, C, P, and correct specification of the model  
 11  $f[A(k)|\bar{A}(k-1), \bar{L}(k); \alpha]$ .

12 The key step in the proof is to note that when  $\widehat{W}$  is converging to  $W$ , the estimate  $\widehat{\psi}$  is converging  
 13 to the (assumed unique)  $\psi$  satisfying

$$0 = E \left[ \sum_{x \in \mathcal{X}} \Delta_x W q^*(x, V) \{Y - h(x, V, \psi)\} (r(x, V)^T, r^*(V)^T)^T \right] \quad (6)$$

15 where  $\Delta_x = \prod_{k=0}^K I(A(k) = d_{x,k}[\bar{A}(k-1), \bar{L}(k)])$  is the indicator that the subject followed regime  
 $\bar{d}_x$ . However, under our assumptions this expectation is

$$17 \quad E \left[ \sum_{x \in \mathcal{X}} \{Y_{\bar{d}_x} - h(x, V, \psi)\} (r(x, V)^T, r^*(V)^T)^T q^*(x, V) \right]$$

18 which is zero under our MSM. Orellana *et al.* [2] also discuss how to construct locally efficient  
 19 estimators and doubly robust estimators.

20 A general MSM is defined analogously. Specifically, given any set of regimes  $\{\bar{d}_x; x \in \mathcal{X}\}$   
 21 (whether static, dynamic, or both) indexed by  $x$  taking values in a (possibly infinite) set  $\mathcal{X}$  (not  
 22 necessarily a subset of the real numbers), a general MSM is defined as model (4) satisfying (5). To  
 23 estimate the parameter  $\psi^*$ , we solve the estimating equations (6) where, of course,  $\Delta_x$  is now the  
 24 indicator of following regime  $\bar{d}_x$ . For example, consider another HIV study, where now subjects  
 25 may repeatedly start and stop HAART therapy and we consider the regimes ‘take therapy at  $t$  if  
 26 and only if the current white blood count exceeds  $w$  and a certain liver function test has value  
 27 less than  $b$ ’. Here  $b$  and  $w$  are nonnegative integers in the range of 0–10000. Then  $x = (w, b)$ . An  
 28 example of a choice for  $h_1(x, V, \psi_1)$  is  $\psi_{1,1}(b-100) + \psi_{1,2}(b-100)^2 + \psi_{1,4}(w-1000) + \psi_{1,5}(w-$   
 29  $1000)^2 + \psi_{1,6}(b-100)V + \psi_{1,7}(w-1000)V + \psi_{1,8}(w-1000)(b-100)$ . Although in our examples  
 30 the number of regimes that can be possibly followed by any subject is finite, dynamic MSMs need  
 31 not assume that this is the case. Orellana *et al.* [2] extend our dynamic MSM methods to the case  
 32 where  $\mathcal{X}$  is uncountable rather than finite.

33 *MSMs and the positivity condition:* Specifying a general MSM can also allow us to weaken  
 34 positivity requirements. For each regime  $\bar{d}_{x^*}$  for which the PO assumption might fail or nearly fail  
 35 (as evidenced by some subject’s having particularly small estimated probabilities of following the  
 36 regime), we simply remove any observation  $(Y, V, x^*)$  from the artificial data. We can then either  
 37 interpret our MSM model as a model for  $E[Y_{\bar{d}_x} | V]$ ,  $x \in \mathcal{X}_{\text{pos}} = \mathcal{X} \setminus \mathcal{X}_{\text{nonpos}} \subset \mathcal{X}$ , where  $\mathcal{X}_{\text{nonpos}}$  is  
 38 the set of  $x^*$  removed, or as a model for  $E[Y_{\bar{d}_x} | V]$ ,  $x \in \mathcal{X}$ . In the latter case, one is identifying  
 39  $E[Y_{\bar{d}_x} | V]$  for the regimes  $\bar{d}_{x^*}$  in  $\mathcal{X}_{\text{nonpos}}$  by model-based extrapolation.



1 The functions  $\gamma_m[\bar{a}(m), \bar{l}(m), \beta^*]$  model the effect on the mean of  $Y$  of a last blip of treatment  
 2 of magnitude  $a(m)$  at  $m$ , as a function of (i.e. as modified by) past treatment and covariate history  
 3  $[\bar{a}(m-1), \bar{l}(m)]$ .

4 Examples of choices of  $\gamma_m[\bar{a}(m), \bar{l}(m), \beta]$  include (i)  $\beta a(m)$ , (ii)  $(\beta_0 + \beta_1 m)a(m)$ , and (iii)  
 5  $\{\beta_0 + \beta_1 m + \beta_2 a(m-1) + \beta_3^T l(m) + \beta_4^T l(m)a(m-1)\}a(m)$ . Choice (i) is tantamount to assuming  
 6 that the effect of a last blip of treatment  $a(m)$  is the same for all  $m$ 's. Under choice (ii) the effect  
 7 varies linearly with the time  $m$  of treatment. Under choice (iii), the effect of a last blip of treatment  
 8 at  $m$  is modified by past treatment and covariate history.

9 We next describe the  $g$ -estimation algorithm for estimating the unknown parameter  $\beta^*$  in an  
 10 observational study under the assumptions C, PO, and SR. To do so, it is convenient to define

$$11 \quad Y_m(\beta) = Y - \sum_{j=m}^K \gamma_j[\bar{A}(j), \bar{L}(j), \beta]$$

12 Note that, for each  $\beta$ ,  $Y_m(\beta)$  can be computed from the observed data. To carry out the  $g$ -  
 13 estimation algorithm we first need to postulate a logistic regression model (pooled over persons  
 14 and time)

$$15 \quad \text{logit Pr}[A(m) = 1 | \bar{L}(m), \bar{A}(m-1)] = \alpha^T B(m) \quad (8)$$

16 for the probability of treatment at time (i.e. week)  $m$  for  $m = 0, \dots, K$ . In this model,  $B(m) =$   
 17  $b_m[\bar{L}(m), \bar{A}(m-1)]$  is a vector of covariates calculated from a subject's covariate and treatment  
 18 data  $[\bar{L}(m), \bar{A}(m-1)]$ ,  $\alpha^T$  is a conformable row vector of unknown parameters. An example of  
 19  $B(m)$  would be the transpose of the row vector

$$(m, A(m-1), L^T(m), A(m-1)L^T(m), A(m-2), L^T(m-1), L^T(m)A(m-1)A(m-2))$$

20 where  $L(m)$  is the vector of covariates measured at time  $m$ .

21 Having postulated model (8) we estimate  $\alpha$  with its MLE  $\hat{\alpha}$ . To compute  $\hat{\alpha}$  we simply fit the  
 22 logistic regression model (8) where each person-week is treated as an independent observation, so  
 23 that each person contributes  $K+1$  observations.

24 Consider first the case in which  $\beta$  is a scalar parameter as in model (i) above. Suppose that  $\beta_{\text{low}}$   
 25 and  $\beta_{\text{up}}$  are numbers much smaller and larger, respectively, than any substantively plausible value  
 26 of  $\beta^*$ . Then, to carry out the  $g$ -estimation algorithm, separately, for each  $\beta$  on a grid from  $\beta_{\text{low}}$  to  
 27  $\beta_{\text{up}}$ , say  $\beta_{\text{low}}, \beta_{\text{low}} + 0.1, \beta_{\text{low}} + 0.2, \dots, \beta_{\text{up}}$ , we perform the score test of the null hypothesis  $\theta = 0$   
 28 in the logistic model

$$29 \quad \text{logit Pr}[A(m) = 1 | \bar{L}(m), \bar{A}(m-1), Y_m(\beta)] = \alpha^T B(m) + \theta Y_m(\beta), \quad m = 0, \dots, K \quad (9)$$

30 that adds the covariate  $Y_m(\beta)$  at each time  $m$  to the above pooled logistic model (8). A 95  
 31 per cent confidence interval for  $\beta^*$  is the set of  $\beta$  for which the two-sided score test of the hypothesis  
 32  $\theta = 0$  at level 0.05 does not reject. The  $g$ -estimate of  $\beta^*$  is the value of  $\beta$  for which the score test  
 33 takes the value zero (i.e. the  $p$ -value is one).

34 A heuristic justification of the  $g$ -estimation procedure is as follows.  $Y_m(\beta^*)$  is an estimate of  
 35  $Y_{\{\bar{a}(m-1), \underline{0}(m)\}}$  since the effect  $\sum_{j=m}^K \gamma_j[\bar{A}(j), \bar{L}(j), \beta^*]$  of all treatments from  $m$  onwards have  
 36 been subtracted from  $Y$ . Thus, one would expect that under the RC assumption,  $\theta = 0$  when  $Y_m(\beta^*)$   
 37 is added to (9). In fact, it can be shown that this is true. Now, we do not know  $\beta^*$ . Therefore, any  
 38 value  $\beta$  for which the data are consistent with the parameter  $\theta$  of the term  $\theta Y_m(\beta)$  being zero might  
 39

1 be the true  $\beta^*$ , and thus belongs in our confidence interval. If consistency with the data is defined  
 2 at the 0.05 level, then our confidence interval will have coverage of 95 per cent. Furthermore,  
 3 the  $g$ -estimate  $\hat{\beta}$  of  $\beta^*$  is that  $\beta$  for which adding the term  $\theta Y_m(\beta)$  does not help to predict  $A(m)$   
 4 whatsoever, which is the  $\beta$  for which the score test of  $\theta=0$ , is precisely zero. The  $g$ -estimate  $\hat{\beta}$  is  
 5 also the value of  $\beta$  for which the OLS estimator of  $\theta$  is precisely zero.

6 Suppose now that the parameter  $\beta$  is a vector. To be concrete suppose we consider the model with  
 7  $\gamma_m[\bar{a}(m), \bar{l}(m), \beta] = a(m)\{\beta_0 + \beta_1 m + \beta_2 a(m-1) + \beta_3 l(m) + \beta_4 l(m)a(m-1)\}$ . In this model,  $\beta$  is  
 8 five dimensional and  $l(m)$  is one dimensional. To estimate  $\beta$  we use a five-dimensional grid, one  
 9 dimension for each component of  $\beta$ . Hence, if we had 20 grid points for each component we would  
 10 have  $20^5$  different values of  $\beta$  on our five-dimensional grid. Now, to estimate the five components  
 11 of  $\beta$  we consider  $Q_m = q_m[\bar{L}(m), \bar{A}(m-1)]$ , a five-dimensional vector of functions of  $\bar{L}(m)$ ,  $\bar{A}(m-1)$ ,  
 12 such as  $q_m^T[\bar{L}(m), \bar{A}(m-1)] = [1, m, A(m-1), L(m), L(m)A(m-1)]$ . We postulate a model  
 13 that extends model (8) with the addition of the five linear functions  $Q_{m,j} Y_m(\beta)$  of  $Y_m(\beta)$ ,  $j =$   
 14  $1, \dots, 5$ , as covariates, i.e.

$$15 \quad \text{logit Pr}[A(m) = 1 | \bar{L}(m), \bar{A}(m-1), Y_m(\beta)] = \alpha^T B(m) + \theta^T Q_m Y_m(\beta)$$

16 Our  $g$ -estimate  $\hat{\beta}$  is the value of the vector  $\beta$  for which the 5 degrees of freedom score test  
 17 statistic for testing the null hypothesis  $\theta=0$  is precisely zero. The particular choice of the functions  
 18  $Q_m = q_m[\bar{L}(m), \bar{A}(m-1)]$  does not affect the consistency of the estimator  $\hat{\beta}$ , but it determines the  
 19 width of its associated confidence interval. See Robins [10] for the optimal choice of  $Q_m$ .

20 When the dimension of  $\beta$  is greater than 2, finding  $\hat{\beta}$  by search over a grid is generally computa-  
 21 tionally prohibitive. However, when, as in all the examples we have discussed,  $\gamma_m[\bar{a}(m), \bar{l}(m), \beta] =$   
 22  $a(m)\beta^T R_m$  is linear in  $\beta$  with  $R_m = r_m(\bar{L}(m), \bar{A}(m-1))$  being a vector of known functions, then,  
 23 there is an explicit closed-form expression for  $\hat{\beta}$ . Specifically, if  $\hat{\alpha}$  denotes the MLE of  $\alpha$  under  
 model (8), then  $\hat{\beta}$  takes the explicit form

$$25 \quad \hat{\beta} = \left\{ \sum_{i=1, m=0}^{i=n, m=K} X_{im}(\hat{\alpha}) Q_{im} S_{im}^T \right\}^{-1} \left\{ \sum_{i=1, m=0}^{i=n, m=K} Y_i X_{im}(\hat{\alpha}) Q_{im} \right\}$$

26 where  $X_{im}(\hat{\alpha}) = [A_i(m) - \text{expit}\{\hat{\alpha}^T B_i(m)\}]$ ,  $S_{im} = \sum_{j=m}^{j=K} A_i(j) R_{ij}$ . [Note that to compute  $\hat{\alpha}$  we  
 27 simply fit the logistic regression model (8) where each person-week is treated as an independent  
 28 observation, so that each person contributes  $K+1$  observations.] In fact, for  $\gamma_m[\bar{a}(m), \bar{l}(m), \beta]$  of  
 29 the form  $a(m)\beta^T R_m$ , we can also obtain a closed-form estimator  $\tilde{\beta}$  of  $\beta^*$ , which is consistent and  
 30 asymptotically normal if either, but not necessarily both, a model  $\zeta^T T_m = \zeta^T t_m[\bar{L}(m), \bar{A}(m-1)]$   
 31 for  $E[Y_m(\beta^*) | \bar{L}(m), \bar{A}(m-1)]$  (and hence for  $E[Y_{\{\bar{A}(m-1), \underline{Q}(m)\}} | \bar{L}(m), \bar{A}(m-1)]$  because by C  
 32 and SR the two conditional expectations are the same) is correct or model (8) is correct. The  
 33 estimator  $\tilde{\beta}$  of  $\beta^*$  is commonly referred to as being doubly robust. The estimator  $\hat{\beta}$ , together with  
 the estimator  $\tilde{\zeta}$  of  $\zeta$ , is jointly defined as

$$35 \quad \begin{pmatrix} \tilde{\beta} \\ \tilde{\zeta} \end{pmatrix} = \left\{ \sum_{i=1, m=0}^{i=n, m=K} \begin{pmatrix} X_{im}(\hat{\alpha}) Q_{im} \\ T_{im} \end{pmatrix} (S_{im}^T, T_{im}^T) \right\}^{-1} \left\{ \sum_{i=1, m=0}^{i=n, m=K} Y_i \begin{pmatrix} X_{im}(\hat{\alpha}) Q_{im} \\ T_{im} \end{pmatrix} \right\}$$

36 **4.4.1. General SNMMs and optimal regime SNMMs.** Suppose we are interested in a particular  
 37  $\bar{d}^*$  with associated functions  $d_m^*[\bar{a}(m-1), \bar{l}(m)]$ . Then we define a  $\bar{d}^*$ -SNMM to be a model for  
 the effect of treatment  $a(m)$  versus treatment 0 at each time  $m$  (as a function of treatment and

1 covariate history up to  $m$ ) when regime  $\bar{d}^*$  is followed beginning at time  $m + 1$ . Formally, let  $\bar{d} =$   
 3  $\{\bar{a}(m - 1), a(m), \underline{d}^*(m + 1)\}$  be the regime that follows the nondynamic regime  $(\bar{a}(m - 1), a(m))$   
 through time (e.g. week)  $m$  and then the regime  $\underline{d}^*(m + 1) = (d_{m+1}^*, \dots, d_K^*)$  from  $m + 1$ . Then  
 5 a  $\bar{d}^*$ -SNMM is defined exactly like the SNMM (7), except that  $Y_{\{\bar{a}(m-1), a(m), \underline{d}^*(m+1)\}}$  replaces  
 $Y_{\{\bar{a}(m-1), a(m), \underline{0}(m+1)\}}$  and  $Y_{\{\bar{a}(m-1), 0, \underline{d}^*(m+1)\}}$  replaces  $Y_{\{\bar{a}(m-1), \underline{0}(m+1)\}}$ . Also we write the known  
 7 function  $\gamma_m[\bar{a}(m), \bar{l}(m), \beta]$  as  $\gamma_m^{\bar{d}^*}[\bar{a}(m), \bar{l}(m), \beta]$  to remind us we are now estimating a  $\bar{d}^*$ -SNMM  
 for a given regime  $\bar{d}^*$ . Note that a  $\bar{d}^*$ -SNMM with  $\bar{d}^*$  the regime where treatment is always  
 withheld is precisely the SNMM (7).

9 In the following  $\gamma_m^{\bar{d}^*}[c, \bar{a}(m - 1), \bar{l}(m), \beta^*]$  is used to denote  $\gamma_m^{\bar{d}^*}[\bar{a}(m), \bar{l}(m), \beta^*]$  with the value  $c$   
 substituted for  $a(m)$ . To estimate the parameter  $\beta^*$  of  $\gamma_m^{\bar{d}^*}[\bar{a}(m), \bar{l}(m), \beta^*]$ , we use  $g$ -estimation as  
 11 described previously except we redefine  $Y_m(\beta)$  to be

$$Y_m(\beta) = Y + \sum_{j=m}^K \gamma_j^{\bar{d}^*}[d_j^*\{\bar{A}(j-1), \bar{L}(j)\}, \bar{A}(j-1), \bar{L}(j), \beta] - \gamma_j^{\bar{d}^*}[\bar{A}(j), \bar{L}(j), \beta] \quad (10)$$

13 Intuitively at each time  $j \geq m$ , if  $\beta = \beta^*$ ,  $Y_m(\beta)$  subtracts from the subject's observed  $Y$  an  
 estimate  $\gamma_j^{\bar{d}^*}[\bar{A}(j), \bar{L}(j), \beta]$  of the effect  $\gamma_j^{\bar{d}^*}[\bar{A}(j), \bar{L}(j), \beta]$  of the subject's observed treatment  
 15  $A(j)$  and replaces it with an estimate of the effect  $\gamma_j^{\bar{d}^*}[d_j^*\{\bar{A}(j-1), \bar{L}(j)\}, \bar{A}(j-1), \bar{L}(j), \beta]$   
 of the treatment  $d_j^*\{\bar{A}(j-1), \bar{L}(j)\}$  that the subject would have had at  $j$  had, possibly contrary to  
 17 fact, she began to follow regime  $\bar{d}^*$  at time  $j$ .

Robins [4] proved that, in the absence of model misspecification, under assumptions SR and  
 19 C, (i) the  $g$ -estimate  $\hat{\beta}$ , now based on expression (10), is consistent for the parameter  $\beta^*$  of  
 $\gamma_m^{\bar{d}^*}[\bar{a}(m), \bar{l}(m), \beta^*]$  and (ii) the sample average  $n^{-1} \sum_{i=1}^n Y_{0,i}(\hat{\beta})$  of  $Y_{0,i}(\hat{\beta})$  is consistent for  $E[Y_{\bar{d}^*}]$ .  
 21 When  $\gamma_j^{\bar{d}^*}[\bar{A}(j), \bar{L}(j), \beta] = A(j)\beta^T R_j$ , we have the closed-form expression

$$\hat{\beta} = \left\{ \sum_{i=1, m=0}^{i=n, m=K} X_{im}(\hat{\alpha}) Q_{im} S_{im}^T \right\}^{-1} \left\{ \sum_{i=1, m=0}^{i=n, m=K} Y_i X_{im}(\hat{\alpha}) Q_{im} \right\}$$

23 with  $S_{im}^T$  redefined as  $\sum_{j=m}^{j=K} \{A_i(j) - d_j^*\{\bar{A}(j-1), \bar{L}(j)\}\} R_{ij}^T$

*Optimal regime SNMMs:* A primary use of  $\bar{d}^*$ -SNMMs is in attempting to estimate the optimal  
 treatment strategy  $\bar{d}^{\text{opt}}$  that maximizes  $E[Y_{\bar{d}}]$  over all treatment regimes  $\bar{d}$ . To do so we specify  
 an optimal SNMM,  $\bar{d}_{\text{opt}}$ -SNMM, based on a function  $\gamma_m^{\bar{d}^{\text{opt}}}[\bar{a}(m), \bar{l}(m), \beta] = \gamma_m^{\bar{d}^{\text{opt}}}[a(m), \bar{a}(m -$   
 1),  $\bar{l}(m), \beta]$ . As an example we might specify that

$$\gamma_m^{\bar{d}^{\text{opt}}}[\bar{a}(m), \bar{l}(m), \beta] = a(m)\{\beta_0 + \beta_1 m + \beta_2 a(m - 1) + \beta_3^T l(m) + \beta_4^T l(m) a(m - 1) + \beta_5^T l(m - 1) + \beta_6^T l(m - 1) a(m - 1)\} \quad (11)$$

If the  $\bar{d}^{\text{opt}}$ -SNMM were correctly specified and we knew the true  $\beta^*$ , then, under assumptions  
 25 SR and C, we would know the optimal treatment regime. Specifically, the optimal treatment  
 $d_{\text{opt}, m}[\bar{a}(m - 1), \bar{l}(m)]$  at time  $m$  given past treatment and covariate history  $[\bar{a}(m - 1), \bar{l}(m)]$  is  
 27  $a(m) \in \mathcal{A}(m)$  that maximizes  $\gamma_m^{\bar{d}^{\text{opt}}}[a(m), \bar{a}(m - 1), \bar{l}(m), \beta^*]$ . In particular, if  $A(m)$  is a binary  
 indicator  $d_{\text{opt}, m}[\bar{a}(m - 1), \bar{l}(m)] = I[\gamma_m^{\bar{d}^{\text{opt}}}[1, \bar{a}(m - 1), \bar{l}(m), \beta^*] > 0]$ .

1 To understand heuristically why this is the case, suppose that  $A(m)$  is binary and that at the  
 2 very last treatment time  $K$ , a subject has past history  $\bar{a}(K-1), \bar{l}(K)$ . If the subject does not take  
 3 treatment at  $K$ , her outcome will be  $Y_{\{\bar{a}(K-1), 0\}}$  while if she takes treatment it will be  $Y_{\{\bar{a}(K-1), 1\}}$ .  
 4 Now, since high values of  $Y$  are desirable the optimal treatment choice is to take treatment if and  
 5 only if  $\gamma_K^{\bar{d}^{\text{opt}}}[\bar{a}(K-1), \bar{l}(K), \beta^*]$  exceeds zero. (If  $\gamma_K^{\bar{d}^{\text{opt}}}[\bar{a}(K-1), \bar{l}(K), \beta^*]$  is precisely zero, it does  
 6 not matter whether treatment is taken; in such cases, we choose not to treat simply to break the  
 7 'tie'.) Now we continue by backward induction. Specifically, suppose we know the optimal regime  
 8 from  $m+1$  onwards. Consider a subject at time  $m$  with past history  $\bar{a}(m-1), \bar{l}(m)$ . Such a subject  
 9 will follow the known optimal regime from  $m+1$  onwards. But she must decide what treatment to  
 10 take at  $m$ . If she does not take treatment at  $m$ , her outcome will be  $Y_{g=\{\bar{a}(m-1), 0, \underline{d}_{\text{opt}}(m+1)\}}$  while  
 11 if she takes treatment at  $m$ , her outcome will be  $Y_{\{\bar{a}(m-1), 1, \underline{d}_{\text{opt}}(m+1)\}}$ . Thus, according to model  
 (11), she should take treatment if and only if  $\gamma_m^{\bar{d}^{\text{opt}}}[\bar{a}(m-1), \bar{l}(m), \beta^*]$  exceeds zero.

13 Now if we knew  $\gamma_m^{\bar{d}^{\text{opt}}}[\bar{a}(m), \bar{l}(m), \beta^*]$  and thus we knew the optimal regime, we would simply  
 14 have each subject in the population follow the optimal regime beginning at time 0, where at  
 15 each time  $m$  the covariates  $L(m)$  must be measured and recorded, so the evolving covariate data  
 necessary to follow the optimal regime will be available.

17 Define  $d_{\text{opt}, m}[\bar{a}(m-1), \bar{l}(m), \beta]$  to be the  $a(m) \in \mathcal{A}(m)$  that maximizes  $\gamma_m^{\bar{d}^{\text{opt}}}[a(m), \bar{a}(m-1),$   
 $\bar{l}(m), \beta]$ . Since the optimal treatment to give at time  $m$  is  $d_{\text{opt}, m}[\bar{a}(m-1), \bar{l}(m), \beta^*]$  then we see that  
 19 to estimate the optimal regime we need an estimate  $\hat{\beta}$  of  $\beta^*$ , which we can obtain by  $g$ -estimation  
 based on the generalization

$$21 \quad Y_m(\beta) = Y + \sum_{j=m}^K \gamma_j^{\bar{d}^{\text{opt}}} [d_{\text{opt}, j}[\bar{A}(j-1), \bar{L}(j), \beta], \bar{A}(j-1), \bar{L}(j), \beta] - \gamma_j^{\bar{d}^{\text{opt}}} [\bar{A}(j), \bar{L}(j), \beta] \quad (12)$$

of expression (10). Note that (12) differs from (10) in that the regime  $d_{\text{opt}, j}[\bar{A}(j-1), \bar{L}(j), \beta]$   
 23 itself is a function of the parameter  $\beta$ . Nonetheless, one can use  $g$ -estimation based on  $Y_m(\beta)$  of  
 (12) to estimate  $\beta^*$  and set confidence intervals by searching over a grid of  $\beta$  values. Furthermore,  
 25 we can also obtain an estimate  $N^{-1} \sum_{i=1}^N Y_{0,i}(\hat{\beta})$  of the mean  $E[Y_{\bar{d}^{\text{opt}}}]$  of  $Y$  when the population is  
 treated optimally. However, there is no longer an explicit closed-form expression for the  $g$ -estimate  
 27  $\hat{\beta}$  based on (12), even when  $\gamma_m^{\bar{d}^{\text{opt}}}[\bar{A}(m), \bar{L}(m), \beta] = A(m) R_m^T \beta$  is linear in  $\beta$ , with  $R_m = r_m\{\bar{A}(m-1),$   
 $\bar{L}(m)\}$  a known vector function. For example, when  $A(m)$  is binary,  $d_{\text{opt}, m}[\bar{A}(m-1), \bar{L}(m), \beta] =$   
 29  $I[R_m^T \beta > 0]$  and so  $Y_m(\beta)$  is no longer linear in  $\beta$  because  $\beta$  now occurs within an indicator  
 function. In fact, when the dimension of  $\beta$  is moderate, the  $g$ -estimate  $\hat{\beta}$  is exceedingly difficult  
 31 to compute by search. However, the following alternative, computationally tractable approach can  
 be used when  $\gamma_m^{\bar{d}^{\text{opt}}}[\bar{A}(m-1), \bar{L}(m), \beta]$  is linear in  $\beta$ , i.e. it is of the form  $\gamma_m^{\bar{d}^{\text{opt}}}[\bar{A}(m), \bar{L}(m), \beta] =$   
 33  $A(m) R_m^T \beta$ .

*A closed-form estimator of the optimal regime:* We only consider the case of binary  $A(m)$ .  
 35 Suppose for the moment that  $\gamma_m^{\bar{d}^{\text{opt}}}[\bar{A}(m), \bar{L}(m), \beta]$  is of the form  $A(m) R_m^T \beta_m$ , that is, it depends  
 linearly on a separate parameter vector  $\beta_m$  at each time  $m$  and we assume that the components of  
 37  $\beta^T = (\beta_0^T, \dots, \beta_K^T)$  are variation independent. We will describe estimators  $\tilde{\beta}_m$  of  $\beta_m^*$  that are doubly  
 robust in the sense of being consistent and asymptotically normal for  $\beta_m^*$  if either model (8) is  
 39 correct for all  $m$ 's or if model

$$E[Y_m(\beta^*) | \bar{L}(m), \bar{A}(m-1)] = \zeta_m^T z_m[\bar{L}(m), \bar{A}(m-1)]$$

- 1 where  $z_m[\bar{L}(m), \bar{A}(m-1)]$  is a known function of  $(\bar{L}(m), \bar{A}(m-1))$  and  $\zeta_m$  is unknown, is correct  
 2 for all  $m$ 's. To compute the estimators  $\tilde{\beta}_m$  we first compute the partial MLE  $\hat{\alpha}$  of  $\alpha$  under model (8).  
 3 Next, beginning with  $\beta_K$ , we recursively compute  $(\tilde{\beta}_m, \tilde{\eta}_m, \tilde{\zeta}_m)$ , the OLS estimator of  $(\beta_m, \eta_m, \zeta_m)$   
 4 in the regression model

5 
$$Y_{m+1}(\tilde{\beta}_{m+1}) = A(m)R_m^T\beta_m + \text{expit}\{\hat{\alpha}^T B(k)\}R_m^T\eta_m + Z_m^T\zeta_m + \varepsilon_{m+1}$$

6 where  $Y_{K+1}(\tilde{\beta}_{K+1}) = Y$ ,  $Y_{m+1}(\tilde{\beta}_{m+1}) = Y + \sum_{j=m+1}^K [I\{R_j^T\tilde{\beta}_j > 0\} - A(j)]R_j^T\tilde{\beta}_j$  for  $0 \leq m \leq K$ , and  
 7  $\varepsilon_{m+1}$  is the unobserved error term.

*Remark*

- 9 The estimators  $\tilde{\beta}_m$  are possibly inefficient members of a general class of estimators  $\tilde{\beta}_m(\mathbf{s}, \mathbf{q})$ ,  
 10 indexed by vectors of functions  $s_m$  and  $q_m, m = 0, \dots, K$ , defined recursively as follows:

11 
$$\tilde{\beta}_m(\mathbf{s}, \mathbf{q}) = \left[ \sum_{i=1}^{i=n} A_i(m) X_{im}(\hat{\alpha}) Q_{im} R_{im}^T \right]^{-1} \left[ \sum_{i=1}^{i=n} \{Y_{m+1}(\tilde{\beta}_{m+1}(\mathbf{s}, \mathbf{q}))_j - S_{im}\} X_{im}(\hat{\alpha}) Q_{im} \right]$$

12 where  $X_m(\hat{\alpha}) = [A(m) - \text{expit}\{\hat{\alpha}^T B(k)\}]B_m$  and  $S_m = s_m[\bar{L}(m), \bar{A}(m-1)]$  and  $Q_m = q_m[\bar{L}(m), \bar{A}(m-1)]$   
 13 are user-specified functions, their choice affecting efficiency but not consistency when the  
 14 treatment model (8) is correct.

15 Now suppose in our  $d_{\text{opt}}$ -SNMM model, the same parameter vector  $\beta$  applies to each time  $m$ .  
 16 To be concrete, consider the  $d_{\text{opt}}$ -SNMM (11). In that case, we first estimate a bigger model that  
 17 has a separate variation-independent parameter vector  $\beta_m$  at each time  $m$ ; model (11) is then the  
 18 submodel that imposes  $\beta_m = \beta$  for all  $m$ 's. Let  $\tilde{\Omega}^{-1}$  be a nonparametric bootstrap estimate of the  
 19 covariance matrix of  $(\tilde{\beta}_0, \dots, \tilde{\beta}_K)$ . We then estimate  $\beta$  by an inverse covariance-weighted average  
 20  $\hat{\beta} = 1_{K+1}^T \tilde{\Omega}^{-1} (\tilde{\beta}_0, \dots, \tilde{\beta}_K)^T / (1_{K+1}^T \tilde{\Omega}^{-1} 1_{K+1})$  of the  $\tilde{\beta}_m$ , where  $1_{K+1}$  is a  $K+1$  vector with all  
 21 components equal to 1.

22 Note that the  $d_{\text{opt}}$ -SNMM model (11) is a nonsaturated model. For example, it assumes that  
 23 the optimal regime does not depend on covariate values two weeks in the past or treatment values  
 24 three weeks in the past, which may be incorrect. If the  $d_{\text{opt}}$ -SNM model is badly misspecified, then  
 25 the estimated optimal regime  $\hat{d}_{\text{opt},m}[\bar{a}(m-1), \bar{l}(m)]$  may be a poor estimate of the actual optimal  
 26 regime. Because in realistic studies highly nonsaturated  $d_{\text{opt}}$ -SNMM models must be employed,  
 27 misspecification can be a serious problem.

28 We note that in using a  $g_{\text{opt}}$ -SNMM model to find the optimal regime, it was necessary  
 29 for us to estimate the treatment strategy  $d_{\text{opt}} = \{d_{\text{opt},0}[\bar{l}(0)], d_{\text{opt},0}[a(0), \bar{l}(1)], \dots, d_{\text{opt},K}[\bar{a}(K-1), \bar{l}(K)]\}$   
 30 that maximized  $E_d[Y]$  over all regimes  $d$ , including regimes in which treatment  
 31 depends on past treatment as well as covariate history. However, one can always construct a  
 32 regime  $d_{\text{opt}}^\dagger = \{d_{\text{opt},0}^\dagger[\bar{l}(0)], d_{\text{opt},0}^\dagger[\bar{l}(1)], \dots, d_{\text{opt},K}^\dagger[\bar{l}(K)]\}$  in which treatment depends only on past  
 33 covariate history such that following regime  $d_{\text{opt}}^\dagger$  from time 0 onwards is precisely equivalent to  
 34 following  $d_{\text{opt}}$  from time 0. Nonetheless, it can be important to know  $d_{\text{opt}}$  rather than only  $d_{\text{opt}}^\dagger$   
 35 as the following example shows. Suppose that a (random) member of the source population has  
 36 observed history  $(\bar{A}(m-1), \bar{L}(m)) = (\bar{a}(m-1), \bar{l}(m))$  (under standard care) that is not consistent  
 37 with following the optimal regime  $d_{\text{opt}}$  and comes to our attention only at time  $m$ . We wish  
 to intervene beginning at  $m$  and give the subject the optimal treatment strategy from time  $m$

- 1 onwards. Under the C and SR assumptions, the optimal treatment strategy for such a subject is  
 { $d_{\text{opt},m}[a(m-1), \bar{l}(m)], \dots, d_{\text{opt},K}[\bar{a}(K-1), \bar{l}(K)]$ }. This strategy can be implemented only if we  
 3 know (or have a good estimate of)  $d_{\text{opt}}$ ; knowledge of  $d_{\text{opt}}^\dagger$  does not suffice.

## 5. STRENGTHS AND WEAKNESSES OF MSMs AND SNMMs

- 5 MSMs have the advantage that they are easy to understand and easy to fit with standard off-the-  
 shelf software that allows for weights. These two points explain their rapid adoption compared  
 7 with SNMMs. The usefulness of MSMs has been extended by the introduction of dynamic MSMs  
 to estimate the optimal regime in a class.

- 9 However, IPTW estimation of MSMs has four drawbacks not shared by  $g$ -estimation of SNMMs.  
 First, if the number of time periods is large the product in the denominator of the weights can  
 11 become very small for some subjects who then receive inordinately large weights, leading both to  
 bias when the weights must be estimated [and to so-called pseudo-bias] even when they are known,  
 13 see Scharfstein *et al.* [11] and to imprecision. Problems with large or even truly infinite weights  
 (when positivity does not hold) can be somewhat ameliorated but not cured, by using bounded  
 15 doubly robust estimators [12], adjusting for baseline covariates and then using the covariates in  
 the numerator of the weights, downweighting or eliminating from consideration regimes  $g = d_x$   
 17 associated with very small weights, using locally semiparametric efficient estimators or bounded  
 influence estimators for nonsaturated MSMs (as these estimators downweight regimes  $g = d_x$  that  
 19 result in excessively large weights in a near optimal fashion), and using diagnostics for the undue  
 influence of large weights and for the consequences of truncating large weights [13]. Second,  
 21 MSMs cannot be used to estimate causal effects when treatment is confounded but an instrumental  
 variable is available. Third, sensitivity analysis models to assess the impact of departures from the  
 23 assumption of SR are much more restrictive for MSMs and less useful than those for SNMMs.  
 Fourth, SNMMs, in contrast to MSMs, allow one to directly model interactions between treatment  
 25 and evolving time-dependent covariates in order to look for qualitative effect modification.

- In terms of estimation of optimal regimes, both MSMs and SNMMs have their distinct place.  
 27 General MSMs are excellent for estimating the optimal regime in a prespecified parametrized class  
 of regimes (such as the optimal CD4 cell count at which to start therapy) that still may include  
 29 all logistically feasible regimes, particularly in settings with resource constraints that preclude  
 implementing complex regimes.

- 31 In contrast, the method of backward induction on which  $g$ -estimation of optimal SNMMs is  
 based requires that the set of potential regimes from which the optimal is to be selected include  
 33 all functions of an increasing (in time) amount of information (i.e. of an increasing sigma field).  
 Thus, optimal regime SNMMs are useful for estimating the optimal regime in the huge class of  
 35 dynamic regimes in which treatment at each  $m$  can depend on any function of the entire measured  
 past  $\bar{l}(m), \bar{a}(m-1)$  (the case considered above) or, as described in Section 7 of Robins [4] in  
 37 the smaller, but still large, class in which treatment at each  $m$  can depend on any function of  
 $\bar{w}(m), \bar{a}(m-1)$ , where  $W(m)$  is a subvector of the covariates in  $L(m)$ . Even if  $W(m)$  is just a  
 39 CD4 cell count at  $m$ , it is possible that the optimal treatment decision at time  $m$  may be a complex  
 function of CD4 cell counts at all past times. Such a regime, though optimal in its class, may  
 41 be logistically impossible to implement, in which case it may be necessary to choose among a  
 smaller class of logistically feasible regimes by fitting a general MSM.

## 6. BETWEEN POPULATION EXTRAPOLATION AND OPTIMIZATION OF PROGNOSTIC TESTING STRATEGIES

Let  $\bar{d}_x$  again denote the nonrandom dynamic regime ‘begin HAART the first time  $t$  the measured CD4 count falls below  $x$ ’, where  $x$  is measured in whole numbers. Let  $\mathcal{X} = \{201, \dots, 500\}$  and let  $\{\bar{d}_x; x \in \mathcal{X}\}$  be the set of candidate regimes. Let  $x_{\text{opt}}$  be the  $x \in \mathcal{X}$  for which the expected utility  $E_{\bar{d}_x}[Y]$  is a maximum. It is clear that  $x_{\text{opt}}$  will depend on the frequency with which subjects have their CD4 count measured. For example, suppose that in a particular patient population, CD4 counts are obtained very frequently, say weekly, and  $x_{\text{opt}}$  is 340. If in the same population, the CD4 counts were measured much less frequently (say every 6 months), then  $x_{\text{opt}}$  would presumably exceed 340, as many subjects who were well above 340 at the time of their last CD4 blood test but were not started on HAART may be well below 340 at the time of their next test 6 months later.

These considerations raise at least two issues. First, suppose the empirical frequency of blood tests to assess CD4 counts differs between two biologically similar populations but good longitudinal data are available only on the first population. How can we use data from the first population to estimate  $x_{\text{opt}}$  in the second? This extrapolation question presumes that, for logistical or financial reasons, we do not have the ability to change the frequency of CD4 blood tests in the second population. Thus, although, for purposes of continuity, we use a CD4 blood test as a prototype, the methods we develop may be more relevant to tests that are either more expensive or present a greater logistical challenge than a CD4 count.

Second, suppose that in a particular population on which we have collected longitudinal data we do have the ability to increase at some financial cost, or decrease with some financial savings, the frequency of CD4 tests and we desire to use the data to determine jointly the optimal CD4 testing schedule and the optimal time to start HAART. This second issue is the well-known issue of assessing the ‘value of information’ in sequential decision making; a CD4 test has no direct biological effect on a patient whatsoever. Its net value, if any, is that the information supplied by the test can be used to fine tune the time to start HAART, leading to a net increase in expected utility, even when the costs of the test are included in the utility function. Of course, to include the costs of a CD4 test in the utility implies that our utility function is in dollars and that we must place a monetary value, usually adjusted for quality of life, on each additional year of life. It is not our purpose to discuss this highly contentious issue. Our goal here is limited to the development of statistical methodology.

### 6.1. Formalization

We formalize the problem as follows. The potentially observed data at time  $m$  are now  $L(m) = (Z(m)^T, I(m)^T)^T$ ,  $A(m)$ , and  $T(m)$ , where  $T(m)$  is the indicator of whether a test was performed at time  $m$ ,  $I(m)$  is the biological function measured by a test (e.g. CD4 count) at  $m-1$ ,  $Z(m)$  are the other components of the covariate vector  $L(m)$ , and  $A(m)$  is the treatment at  $m$ . Let  $O(m) = (Z(m), I(m), A(m), T(m))$ , which we assume is temporally ordered in the sense that a decision whether to test at  $m$  can depend on  $Z(m), I(m), A(m)$  and the decision on treatment can potentially depend on  $(Z(m), I(m))$ . However, we observe  $I(m)$  only if  $T(m-1) = 1$  while  $Z(m)$  and  $A(m)$  are always observed. [The fact that the test at  $m-1$  gives us knowledge of  $I$  at  $m$  rather than  $m-1$  is inconsequential and can be taken as a convention that simplifies the notation.] Thus, the actually observed data at time  $m$  are  $O^*(m) = (Z(m), I^*(m), A(m), T(m))$ ,

1 where  $I^*(m) = T(m-1)I(m)$ , i.e.  $I^*(m)$  is equal to the biological function at time  $m-1$  if the  
 2 test was actually performed, and it is equal to 0 otherwise. The vector  $L^*(m) \equiv (Z(m), I^*(m))$   
 3 encodes all new information about the patient's health status that the physician has available at  
 4 time  $m$ . In contrast, the vector  $J(m) \equiv (A(m), T(m))$  encodes the pair of intervention variables  
 5 whose values depend on the doctor's decision at time  $m$  (i.e. which treatment to assign at time  $m$   
 6 and whether or not to take a test at time  $m$ ). Throughout, we let  $\bar{\mathcal{J}}$  denote the sample space of  
 7  $\bar{J}(K)$ , where we continue to use our convention for overbars, i.e.  $\bar{J}(m) = (J(0), \dots, J(m))$ .

8 For later use, it will be convenient to define the vector  $\bar{O}^*(k) = (O^*(0), \dots, O^*(k))$  of all the  
 9 data observed up to time  $k$ , and the vectors  $\bar{O}^{*t}(k) = (\bar{O}^*(k-1), Z(k), I^*(k), A(k))$ ,  $\bar{O}^{*.a}(k) =$   
 10  $(\bar{O}^*(k-1), Z(k), I^*(k))$ , and  $\bar{O}^{*.i}(k) = (\bar{O}^*(k-1), Z(k))$ , which are equal to  $\bar{O}^*(k)$  but with  
 11  $T(k)$ ,  $(A(k), T(k))$ , and  $(I^*(k), A(k), T(k))$  removed.

12 The counterfactual  $L$ -history  $\bar{L}_{\bar{j}}(m) = \{L(0), L_{a(0), t(0)}(1), \dots, L_{\bar{a}(m-1), \bar{t}(m-1)}(m)\}$  through  $m$   
 13 under the joint treatment and testing regime  $\bar{j} = (\bar{a}, \bar{t})$  is assumed to satisfy the following assump-  
 14 tion. To state this assumption, let  $\bar{L}_{\bar{a}}(m) = \{L(0), L_{a(0)}(1), \dots, L_{\bar{a}(m-1)}(m)\}$ .

15 *No direct effect (NDE) assumption:*  $\bar{L}_{\bar{a}, \bar{t}}(m) = \bar{L}_{\bar{a}}(m)$  w.p.1. for all  $m$ 's.

16 The NDE assumption encodes the fact that testing *per se* has no direct effect on  $L(k)$  when  
 17 treatment is set to  $\bar{a}$ . The assumption implies that  $\bar{L}_{\bar{a}, \bar{t}} = \bar{L}_{\bar{a}} \equiv L_{\bar{a}(K)}(K+1)$  and consequently the set  
 18  $\bar{L}_{\bar{\mathcal{J}}} \equiv \{\bar{L}_{\bar{j}}; \bar{j} \in \bar{\mathcal{J}}\}$ , denoting all vectors of counterfactual health status variables in the hypothetical  
 19 scenarios in which the intervention variables are set to each of their possible configurations  $\bar{j} =$   
 20  $(\bar{a}, \bar{t})$ , is equal to the set  $\bar{L}_{\bar{\mathcal{A}}} \equiv \{\bar{L}_{\bar{a}}; \bar{a} \in \bar{\mathcal{A}}\}$  of all counterfactuals obtained when setting only the  
 21 treatment variables.

22 We also define the counterfactual vector  $\bar{L}_{\bar{a}, \bar{t}}^*(m) \equiv \bar{L}_{\bar{j}}^*(m) = \{L(0), L_{j(0)}^*(1), \dots, L_{\bar{j}(m-1)}^*(m)\}$   
 23 with  $L_{\bar{j}(m-1)}^*(m) = (Z_{\bar{j}(m-1)}(m), I_{\bar{j}(m-1)}^*(m))$  and  $I_{\bar{j}(m-1)}^*(m) = I_{\bar{j}(m-1)}(m)t(m-1)$ . The vector  
 24  $\bar{L}_{\bar{j}(m-1)}^*(m)$  encodes all health outcomes that would actually be recorded up to time  $m$  if treatment  
 25  $\bar{A}(m-1) = \bar{a}(m-1)$  and test decisions  $\bar{T}(m-1) = \bar{t}(m-1)$  were implemented. Under the NDE  
 26 assumption  $I_{\bar{j}(m-1)}^*(m) = I_{\bar{a}(m-1)}(m)t(m-1)$  but  $\bar{I}_{\bar{j}(m-1)}(m) = I_{\bar{a}(m-1)}(m)$ ; hence, in contrast to  
 27  $\bar{I}_{\bar{j}}(m) = \bar{I}_{\bar{j}(m-1)}(m)$ ,  $\bar{I}_{\bar{j}}^*(m) = I_{\bar{j}(m-1)}^*(m)$  depends on  $\bar{t}$  even under the NDE assumption.

28 For notational convenience, we also define  $\bar{I}_{\bar{t}(m-1)}^*(m) = \bar{I}_{\bar{A}(m-1), \bar{t}(m-1)}^*(m)$  and  $\bar{L}_{\bar{t}(m-1)}^*(m) =$   
 29  $\bar{L}_{\bar{A}(m-1), \bar{t}(m-1)}^*(m)$  so  $\bar{L}_{\bar{t}(m-1)}^*(m)$  is a subject's counterfactual  $L^*$ -history through  $m$  with treatment  
 30 history equal to the observed history  $\bar{A}(m-1)$  but testing history equal to  $\bar{t}(m-1)$ .

31 As in the preceding sections, we again make a consistency assumption (C), which links a specific  
 32 vector of the counterfactual set  $\bar{L}_{\bar{\mathcal{J}}}$  to the observed data. Specifically, we assume

33 *Consistency assumption (C):*  $\bar{I}^*(m) = \bar{I}_{\bar{J}(m-1)}^*(m) \equiv \bar{I}_{\bar{T}(m-1)}^*(m)$  and  $\bar{L}(m) = \bar{L}_{\bar{A}(m-1)}(m)$  for  
 34  $m = 0, 1, \dots, K$ .

35 A random dynamic  $j$ -regime is a conditional law  $G$  for  $\bar{J}$  given  $\bar{L}_{\bar{\mathcal{J}}}$  with density denoted as  
 36  $g(\bar{j}|\bar{l}_{\bar{\mathcal{J}}})$ . We denote the  $G$  generating the data in our study as  $G^\top$  and its density as  $g^\top(\bar{j}|\bar{l}_{\bar{\mathcal{J}}})$ . We  
 37 let  $P$  denote a (generic) marginal distribution of  $\bar{L}_{\bar{\mathcal{J}}}$  and  $p(\bar{l}_{\bar{\mathcal{J}}})$  its density evaluated at  $\bar{l}_{\bar{\mathcal{J}}}$ . We let  
 38  $P^\top$  denote the actual  $P$  that generates the (counterfactual) data  $\bar{L}_{\bar{\mathcal{J}}}$  in the population under study.

39 Let  $F_{(G, P)}$  and  $f_{(G, P)}(\bar{l}_{\bar{\mathcal{J}}}, \bar{j})$  denote the distribution and density of  $(\bar{L}_{\bar{\mathcal{J}}}, \bar{J})$  under the joint law  
 40  $(G, P)$ . Thus,  $f_{(G, P)}(\bar{l}_{\bar{\mathcal{J}}}, \bar{j}) = p(\bar{l}_{\bar{\mathcal{J}}})g(\bar{j}|\bar{l}_{\bar{\mathcal{J}}})$ . Throughout, in a slight abuse of notation, we use the  
 41 same symbol, say  $g$ , to denote different conditional densities associated with the distribution  $G$ ,

1 the actual random variables connected to the conditional densities being those that take values  
 2 that appear in the expression for  $g$ . Thus, for example,  $g[j(k)|\bar{\mathcal{O}}^{*,a}(k)]$  stands for the conditional  
 3 density of  $J(k)$  (evaluated at  $j(k)$ ) given  $\bar{\mathcal{O}}^{*,a}(k) = \bar{\mathcal{O}}^{*,a}(k)$  while  $g(\bar{j}|\bar{\mathcal{L}}_{\mathcal{J}})$  stands for the conditional  
 4 density of  $\bar{J}$  (evaluated at  $\bar{j}$ ) given  $\bar{\mathcal{L}}_{\mathcal{J}} = \bar{\mathcal{L}}_{\mathcal{J}}$ .

5 We say  $G$  is sequentially randomized given data  $\bar{\mathcal{O}}^{*,a}$  ( $\bar{\mathcal{O}}^{*,a}$ -SR) if for all  $\bar{j}$ ,  $\bar{\mathcal{L}}_{\mathcal{J}}$

$$g(\bar{j}|\bar{\mathcal{L}}_{\mathcal{J}}) = \prod_{k=0}^K g[j(k)|\bar{\mathcal{O}}^{*,a}(k)]$$

7 The density  $f_{(G^{\top}, P^{\top})}(\bar{\mathcal{L}}_{\mathcal{J}}, \bar{j})$  is said to satisfy coarsening at random (CAR) with respect to the  
 8 underlying full data  $\bar{\mathcal{L}}_{\mathcal{J}}$  and observed data  $\bar{\mathcal{O}}^* = (\bar{\mathcal{L}}^*, \bar{J})$  if  $g^{\top}(\bar{j}|\bar{\mathcal{L}}_{\mathcal{J}})$  depends on  $\bar{\mathcal{O}}^*$  only. It follows  
 9 that if  $G^{\top}$  is  $\bar{\mathcal{O}}^{*,a}$ -SR, then  $f_{(G^{\top}, P^{\top})}(\bar{\mathcal{L}}_{\mathcal{J}}, \bar{j})$  satisfies CAR.

10 As with dynamic treatment regimes, we can also define nonrandom  $j$ -regimes that are defined  
 11 by functions  $\bar{b} = (b_0, \dots, b_K)$ , so that at each time  $k$ , a subject with observed past  $\bar{\mathcal{O}}^{*,a}(k) = \bar{\mathcal{O}}^{*,a}(k)$   
 12 is assigned to treatment and testing status  $J(k) = (A(k), T(k))$  equal to  $b_k[\bar{\mathcal{O}}^{*,a}(k)] \in \mathcal{J}(k)$ . Any  
 13 nonrandom  $j$ -regime  $\bar{b} = (b_0, \dots, b_K)$  is indeed a special case of a  $\bar{\mathcal{O}}^{*,a}$ -SR random regime in  
 14 which, for each  $k$ ,  $g_k[j(k)|\bar{\mathcal{O}}^{*,a}(k)]$  is zero for all  $j(k) \in \mathcal{J}(k)$ , except for  $j(k) = b_k[\bar{\mathcal{O}}^{*,a}(k)]$  for  
 15 which it is one. In the next theorem, we shall also need the following generalization of the earlier  
 16 assumption PO.

17 *Joint positivity assumption (PO\*) for a regime  $G^{\top}$  with respect to another regime  $G$ :  $g(\bar{j}|\bar{\mathcal{L}}_{\mathcal{J}})$*   
 18 *is dominated by (i.e. absolutely continuous w.r.t.)  $g^{\top}(\bar{j}|\bar{\mathcal{L}}_{\mathcal{J}})$  with  $P^{\top}$ -probability 1, i.e.*

19 
$$g(\bar{j}|\bar{\mathcal{L}}_{\mathcal{J}}) > 0 \text{ implies } g^{\top}(\bar{j}|\bar{\mathcal{L}}_{\mathcal{J}}) > 0 \text{ w.p.1. under } P^{\top} \tag{13}$$

20 For  $\bar{\mathcal{O}}^{*,a}$ -SR regimes  $G^{\top}$  and  $G$ , the PO\* assumption for  $G^{\top}$  w.r.t.  $G$  is equivalent to the assumption  
 21 that, for all  $k \leq K$ ,  $\Pr_{(G, P^{\top})}[g^{\top}\{J(k)|\bar{\mathcal{O}}^{*,a}(k)\} > 0] = 1$ . That is, if under a  $j$ -regime  $G$ , a treatment  
 22 assignment and test decision were feasible at time  $k$ , i.e. had positive probability of occurring at  $k$ ,  
 23 for a given observed past  $\bar{\mathcal{O}}^{*,a}(k)$ , then they would also have positive probability of occurring in  
 24 the actual population from where the observed data were sampled.

25 The following theorem establishes a key result connecting the mean of any function  $h(\bar{\mathcal{O}})$  of  
 26  $\bar{\mathcal{O}}$  in the hypothetical world in which the  $j$ -regime  $G$  is implemented to the mean of  $h(\bar{\mathcal{O}})$  in the  
 27 actual study under the joint positivity assumption PO\*. In the following subsection, we exploit  
 28 the results of this theorem to develop between-population extrapolation and estimation of joint  
 29 optimal treatment assignment and testing decision strategies.

*Theorem 6.1*

31 Suppose assumption C holds and the  $\bar{\mathcal{O}}^{*,a}$ -SR holds for  $G^{\top}$  and  $G$ . Then,

$$E_{(G, P^{\top})}[h(\bar{\mathcal{O}})] = E_{(G^{\top}, P^{\top})} \left[ \frac{\prod_{k=0}^K g[J(k)|\bar{\mathcal{O}}^{*,a}(k)]}{\prod_{k=0}^K g^{\top}[J(k)|\bar{\mathcal{O}}^{*,a}(k)]} h(\bar{\mathcal{O}}) \right]$$

32 for all  $h(\bar{\mathcal{O}})$  for which  $E_{(G, P^{\top})}[|h(\bar{\mathcal{O}})|] < \infty$  if and only if assumption PO\* for  $G^{\top}$  with respect to  
 33  $G$  holds.

34 Theorem 6.1 is just the Radon-Nikodym theorem applied to the laws  $(G, P^{\top})$  and  $(G^{\top}, P^{\top})$ . Note  
 35 that under assumptions PO\*, C, and  $\bar{\mathcal{O}}^{*,a}$ -SR for  $G^{\top}$  and  $G$ ,  $\prod_{k=0}^K g[J(k)|\bar{\mathcal{O}}^{*,a}(k)] / \prod_{k=0}^K g^{\top}[J(k)$

1  $|\overline{\mathcal{O}}^{*,a}(k)|$  is indeed the likelihood ratio (Radon-Nikodym derivative) of  $(G, P^\top)$  with respect to  $(G^\top, P^\top)$ .

3 *6.2. Between-population extrapolation and optimal strategies*

5 In this subsection, we assume that assumption  $\text{PO}^*$  for  $G^\top$  with respect to  $G$  holds. Further, in short, we refer to the study population on whom we have obtained data as population  $G^\top$ .

7 *6.2.1. Between-population extrapolation.* In this section, we will apply Theorem 6.1 to derive  
 9 estimators of the optimal treatment strategy in a population, throughout referred to as population  $G$ ,  
 11 which follows the testing regime with conditional probabilities  $g[t(k)|\bar{a}(k), \bar{i}(k-1), \bar{l}^*(k)]$ . The  
 13 estimators are based on data from the study population  $G^\top$ , which follows a possibly different  
 15 testing regime with conditional probabilities  $g^\top[t(k)|\bar{a}(k), \bar{i}(k-1), \bar{l}^*(k)]$ . In this section, we only  
 17 wish to optimize the treatment regime, taking the testing regime  $g$  as given. In the following  
 19 section, we shall consider jointly optimizing treatment and testing regimes. We will assume that  
 21 the  $\overline{\mathcal{O}}^{*,a}$ -SR assumption holds in both populations  $G^\top$  and  $G$ . Furthermore, we assume that for  
 each  $k$ , the conditional probability  $g[t(k)=1|\bar{a}(k), \bar{i}(k-1), \bar{l}^*(k)]$  of performing a test at  $k$  (with  
 result  $I(k+1)$ ) in population  $G$  given the observed data  $(\bar{a}(k), \bar{i}(k-1), \bar{l}^*(k))$  is known. In practice,  
 the testing schedule will not be known for population  $G$  and our specification of  $g$  will reflect a  
 best guess, which we nevertheless treat as known in the following analysis. However, in practice,  
 the selected  $g$  could be varied in a sensitivity analysis or be replaced by an empirical estimate if  
 appropriate data were available on population  $G$ . We assume that populations  $G$  and  $G^\top$  have the  
 same marginal distribution  $P^\top$  of  $\underline{L}_{\mathcal{A}}$ . In certain settings, this latter assumption can be understood  
 as a formalization of the assumption that the two populations are biologically similar.

Suppose that we are given a set of nonrandom treatment regimes  $\{\bar{d}_x, x \in \mathcal{X}\}$  to be implemented  
 in a setting in which testing for  $I(k)$  is not necessarily done at each time  $k$ . In this setting,  $\bar{d}_x$   
 is equal to a collection of functions  $\{d_{x,k}; k=0, \dots, K\}$  where each  $d_{x,k}$  maps the data  $(\bar{A}(k-1),$   
 $\bar{T}(k-1), \bar{L}^*(k))$  to a treatment  $a(k)$ , that is,  $d_{x,k}[\bar{a}(k-1), \bar{i}(k-1), \bar{l}^*(k)] \in \mathcal{A}(k)$ .

The collection of conditional densities  $\{g[t(k)|\bar{a}(k), \bar{i}(k-1), \bar{l}^*(k)], k=0, \dots, K\}$ , together with  
 a given treatment regime  $\bar{d}_x$ , determines an  $\overline{\mathcal{O}}^{*,a}$ -SR random dynamic  $j$ -regime  $G_x$  in population  $G$ .  
 Specifically, define the conditional densities as

$$g_x[a(k)|\bar{a}(k-1), \bar{i}(k-1), \bar{l}^*(k)] = \begin{cases} 1 & \text{if } a(k) = d_{x,k}[\bar{a}(k-1), \bar{i}(k-1), \bar{l}^*(k)] \\ 0 & \text{otherwise} \end{cases} \quad (14)$$

$$g_x[t(k)|\bar{a}(k), \bar{i}(k-1), \bar{l}^*(k)] = g[t(k)|\bar{a}(k), \bar{i}(k-1), \bar{l}^*(k)] \quad (15)$$

By definition,  $g_x[j(k)|\overline{\mathcal{O}}^{*,a}(k)] = g_x[a(k)|\bar{a}(k-1), \bar{i}(k-1), \bar{l}^*(k)]g_x[t(k)|\bar{a}(k), \bar{i}(k-1), \bar{l}^*(k)]$  and,  
 by the  $\overline{\mathcal{O}}^{*,a}$ -SR assumption,  $g_x(\underline{j}|\underline{l}_{\mathcal{A}}) = \prod_{k=0}^K g_x[t(k)|a(k), \overline{\mathcal{O}}^{*,a}(k)]g_x[a(k)|\overline{\mathcal{O}}^{*,a}(k)]$ . Note, since  
 $d_{x,k}[\bar{a}(k-1), \bar{i}(k-1), \bar{l}^*(k)] = d_{x,k}[\overline{\mathcal{O}}^{*,a}(k)]$  is a deterministic treatment regime,  $g_x[a(k)|\overline{\mathcal{O}}^{*,a}(k)] =$   
 $g_x[a(k)|\bar{a}(k-1), \bar{i}(k-1), \bar{l}^*(k)]$  automatically holds and thus is not an assumption. Thus, for  
 regime  $g_x$ , the  $\overline{\mathcal{O}}^{*,a}$ -SR assumption reduces to the assumption that  $g_x[t(k)|\bar{a}(k), \bar{i}(k-1), \bar{l}^*(k)] =$   
 $g_x[t(k)|\bar{a}(k), \bar{i}(k-1), \bar{l}^*(k)]$ . To be concrete we will consider the following running example.

*Running example:* Let  $\bar{d}_x$  again denote the nonrandom dynamic regime ‘begin HAART the first  
 time  $k$  the measured CD4 count falls below  $x$ ,’ with  $x \in \mathcal{X}\{201, \dots, 500\}$ . In order to avoid additional

1 complications, it will be useful to assume that, under both  $g^\top$  and  $g_x$ , a subject who initiates  
 HAART remains on the same HAART regimen thereafter and takes no other HIV medications, in  
 3 which case there is no reason to obtain a CD4 test once HAART has been started. We formalize  
 this assumption by assuming

$$\text{pr}_{G^*}[A(k) = 1 | \bar{a}(k-1), \bar{r}(k-1), \bar{L}^*(k)] = 1 \quad \text{if } a(k-1)s(k) = 1 \tag{16}$$

$$\text{pr}_{G^*}[T(k) = 1 | \bar{a}(k), \bar{r}(k-1), \bar{L}^*(k)] = 0 \quad \text{if } a(k) = 1 \text{ or } s(k) = 0$$

hold for  $G^*$  equal to  $G^\top$  or  $G_x$  where  $s(k)$  is a realization of  $S(k) \in L^*(k)$ , the indicator variable  
 7 of survival at week  $k$ . [Without this assumption and with  $A(t)$ , the indicator variable that takes  
 the value 1 if and only if HAART has been initiated by time  $t$ , the NDE assumption would be  
 9 unlikely to hold, because, the result of a CD4 test might then have a direct effect on survival not  
 through  $A(t)$  if the test result is used to decide when to switch an initial HAART regimen to a  
 11 new HAART regimen. In studies in which subjects do switch treatment regimens based on CD4  
 tests obtained after HAART initiation, the NDE assumption would only hold if we redefined  $A(t)$   
 13 to be the vector of all treatments that physicians (or patients) might modify at time  $t$  based on the  
 result of a CD4 test.]

15 Let  $Y = y(\bar{A}, \bar{L})$  be a prespecified utility function. The mean  $E_{(G_x, P_T)}(Y)$  computed under the  
 joint law  $(G_x, P_T)$  is interpreted as the expected utility in population  $G$  if the treatment strategy  
 17  $\bar{d}_x$  is followed. Similarly, if  $G_x^\top$  is defined like  $G_x$  but with  $g^\top$  instead of  $g$ , the resulting mean  
 $E_{(G_x^\top, P_T)}(Y)$  is the expected utility in the study population  $G^\top$  if the treatment regime  $\bar{d}_x$  is  
 19 followed. Note that this expected utility was denoted as  $E(Y_{\bar{d}_x})$  in Section 4.

Our goal is to find  $x_{\text{opt}}(V)$  in  $\mathcal{X}$  that maximizes  $E_{(G_x, P_T)}[Y|V]$  over  $x \in \mathcal{X}$ , where  $V$  is a  
 21 (possibly improper) subset of the baseline covariates. The key observation that will allow us to  
 estimate  $x_{\text{opt}}(V)$  is that under the conditions of Theorem 6.1 (which, in this subsection, we assume  
 23 to hold) and the PO\* assumption we have

$$E_{(G_x, P_T)}[Y|V] = E_{(G^\top, P_T)}[U_x Y | V] \tag{17}$$

25 where

$$U_x \equiv \frac{\prod_{k=0}^K g_x[J(k) | \bar{O}^{*,a}(k)]}{\prod_{k=0}^K g^\top[J(k) | \bar{O}^{*,a}(k)]} = \frac{\Delta_x \prod_{k=0}^K g_x[T(k) | \bar{O}^{*,t}(k)]}{\prod_{k=0}^K g^\top[J(k) | \bar{O}^{*,a}(k)]} \tag{18}$$

27 and

$$\Delta_x = \prod_{k=0}^K I(A(k) = d_{x,k}[\bar{A}(k-1), \bar{T}(k-1), \bar{L}^*(k)])$$

29 is the indicator that the subject followed treatment regime  $\bar{d}_x$ .

Suppose, as in Section 4.3, we specify an MSM model

$$E_{(G_x, P_T)}[Y|V] = h(x, V, \psi^*) \tag{19}$$

with  $h(x, V, \psi) = (r(x, V)^\top, r^*(V)^\top)^\top \psi$ . Then, it follows from (17) that, for any user-specified  
 33 function  $q^*(x, V)$ ,

$$E_{(G^\top, P_T)} \left[ \sum_{x \in \mathcal{X}} U_x \{Y - h(x, V, \psi^*)\} (r(x, V)^\top, r^*(V)^\top)^\top q^*(x, V) \right] = 0 \tag{20}$$

1 Consequently, letting  $\mathbb{P}_n(A)$  stand for  $n^{-1} \sum_{i=1}^n A_i$ , we have that under standard regularity conditions, a CAN estimator of  $\psi^*$  is the  $\widehat{\psi}$  solving

$$3 \quad \mathbb{P}_n \left[ \sum_{x \in \mathcal{X}} \widehat{U}_x \{Y - h(x, V, \psi)\} (r(x, V))^T, r^*(V)^T \right]^T q^*(x, V) = 0 \quad (21)$$

where

$$5 \quad \widehat{U}_x \equiv \frac{\Delta_x \prod_{k=0}^K g[T(k) | \overline{O}^{*,t}(k)]}{\prod_{k=0}^K g^\top[J(k) | \overline{O}^{*,a}(k); \widehat{\alpha}]} \quad (22)$$

provided (i) the model  $g^\top[J(k) | \overline{O}^{*,a}(k); \alpha]$  used to estimate  $g^\top[J(k) | \overline{O}^{*,a}(k)]$  is correct and  $\widehat{\alpha}$  maximizes the partial log-likelihood  $\mathbb{P}_n[\sum_{k=0}^K \log g^\top[J(k) | \overline{O}^{*,a}(k); \widehat{\alpha}]]$ , (ii)  $\widehat{U}_x Y$  is a function of the observed data  $\overline{O}^*$ , and (iii) the PO\* assumption holds for all  $x \in \mathcal{X}$ . In practice, as discussed in Section 4.3, to ensure (iii), we should also eliminate from  $\mathcal{X}$  any  $x$  for which there exists empirical evidence that the PO\* assumption almost fails. Note a sufficient condition for (ii) to hold is that the utility function  $y(\overline{A}, \overline{L})$  does not depend on a subject's possibly unmeasured covariate history  $\overline{T}$  (e.g. CD4 count history in our running example) and thus is only a function of the always observed data  $(\overline{A}, \overline{Z})$ .

Once we have obtained a CAN estimator of  $\psi^*$ , we can estimate  $x_{\text{opt}}(V) = x_{\text{opt}}(V; \psi^*)$  as in Section 4.3. The estimator  $\widehat{\psi}$  will be far from the most efficient possible estimator of  $\psi^*$  under the above assumptions. However, the theory of efficient estimation in CAR models could be used to obtain much more efficient estimators. See Robins and Rotnitzky [14].

6.2.2. *Estimation of joint optimal testing and treatment regimes.* Suppose we are given a set of nonrandom testing and treatment regimes  $\{G_x \equiv \overline{\mathbf{d}}_x \equiv (\overline{d}_{x_a}, \overline{d}_{x_t}); x \in \mathcal{X}\}$  where  $x = (x_a, x_t) \in \mathcal{X} = \mathcal{X}_a \times \mathcal{X}_t$ . Here  $\{\overline{d}_{x_a}; x_a \in \mathcal{X}_a\}$  is a set of treatment regimes with  $\overline{d}_{x_a} = \{d_{x_a,k}; k=0, \dots, K\}$ , each  $d_{x_a,k}[\overline{a}(k-1), \overline{t}(k-1), \overline{L}^*(k)]$  being a function taking values in  $\mathcal{A}(k)$ . Similarly,  $\{\overline{d}_{x_t}; x_t \in \mathcal{X}_t\}$  is a set of testing regimes with  $\overline{d}_{x_t} = \{d_{x_t,k}; k=0, \dots, K\}$ , each  $d_{x_t,k}[\overline{a}(k), \overline{t}(k-1), \overline{L}^*(k)]$  being a function taking values in  $\{0, 1\}$ . Note that  $G_x$  as defined here is the  $G_x$  defined in the preceding section except now with

$$25 \quad g[t(k) | \overline{a}(k), \overline{t}(k-1), \overline{L}^*(k)] = I(t(k) = d_{x_t,k}[\overline{a}(k), \overline{t}(k-1), \overline{L}^*(k)])$$

Also, note that in this section  $\overline{\mathbf{d}}_x$  (in bold) denotes a joint nonrandom treatment and testing regime, and  $\overline{d}_{x_a}$  denotes the treatment part of the joint regime. In contrast, in earlier sections, a nonrandom treatment regime was denoted simply by  $\overline{d}_x$  because we did not need to distinguish between treatment and testing regimes.

Suppose there is a cost  $c$  to performing a test. Then if  $Y = y(\overline{A}, \overline{L})$  is our previously defined public health utility converted somehow into monetary units, our new utility is  $Y^* = Y - c \sum_{m=0}^{K-1} T(m)$ , where  $\sum_{m=0}^{K-1} T(m)$  denotes the number of tests received. Our goal is to find  $x_{\text{opt}}(V) = (x_{a,\text{opt}}(V), x_{t,\text{opt}}(V))$  that maximizes the expected utility  $E_{(G_x, P_T)}[Y^* | V]$  over all joint regimes  $x = (x_a, x_t)$ . More generally, we can let the cost at  $m$  depend on the entire observed past. That is,  $C(m) \equiv c_m(\overline{O}^{*,t}(m)) \equiv c_m(\overline{A}(m), \overline{T}(m-1), \overline{L}^*(m))$  for some known function  $c_m(\overline{O}^{*,t}(m)) \equiv c_m(\overline{A}(m), \overline{T}(m-1), \overline{L}^*(m))$ . The utility in such a case becomes  $Y^* = Y - \sum_{m=0}^{K-1} T(m)C(m)$ .

1 Under the conditions of Theorem 6.1 and assumption PO\* (which we assume to hold in this  
 subsection), (17), and consequently (20), holds if  $Y$  is replaced by  $Y^*$  and  $U_x$  is defined as in (18)  
 3 except that  $\Delta_x$  is replaced by  $\Delta_{x_a}$  and  $g[T(k)|\bar{O}^{*,t}(k)]$  is replaced by  $I(T(k)=d_{x_t,k}[\bar{O}^{*,t}(k)])$ .  
 Suppose we specify an MSM

5 
$$E_{(G_x, P_T)}[Y^*|V]=h(x, V, \psi^*) \tag{23}$$

with  $h(x, V, \psi)=(r(x, V)^T, r^*(V)^T)\psi$ . Then, reasoning as in the preceding section, with  $Y^*$   
 7 replacing  $Y$ , a CAN estimator of  $\psi^*$  is the  $\hat{\psi}$  solving equation (21) provided conditions (i)–(iii)  
 of the preceding subsection hold and  $\hat{U}_x$  is defined as in (22) but with  $\Delta_x$  replaced by  $\Delta_{x_a}$  and  
 9  $g[T(k)|\bar{O}^{*,t}(k)]$  replaced by  $I(T(k)=d_{x_t,k}[\bar{O}^{*,t}(k)])$ . As in the previous subsection, once we have  
 obtained a CAN estimator of  $\psi^*$ , we can estimate the optimal joint strategy in our candidate class  
 11 by the  $\hat{x}_{opt}(V)$  that maximizes  $h(x, V, \hat{\psi})$ .

*Running example (continuation 1):* Let  $\bar{d}_{x_a}=\{d_{x_a,k}; k=0, \dots, K\}$  denote the nonrandom  
 dynamic treatment regime ‘begin HAART the first time  $t$  the measured CD4 count falls below  
 $x_a$ ’ and  $\bar{d}_{x_t}$  the testing regime ‘if a subject is still at risk to initiate HAART, perform a CD4  
 test every  $x_t$  weeks’. Our goal is to find the  $x_{opt}(V)=(x_{a,opt}(V), x_{t,opt}(V))$  that minimizes  
 $E_{(G_x, P_T)}[Y^*|V]=E_{(G_x, P_T)}[Y-\sum_{m=0}^{K-1} T(m)C(m)|V]$  as a function of  $V$ . A possible choice for  
 $h(x, V, \psi)$  in model (23) that allows the effect of the treatment regime  $\bar{d}_{x_a}$  to depend (as it should)  
 on the testing regime  $\bar{d}_{x_t}$  is

$$h(x, V, \psi) = \sum_{k=1}^5 \psi_{1,1,k} x_a^k + \sum_{k=1}^5 \psi_{1,2,k}^T V x_a^k + \sum_{k=1}^5 \psi_{2,1,k} x_t^k + \sum_{k=1}^5 \psi_{2,2,k}^T V x_t^k \\ + \sum_{\{(k,l); k+l \leq 4, k, l \geq 0\}} \psi_{3,1,k,l} x_a^k x_t^l + \sum_{\{(k,l); k+l \leq 4, k, l \geq 0\}} \psi_{3,2,k,l}^T V x_a^k x_t^l + \psi_4^T V$$

13 Elsewhere, we show that additional substantive knowledge concerning the dependence of  
 $E_{(G_x, P_T)}[Y|V]$  as a function of  $x=(x_a, x_t)$  can be incorporated into the functional form of our  
 15 models if we specify separate models for  $E_{(G_x, P_T)}[Y|V]$  and  $E_{(G_x, P_T)}[\sum_{m=0}^{K-1} T(m)C(m)|V]$  and  
 then combine the fits to estimate  $x_{opt}(V)$ .

17 **6.3. Usefulness of the NDE assumption**

The results obtained in Section 6.2 were a straightforward generalization of the results of  
 19 Section 4.3. In particular, we did not use the fact that the NDE assumption holds. However, the  
 consistency of our estimators required that (a) the PO\* assumption hold and (b) that  $\hat{U}_x Y$  is a  
 21 function of the observed data  $\bar{O}^*$ . In this section, we shall show that when (a) and/or (b) are/is  
 false, between-population extrapolation and estimation of joint optimal treatment and testing  
 23 regimes often remain possible by exploiting the NDE assumption to construct alternative CAN  
 estimators. Because the methodology developed in this section is new, we treat several special  
 25 cases based on our running example, beginning with the simplest. The most general case is  
 reserved for Appendix A. It is pedagogically useful to begin with the problem of estimation of a  
 27 joint optimal testing and treatment regimes.

6.3.1. *Special case 1.* Consider running example (continuation 1) with  $x=(x_a, x_t)$  fixed and  
 29  $Y=y(\bar{A}, \bar{L})$  being a prespecified function, say  $y_1(\bar{A}, \bar{Z})$ , of  $(\bar{A}, \bar{Z})$  only. Suppose in population  $G^T$

1 all subjects at risk to initiate HAART receive a CD4 blood test every week and thus  $\text{pr}_{G^\top}[T(k) =$   
 2  $1|\bar{a}(k), \bar{t}(k-1), \bar{l}^*(k)] = 1$  if  $a(k) = 1 - s(k) = 0$ . In contrast, suppose under  $G_x$ , CD4 tests are  
 3 performed only every  $x_t$  weeks. Thus,  $\text{pr}_{G_x}[T(k) = 1|\bar{a}(k), \bar{t}(k-1), \bar{l}^*(k)]$  is equal to 1 if  $a(k) =$   
 4  $1 - s(k) = 0$  and  $k$  is divisible by  $x_t$ , but it is equal to 0 otherwise. Then the assumption  $\text{PO}^*$  for  
 5  $G^\top$  with respect to  $G_x$  is false for  $x_t > 1$ , since, given  $a(k) = 1 - s(k) = 0$  for  $k$  not divisible by  
 6  $x_t$ , the test decision  $T(k) = 0$  has positive probability under  $G_x$  but has probability 0 under  $G^\top$ .  
 7 Thus, the approach of Section 6.2.2 cannot be used to estimate  $E_{(G_x, P^\top)}[Y^*]$  or  $E_{(G_x, P^\top)}[Y^*|V]$ .  
 8 However, under the NDE assumption, consistent estimators of these quantities can be obtained  
 9 provided the following positivity assumption holds.

10 *Treatment positivity (TPO\*) assumption for a regime  $G^\top$  with respect to another regime  $G$ :* The  
 11 conditional measure  $g(\bar{a}|\bar{L}_{\bar{a}})$  is dominated by (i.e. absolutely continuous w.r.t.)  $g^\top(\bar{a}|\bar{L}_{\bar{a}})$  with  
 12  $P^\top$ -probability 1, i.e.

$$13 \quad g(\bar{a}|\bar{L}_{\bar{a}}) > 0 \text{ implies } g^\top(\bar{a}|\bar{L}_{\bar{a}}) > 0 \text{ w.p.1. under } P^\top \quad (24)$$

Note that the  $\text{PO}^*$  assumption implies the  $\text{TPO}^*$  assumption but the converse is false.

15 The following algorithm returns a consistent estimator of  $E_{(G_x, P^\top)}[Y^*]$  under the NDE and  
 16  $\text{TPO}^*$  assumptions.

17 *Algorithm 1*

- 18 1. Construct a modification of the data set generated under  $(G^\top, P^\top)$  by both recoding  $T(k) = 1$   
 19 as  $T(k) = 0$  and discarding the CD4 count data  $I(k+1)$  whenever  $k$  is not divisible by  $x_t$ ,  
 20 where  $x_t$  is the frequency of CD4 testing under regime  $G_x$ .
- 21 2. Use the modified data to determine the set of subjects who followed the treatment regime  
 22  $\bar{d}_{x_a}$ . [Note that this set will differ from the set of subjects who followed the treatment regime  
 23  $\bar{d}_{x_a}$  in the original unmodified data. For example, consider a subject whose CD4 count in  
 24 the unmodified data first fell below  $x_a$  in week  $k$  and who started HAART in week  $k$ . If  $k$   
 25 is not divisible by  $x_t$ , then the subject will have followed the regime  $x_a$  in the unmodified  
 26 data but not in the modified data. That is, although the treatment history in the modified data  
 27 agrees with that in the unmodified data, by modifying a subject's testing history, a subject  
 28 can have followed the treatment regime  $\bar{d}_{x_a}$  in the original data set but not in the modified  
 29 data or *vice versa*.]
- 30 3. Estimate  $E_{(G_x, P^\top)}[Y^*]$  by a weighted average over the members of the set in step 2 of the  
 31 utilities  $Y_{\text{mod}}^*$  calculated from the modified data set with weights equal to an estimate of  
 32  $1/\prod_{k=0}^K g^\top[A(k)|\bar{O}^{*,a}(k)]$  with  $\bar{O}^{*,a}(k)$  based on the original unmodified data.

Algorithm 1 is formalized as follows:

35 Recursively define  $t_{x_t,0}^*(a(0), l_{a(0)}^*(0)) \equiv d_{x_t,0}[a(0), t(-1), l(0)]$  where, by convention,  $t(-1) = 1$   
 for all subjects and for  $k = 1, \dots, K$ ,  $t_{x_t,k}^*(\bar{a}(k), \bar{l}_{\bar{a}(k-1)}^*(k)) \equiv d_{x_t,k}[\bar{a}(k), \bar{t}^{**}(k-1), \bar{l}_{\bar{a}(k-1), \bar{t}^{**}(k-1)}^*$   
 37  $(k)]$  where  $\bar{t}^{**}(j) = t_{x_t,j}^*(\bar{a}(j), \bar{l}_{\bar{a}(j-1)}^*(j))$ . Furthermore, define  $\bar{T}_{x_t}^*(0) = t_{x_t,0}^*(A(0), L(0))$  and  
 $\bar{T}_{x_t}^*(k) \equiv t_{x_t,k}^*(\bar{A}(k), \bar{L}(k))$ . Thus,

$$39 \quad \bar{T}_{x_t}^* \equiv \bar{t}_{x_t}^*(\bar{A}, \bar{L}) \equiv \bar{t}_{x_t,K}^*(\bar{A}, \bar{L})$$

is the test history a subject with observed data  $(\bar{A}, \bar{L})$  would have if he followed the testing regime  $\bar{d}_{x_t}$  and his observed treatment history. Further define

$$\delta_{x_a}(\bar{a}, \bar{t}, \bar{L}_{\bar{a}}) = \prod_{k=0}^K I(a(k) = d_{x_a, k}[\bar{a}(k-1), \bar{t}(k-1), \bar{L}_{\bar{a}(k-1), \bar{t}(k-1)}^*(k)]) \quad (25)$$

$$\Delta_{x_a}(\bar{t}) = \delta_{x_a}(\bar{A}, \bar{t}, \bar{L}_{\bar{A}}) \quad (26)$$

- 1 so  $\Delta_{x_a}(\bar{t})$  is the indicator that a subject's observed treatment is equal to the treatment he would
- 2 have received had he followed the treatment regime  $\bar{d}_{x_a}$  and the nondynamic testing regime  $\bar{t}$ .
- 3 Hence,  $\Delta_{x_a}(\bar{T}_{x_t}^*)$  is the indicator that a subject's observed treatment is equal to the treatment he
- 4 would have received had he followed the treatment and testing regime  $G_x = \bar{d}_{x=(x_a, x_t)}$ . The set of
- 5 subjects with  $\Delta_{x_a}(\bar{T}_{x_t}^*) = 1$  is precisely the set constructed in step 2 of the above algorithm. The
- 6 estimator described in step 3 of the algorithm is then

$$\mathbb{P}_n \left[ \Delta_{x_a}(\bar{T}_{x_t}^*) Y_{\text{mod}}^* / \left\{ \prod_{k=0}^K g^\top \{A(k) | \bar{O}^{*,a}(k); \hat{\alpha}\} \right\} \right] \quad (27)$$

where, under the NDE assumption that  $T(k)$  has no causal effect on  $\bar{L}$ ,

$$Y_{\text{mod}}^* = Y - \sum_{m=0}^{K-1} T_{x_t}(m) c_m(\bar{A}(m), \bar{T}_{x_t}^*(m-1), \bar{L}_{\bar{T}_{x_t}^*(m-1)}^*(m)) \quad (28)$$

for any subject with  $\Delta_{x_a}(\bar{T}_{x_t}^*) = 1$ , since the right-hand side (RHS) of the last display is the counterfactual value of  $Y^*$  that would have been observed, if possibly, contrary to fact, the subject had followed the regime  $G_x$  by modifying his testing history while leaving his treatment history unchanged. [Note this last statement would not be true were the NDE assumption false, since then simply recoding  $T(k) = 1$  as  $T(k) = 0$  could not undo the actual causal effect of  $T(k) = 1$  on  $Y$ ]. The consistency of (27) as an estimator of  $E_{(G_x, P_T)}[Y^*]$  is a consequence of Corollary A.1 in Appendix A. Here we give a heuristic argument for its consistency.

Suppose for the moment the set constructed in step 2 consisted of all  $n$  study subject's because treatment regime  $\bar{d}_x$  is followed with probability 1 when  $\bar{T} = \bar{T}_{x_t}^*$ . In that case, under the NDE assumption, we could calculate from the modified data set the utility of each of the  $n$  subjects under the regime  $G_x$  using equation (28). Their sample average would be an unbiased estimate of  $E_{(G_x, P_T)}[Y^*]$ . In practice, some subjects will have  $\Delta_{x_a}(\bar{T}_{x_t}^*) = 0$  and thus will not be included in the set in step 2. Therefore, to preserve (asymptotic) unbiasedness we must, as in step 3 of the algorithm, weight those with  $\Delta_{x_a}(\bar{T}_{x_t}^*) = 1$  by the estimated inverse  $1 / \prod_{k=0}^K g^\top [A(k) | \bar{O}^{*,a}(k); \hat{\alpha}]$  of their conditional probability (based on the unmodified data) of having  $\Delta_{x_a}(\bar{T}_{x_t}^*) = 1$  so as to represent those with  $\Delta_{x_a}(\bar{T}_{x_t}^*) = 0$  that were removed from the data set in step 2. This inverse probability weighting is formally justified by the fact that, as shown in the proof of Theorem A.1 in Appendix A, under the TPO\* assumption,

- (i) the denominator  $\text{pr}_{G^\top}[\bar{A} = \bar{a} | \bar{L}_{\bar{a}}]$  is nonzero whenever  $\bar{a} \in \bar{\mathcal{A}}_g$ , where  $\bar{\mathcal{A}}_g$  is the support of  $\bar{A}$  under  $(G, P^\top)$  and
- (ii) the expression in square brackets in (27) (with the true  $\alpha$  in place of  $\hat{\alpha}$ ) equals  $\sum_{\bar{a} \in \bar{\mathcal{A}}_g} I(\bar{A} = \bar{a}) m(x, \bar{a}, \bar{L}_{\bar{a}}) / \text{pr}_{G^\top}[\bar{A} = \bar{a} | \bar{L}_{\bar{a}}]$  for a function  $m(x, \bar{a}, \bar{L}_{\bar{a}})$  satisfying

1  $\sum_{\bar{a} \in \bar{\mathcal{A}}_g} E_{P^\top} [m(x, \bar{a}, \bar{L}_{\bar{a}})] = E_{(G_x, P^\top)} [Y^*]$ . Specifically,  $m(x, \bar{a}, \bar{L}_{\bar{a}})$  is  $\Delta_{x_a}(\bar{T}_{x_t}^*) Y_{\text{mod}}^*$  except  
 with  $(\bar{A}, \bar{L}_{\bar{A}})$  replaced by  $(\bar{a}, \bar{L}_{\bar{a}})$ . That is,  $m(x, \bar{a}, \bar{L}_{\bar{a}}) = \delta_{x_a}(\bar{a}, \bar{t}_{x_t}^*(\bar{a}, \bar{L}_{\bar{a}}), \bar{L}_{\bar{a}}) \times \{y_1(\bar{a}, \bar{Z}_{\bar{a}}) -$   
 3  $\sum_{m=0}^{K-1} t_{x_t, m}^*(\bar{a}, \bar{L}_{\bar{a}}) c_m(\bar{a}(m), \bar{t}_{x_t, m-1}^*(\bar{a}, \bar{L}_{\bar{a}}), \bar{L}_{\bar{a}(m-1)}, \bar{t}_{x_t, m-1}^*(\bar{a}, \bar{L}_{\bar{a}})(m))\}$ .

6.3.2. *Special case 2.* Special case 2 differs from special case 1 only in that we no longer assume  
 5 that all subjects in population  $G^\top$  at risk to initiate HAART receive a CD4 blood test every week.  
 That is, we no longer place *a priori* qualitative restrictions on  $g^\top [t(k)|\bar{a}(k), \bar{t}(k-1), \bar{t}^*(k)]$ . In this  
 7 setting, it will be useful to define

$$\Delta(\bar{t}) = \prod_{k=0}^K I(T(k) \geq t(k)) \tag{29}$$

9 Note  $\Delta(\bar{t})$  is 1 if and only if at each time  $k$  that a subject would have been tested under the given  
 testing history  $\bar{t}$ , they were, in fact, tested under their observed testing history  $\bar{T}$ . Furthermore, in  
 11 special case 1 but not in special case 2,  $\Delta(\bar{T}_{x_t}^*) = 1$  with probability one since, in case 1, subjects  
 were in fact tested every week while at risk to initiate HAART. When, as in case 2,  $\Delta(\bar{T}_{x_t}^*)$  may be 0,  
 13  $\Delta_{x_a}(\bar{T}_{x_t}^*) = \prod_{k=0}^K I(A(k) = d_{x_a, k}[\bar{A}(k-1), \bar{T}_{x_t}^*(k-1), \bar{L}_{\bar{T}_{x_t}^*(k-1)}(k)])$  may not be a function of the  
 observed data  $\bar{O}^*$  that was generated under  $(G^\top, P^\top)$  because (i)  $\bar{L}_{\bar{T}_{x_t}^*(k-1)}(k)$  may then be unknown  
 15 (i.e. missing) for certain values of  $k$  and (ii) the function  $d_{x_a, k}[\bar{A}(k-1), \bar{T}_{x_t}^*(k-1), \bar{L}_{\bar{T}_{x_t}^*(k-1)}(k)]$   
 associated with the regime ‘start HAART the first time CD4 count drops below  $x_a$ ’ depends  
 17 nontrivially on  $\bar{L}_{\bar{T}_{x_t}^*(k-1)}(k)$ . Thus, estimator (27) of  $E_{(G_x, P^\top)} [Y^*]$  cannot be used as it may fail to  
 be a function of the observed data. To overcome this difficulty, we instead estimate  $E_{(G_x, P^\top)} [Y^*]$   
 19 for a given  $x = (x_a, x_t)$  by

$$\mathbb{P}_n [\Delta(\bar{T}_{x_t}^*) \Delta_{x_a}(\bar{T}_{x_t}^*) Y_{\text{mod}}^* \widehat{W}_{x_t}] \tag{30}$$

21 where

$$\widehat{W}_{x_t} \equiv \left\{ \prod_{k=0}^K g^\top [A(k) | \bar{O}^{*,a}(k); \widehat{\alpha}] \prod_{\{k; T_{x_t}^*(k)=1\}} g^\top [T(k) | \bar{O}^{*,t}(k); \widehat{\alpha}] \right\}^{-1}$$

23 By replacing  $\Delta_{x_a}(\bar{T}_{x_t}^*)$  by  $\Delta(\bar{T}_{x_t}^*) \Delta_{x_a}(\bar{T}_{x_t}^*)$  we guarantee that equation (30) is a function  
 of the observed data. Furthermore, since not all subjects have  $\Delta_{x_t}(\bar{T}_{x_t}^*) \Delta_{x_a}(\bar{T}_{x_t}^*) = 1$ , to  
 25 ensure unbiasedness (asymptotically) it is necessary to weight by  $\widehat{W}_{x_t}$ . Note that the product  
 $\prod_{\{k; T_{x_t}^*(k)=1\}} g^\top [T(k) | \bar{O}^{*,t}(k); \widehat{\alpha}]$  is computed only over the times  $k$  at which  $T_{x_t}^*(k)$  equals 1.  
 27 Furthermore, note that in this product we can replace  $g^\top [T(k) | \bar{O}^{*,t}(k); \widehat{\alpha}]$  with  $\text{pr}_{G^\top} [T(k) =$   
 $1 | \bar{O}^{*,t}(k); \widehat{\alpha}]$  because this product is premultiplied by the indicator  $\Delta(\bar{T}_{x_t}^*)$  and in fact,  
 29  $\Delta(\bar{T}_{x_t}^*) = 1$  implies  $T(k) = 1$  whenever  $T_{x_t}^*(k) = 1$ . An informal understanding as to why  $\widehat{W}_{x_t}$   
 is the appropriate inverse probability weight can be obtained by considering a hybrid inter-  
 31 vention in which every  $x_t$  weeks we intervene and force subjects to be tested. However,  
 for any week  $k$  with  $k$  not divisible by  $x_t$ , we do not prevent all testing; rather we apply the

1 random testing regime  $g^\top[t(k)|\bar{O}^{*,t}(k)]$ . However, in deciding treatment, we force each subject  
 2 to take the treatment history they would have taken if they followed the regime  $\bar{\mathbf{d}}_{x=(x_a, x_t)}$ ,  
 3 thereby effectively ignoring the results of tests taken in weeks  $k$  not divisible by  $x_t$ . Under  
 4 assumption I, the law of the hybrid regime is absolutely continuous with respect to  $G^\top$   
 5 and the likelihood ratio (Radon-Nikodym derivative) of the law under the hybrid regime to  
 6 that under the regime  $G^\top$  generating the observed data is precisely  $\Delta(\bar{T}_{x_t}^*)\Delta_{x_a}(\bar{T}_{x_t}^*)W_{x_t}$  with  
 7  $W_{x_t} = 1/\prod_{k=0}^K g^\top[A(k)|\bar{O}^{*,a}(k)]\prod_{\{k:T_{x_t}^*(k)=1\}} g^\top[T(k)|\bar{O}^{*,t}(k)]$ . Furthermore, if in calculating a  
 8 subject's utility, only the costs of the tests obtained for weeks  $k$  divisible by  $x_t$  are included,  
 9 the utility  $Y^*$  calculated under the hybrid regime equals that under the regime  $\bar{\mathbf{d}}_{x=(x_a, x_t)}$ . Thus  
 10 our parameter of interest, the expected utility  $E_{(G_x, P^\top)}[Y^*]$  under  $G_x = \bar{\mathbf{d}}_{x=(x_a, x_t)}$ , will equal the  
 11 expected utility under the hybrid regime. Thus, under assumption I, the expected utility under the  
 12 hybrid regime will equal  $E_{(G^\top, P^\top)}[\Delta(\bar{T}_{x_t}^*)\Delta_{x_a}(\bar{T}_{x_t}^*)Y_{\text{mod}}^*W_{x_t}]$  by the Radon-Nikodym theorem.  
 13 [Recall that for subjects with  $\Delta_{x_a}(\bar{T}_{x_t}^*) = 1$ ,  $Y_{\text{mod}}^*$  equals the utility  $Y^*$  that would be obtained  
 14 under  $G_x = \bar{\mathbf{d}}_{x=(x_a, x_t)}$ .]

15 In Appendix A, we prove in Corollary A.1 that (30) is a consistent estimator of  $E_{(G_x, P^\top)}[Y^*]$   
 16 when  $G^\top$  and  $G_x$  are  $\bar{O}^{*,a}$ -SR, the treatment and testing model parametrized by  $\alpha$  is correct, the  
 17 consistency assumption C holds and the following assumption also holds.

Assumption identify (I): The set

$$19 \left\{ \bar{t}; \bar{t} > \bar{T}_{G_x} \text{ and } \prod_{k=0}^K g^\top[A_{G_x}(k), t(k)|\bar{A}_{G_x}(k-1), \bar{t}(k-1), \bar{L}_{\bar{A}_{G_x}(k-1), \bar{t}(k-1)}^*(k)] > 0 \right\}$$

is nonempty with w.p.1. under  $P^\top$ .

21 *Remark*

We now provide a heuristic explanation of assumption I. The counterfactual random variables  $\bar{A}_{G_x}$   
 22 and  $\bar{T}_{G_x}$  in the statement of assumption I are those naturally associated with the deterministic  
 23 treatment and testing regime  $G_x = \bar{\mathbf{d}}_{x=(x_a, x_t)}$ . They are recursively constructed in a manner similar  
 24 to that of Section 4.2. They can alternatively be defined as follows.  $\bar{A}_{G_x}$  is the unique solution to  
 25  $\delta_{x_a}(\bar{a}, \bar{t}_{x_t}^*(\bar{a}, \bar{L}_{\bar{a}}), \bar{L}_{\bar{a}}) = 1$ . Furthermore,  $\bar{T}_{G_x} = \bar{t}_{x_t}^*(\bar{A}_{G_x}, \bar{L}_{\bar{A}_{G_x}})$ . In addition, in what follows we will  
 26 also use the counterfactual  $\bar{L}_{G_x}$  which is defined as  $\bar{L}_{G_x} \equiv \bar{L}_{\bar{A}_{G_x}}$ . Note that with these definitions,  
 27  $\Delta_{x_a}(\bar{T}_{x_t}^*) = 1$  if and only if  $\bar{A}_{G_x} = \bar{A}$ . Also, if  $\bar{A}_{G_x} = \bar{A}$ , then  $\bar{L}_{G_x} = \bar{L}$  and  $\bar{T}_{G_x} = \bar{T}_{x_t}^*$ . Informally  
 28 assumption I states that for every possible *treatment* and testing history  $(\bar{A}_{G_x}, \bar{T}_{G_x})$  that can occur  
 29 under  $(G_x, P^\top)$ , there must exist a testing history  $\bar{t}$  that results in a test each time  $\bar{T}_{G_x}$  does (and  
 30 possibly at other times as well) such that  $(\bar{A}_{G_x}, \bar{t})$  has a nonzero probability of occurring under  
 31  $(G^\top, P^\top)$ . Assumption I is identifiable in the sense that if we knew the marginal distribution of  $O^*$   
 32 in population  $G^\top$ , we could determine whether assumption I hold. Thus, we can determine from  
 33 the data whether it 'almost fails' as discussed in Section 4.3.

34 Although not explicitly stated as one of the conditions for consistency of (30), the TPO\*  
 35 assumption is indeed implicitly assumed since it is implied by the assumption I, as proved in  
 36 Theorem A.1 and Corollary A.1. Furthermore, it can be shown that the assumption I implies that  
 37 the hybrid regime is absolutely continuous with respect to  $G^\top$ .

38 *Estimation for arbitrary treatment and testing regimes when the utility function does not depend*  
 39 *on  $\bar{t}$* : In both special cases 1 and 2, we assumed a particular treatment and testing regime  $\bar{\mathbf{d}}_{x=(x_a, x_t)}$ .

1 In fact, Corollary A.1 in Appendix A implies that the estimator equation (30) is consistent for  
 2  $E_{(G_x, P_T)}[Y^*]$  for any deterministic treatment and testing regime  $\bar{\mathbf{d}}_{x=(x_a, x_t)}$  when  $G^\top$  and  $G_x$   
 3 are  $\bar{O}^{*,a}$ -SR, assumptions C and I hold, and the model for treatment and testing is correct.  
 4 Furthermore, if the same assumptions required for the consistency of (30) hold for all  $x = (x_a, x_t)$   
 5 in a set  $\mathcal{X}$ , a CAN estimator of the parameter  $\psi^*$  of MSM (23) is the  $\hat{\psi}$  solving equation (21)  
 6 with  $\hat{U}_x$  redefined as  $\Delta(\bar{T}_{x_t}^*)\Delta_{x_a}(\bar{T}_{x_t}^*)\hat{W}_{x_t}$  and  $Y$  replaced by  $Y_{\text{mod}}^*$ . Thus, we can view the data  
 7 as consisting of  $n \times \text{card}(\mathcal{X}_a) \times \text{card}(\mathcal{X}_t)$  subjects indexed by the ordered triple  $(i, x_1, x_2)$ , each  
 8 of whom is entered into a weighted least-squares regression of  $Y_{\text{mod}}^*$  on  $(r(x, V)^\top, r^*(V)^\top)^\top$  with  
 9 weight  $q^*(x, V)\Delta(\bar{T}_{x_t}^*)\Delta_{x_a}(\bar{T}_{x_t}^*)\hat{W}_{x_t}$  if and only if  $\Delta(\bar{T}_{x_t}^*)\Delta_{x_a}(\bar{T}_{x_t}^*)=1$ . The resulting weighted  
 10 least-squares estimator is precisely the estimator  $\hat{\psi}$ . As above, once we have obtained a CAN  
 11 estimator of  $\psi^*$ , we can estimate the optimal joint strategy in our candidate class by the  $\hat{x}_{\text{opt}}(V)$   
 that maximizes  $h(x, V, \hat{\psi})$ .

13 *6.3.3. Special case 3.* In special cases 1 and 2 we assumed that  $Y$  was a function  $y_1(\bar{A}, \bar{Z})$  of  
 14 the always observed variables  $(\bar{A}, \bar{Z})$  and in particular did not depend on any component of CD4  
 15 count history  $\bar{T}$ . Case 3 differs from case 2 only in that we now suppose instead that  $Y = y(\bar{A}, \bar{T})$   
 16 is a nontrivial function of every component of  $\bar{T}$ . This would be the case, for example, if the  
 17 study followed HIV-infected subjects with baseline CD4 count equal to 500 for one year and the  
 utility  $Y$  were the integrated CD4 count  $\sum_{m=0}^K I(m)$ .

18 Consider the estimator (30) of  $E_{(G_x, P_T)}[Y^*]$  with  $G_x = \bar{\mathbf{d}}_{x=(x_a, x_t)}$  and with  $Y$  now a nontrivial  
 19 function of  $\bar{T}$ , for example,  $Y = \sum_{m=0}^K I(m)$ . The quantity displayed in (30) is no longer a function  
 20 of the observed data  $\bar{O}^*$ . However, this quantity again becomes a function of the observed data if  
 21 we substitute  $I(\bar{T} = \bar{\mathbf{1}})$  for  $\Delta(\bar{T}_{x_t}^*)$  where  $\bar{\mathbf{1}}$  is the vector of all 1's.

22 However, this substitution requires us to replace the product  $\prod_{\{k: T_{x_t}^*(k)=1\}}$  by the product  $\prod_{k=0}^K$   
 23 in the definition of  $\hat{W}_{x_t}$  in order to obtain inverse probability weights that preserve consistency.  
 24 Corollary A.1 of Appendix A implies that with these changes, the modified quantity in (30) is  
 25 consistent for  $E_{(G_x, P_T)}[Y^*]$  provided  $G^\top$  and  $G_x$  are  $\bar{O}^{*,a}$ -SR, the testing and treatment model  
 26 is correct, and assumption C and the following assumption holds.

*Assumption*

27 For  $\bar{\mathbf{t}} = \bar{\mathbf{1}}$ ,

$$\prod_{k=0}^K g^\top[\bar{A}_{G_x}(k), \bar{\mathbf{t}}(k) | \bar{A}_{G_x}(k-1), \bar{\mathbf{t}}(k-1), \bar{L}_{\bar{A}_{G_x}(k-1), \bar{\mathbf{t}}(k-1)}^*(k)] > 0 \quad \text{with w.p.1. under } P^\top$$

31 Note that because  $G^\top$  is  $\bar{O}^{*,a}$ -SR, this latter assumption is equivalent to the assumption that  
 $\text{pr}_{G^\top}[\bar{A} = \bar{A}_{G_x}, \bar{\mathbf{T}} = \bar{\mathbf{1}} | \bar{L}_{\bar{\mathcal{A}}}^*] \equiv \text{pr}_{G^\top}[\Delta_{x_a}(\bar{T}_{x_t}^*) = 1, \bar{\mathbf{T}} = \bar{\mathbf{1}} | \bar{L}_{\bar{\mathcal{A}}}^*] > 0$  w.p.1. under  $P^\top$ .

*6.3.4. Special case 4.* We return to the problem of between-population extrapolation. We are  
 given data  $\bar{O}^*$  generated under  $(G^\top, P_T)$  and wish to estimate  $E_{(G_x, P_T)}[Y]$  for  $G_x$  as defined in  
 equations (14) and (15), with  $g[t(k)|\bar{a}(k), \bar{\mathbf{t}}(k-1), \bar{\mathbf{t}}^*(k)]$  the known conditional testing density in  
 a population  $G$  and  $\bar{d}_x$  a deterministic treatment regime. However, we no longer assume that the  
 PO\* assumption holds so the approach of Section 6.2.1 is unavailable. For simplicity, we assume

that  $Y$  is only a function of  $(\bar{A}, \bar{Z})$ . Consider the estimator

$$\mathbb{P}_n \left[ \sum_{\bar{t}^* \in \bar{\mathcal{T}}} \Delta(\bar{t}^*) \Delta_x(\bar{t}^*) Y \widehat{W}(\bar{t}^*) \prod_{k=0}^K g[t^*(k) | \bar{A}(k), \bar{t}^*(k-1), \bar{L}_{\bar{t}^*(k-1)}^*(k)] \right]$$

$$\widehat{W}(\bar{t}^*) = \left\{ \prod_{k=0}^K g^\top[A(k) | \bar{O}^{*,a}(k); \widehat{\alpha}] \prod_{\{k; t^*(k)=1\}} g^\top[T(k) | \bar{O}^{*,t}(k); \widehat{\alpha}] \right\}^{-1} \quad (31)$$

- 1 with  $\Delta_x(\bar{t}^*)$  as in equation (26) with  $x_a = x$  and  $\bar{\mathcal{T}}$  the set of  $K+1$  vectors of 0 and 1's. Note that
- 3 estimator (31) is a sum of  $2^{K+1}$  terms indexed by the vectors in  $\bar{\mathcal{T}}$  with each term identical to
- 5 those in estimator (30) except that  $Y_{\text{mod}}^*$  is redefined to be  $Y$  and  $\bar{T}_{x_t}^*$  is replaced by a given vector
- 7  $\bar{t}^* \in \bar{\mathcal{T}}$ . This estimator, while feasible in theory, will be computationally intractable when  $K$  is
- 9 large because the set  $\bar{\mathcal{T}}$  contains  $2^{K+1}$  elements.

To decrease the computational burden, we construct a simulation-based estimator, motivated by the observation that the subject-specific contribution to estimator (31) is the expectation of  $\Delta(\bar{t}^*) \Delta_x(\bar{t}^*) Y \widehat{W}(\bar{t}^*)$  with respect to the conditional density  $\tilde{g}(\bar{t}^* | \bar{A}, \bar{L}, \bar{T}) \equiv \prod_{k=0}^K g[t^*(k) | \bar{A}(k), \bar{t}^*(k-1), \bar{L}_{\bar{t}^*(k-1)}^*(k)]$ . Therefore, we consider the simulation estimator

$$\mathbb{P}_n \left[ S^{-1} \sum_{s=1}^S \Delta(\bar{T}_s^*) \Delta_x(\bar{T}_s^*) Y \widehat{W}(\bar{T}_s^*) \right]$$

- 11 where, for each subject, the  $\bar{T}_s^*$  are sampled independently from  $\tilde{g}(\bar{t}^* | \bar{A}, \bar{L}, \bar{T})$  by recursively
- 13 drawing from the Bernoulli densities  $g[t^*(k) | \bar{A}(k), \bar{t}^*(k-1), \bar{L}_{\bar{t}^*(k-1)}^*(k)]$ ,  $k=0, \dots, K$ . Corollary
- 15 A.2 of Appendix A implies that both estimator (31) and the associated simulation estimator are
- 17 consistent for  $E_{(G_x, P_T)}[Y^*]$  provided  $G^\top$  and  $G_x$  are  $\bar{O}^{*,a}$ -SR, the model for treatment and testing
- is correct, assumption C and the NDE assumption hold, and the identifying assumption (A1) given
- in Appendix A holds. Assumption (A1) is the generalization of Assumption I above to the setting
- of a random testing regime. Like Assumption I it implies the TPO\* assumption.

Furthermore, under these same conditions, for a given set of treatment regimes  $\{\bar{d}_x; x \in \mathcal{X}\}$  for which assumption (A1) holds, a CAN estimator of the parameter  $\psi^*$  of the MSM (19) can be obtained by weighted least squares as follows. View the data set as consisting of  $n \times S \times \text{card}(\mathcal{X})$  subjects indexed by the ordered triple  $(i, s, x)$ , each of whom is entered into the weighted least-squares regression of  $Y$  on  $(r(x, V)^\top, r^*(V)^\top)$  with weight  $q^*(x, V) \widehat{W}(\bar{T}_s^*)$  if and only if  $\Delta(\bar{T}_s^*) \Delta_x(\bar{T}_s^*) = 1$ . Once we have obtained a CAN estimator of  $\psi^*$ , we can estimate the optimal strategy in our candidate class by the  $\widehat{x}_{\text{opt}}(V)$  that maximizes  $h(x, V, \widehat{\psi})$ .

## 7. EXTRAPOLATION UNDER A NONIGNORABLE VISIT PROCESS

Suppose we have data from a comprehensive HMO database that records all patient visits. HIV-infected patients come to a clinic to be seen by a physician at a time  $t$  either because of acute symptoms or because of a scheduled follow-up appointment. Data on the reason for a given visit are often not recorded for data analysis. This random clinic visit process, unlike the regular weekly visit process we have assumed heretofore, results in an association between visits and risk since

1 patients who are sick are generally more likely to return to the clinic at frequent intervals both  
 3 spontaneously and to keep frequent appointments (although it is possible moderately ill patients  
 who are not getting better come infrequently and miss many scheduled visits).

5 In this section, we consider the realistic setting of a random visit process. The visit process will  
 7 result in nonignorable missing data unless we collect data at  $t$  on the health status of not only those  
 9 who return to the clinic at  $t$  (which we typically do) but also those who do not come to the clinic  
 11 at  $t$  (which we almost never do). Although we shall assume that the visit process is nonignorable,  
 13 it is often reasonable to assume that among patients coming to the clinic at  $t$ , the decision to treat  
 or not can be viewed as effectively randomized (i.e. ignorable) given the past including data on  
 the health status measured at a visit at time  $t$ . Under this assumption, as shown below, we can  
 still estimate the optimal CD4 count at which to start HAART in the study population (provided  
 the utility  $Y$  is always observed) but extrapolation to another population of biologically similar  
 individuals with a different visit process becomes problematic.

15 We shall assume that a subject's treatment only changes at the time of a clinic visit. This  
 17 assumption may (approximately) hold if we are interested in the causal effect of a treatment being  
 prescribed by a physician rather than the effect of the actual treatment taken by the patient, as  
 would be the case if either an intervention that would increase patient compliance is unavailable  
 or the only treatment data recorded for data analysis are the prescription data.

19 We shall also assume that the diagnostic and/or prognostic tests discussed earlier are obtained  
 21 at and only at each clinic visit. This assumption allows us to consider the clinic visit problem  
 without having to also worry about the diagnostic testing problem as well. We can then reuse our  
 previous notation by redefining  $T(m)$  to be the indicator of a clinic visit in week  $m + 1$ , deleting  
 23  $Z(m)$ , and redefining  $I(m)$  to be all covariates that would be recorded at week  $m$  if a visit occurred  
 so that now  $L(m) = I(m)$ . Therefore,  $L^*(m) = I^*(m) = T(m - 1)L(m)$  becomes the covariate data  
 25 actually observed at  $m$ . In this context, the NDE assumption that  $\bar{L}_{\bar{a}} = \bar{L}_{\bar{j}}$  with probability one for  
 $\bar{j} = (\bar{a}, \bar{t})$  becomes the assumption that a clinic visit has no effect on the responses  $L(m)$  except  
 27 through its effect on the treatments prescribed. For the NDE assumption to hold,  $A(t)$  would need  
 to encode the vector of all active treatments that a physician might prescribe to a patient at a clinic  
 29 visit in week  $t$ . Thus, if  $A(t)$  were simply the indicator variable that takes the value 1 if and only  
 if HAART has been initiated by time  $t$ , the NDE assumption would only hold if, as would never  
 31 actually be the case, physicians make no treatment interventions whatsoever once HAART has  
 been initiated.

33 As mentioned above, even were our goal only to estimate the optimal treatment regime in the  
 study population, we require that the utility  $Y$  be observed for all study subjects. Therefore, we  
 35 assume that there exist 'end point' variables, such as the minimum of time of death and end of  
 follow-up at  $K + 1$ , that are observed regardless of visit history but only become available after  
 37  $K + 1$ , say by consultation of the national death index. Such 'end point' variables can be easily  
 appended to our data by adding a formal 'time'  $K + 2$  to the data, setting by convention  $T(K + 1)$   
 39 to 1 for all subjects, and letting  $L(K + 2)$  encode the vector of 'end point' variables. We take our  
 prespecified utility function to be a function  $Y = y(\bar{A}, L(K + 2))$  of treatment history and such  
 41 'end point' variables.

43 Again we are given data  $\bar{O}^*$  generated under  $(G^\top, P^\top)$  and wish to estimate the mean utility  
 $E_{(G_x, P^\top)}[Y]$  for  $x \in \mathcal{X}$  in a second population  $G$  with  $G_x$  as defined in equations (14) and (15).

The following encodes the assumption that the treatment process is ignorable in the study  
 population  $G^\top$ .

1 *Assumption treatment (Tr)- $\overline{\mathcal{O}}^{*,a}$ -SR:* We say a conditional law  $G$  of  $(\overline{A}, \overline{T})$  given  $\overline{L}_{\overline{\mathcal{A}}}$  is  
 treatment sequentially randomized given data  $\overline{\mathcal{O}}^*$  if for all  $k$

3 
$$g^{\top}[a(k)|\overline{a}(k-1), \overline{t}(k-1), \overline{L}_{\overline{\mathcal{A}}}] = g^{\top}[a(k)|\overline{a}(k-1), \overline{t}(k-1), \overline{L}_{\overline{\mathcal{A}}(k-1), \overline{t}(k-1)}^*(k)] \quad (32)$$

where we recall that the RHS of (32) can be written as  $g^{\top}[a(k)|\overline{\mathcal{O}}^{*,a}(k)]$ . The assumption

5 
$$g^{\top}[a(k)|\overline{a}(k-1), \overline{t}(k-1), \overline{L}_{\overline{\mathcal{A}}(k-1), \overline{t}(k-1)}^*(k)] = I(a(k) = a(k-1)) \quad \text{if } t(k-1) = 0$$

encodes the assumption that if, in the observed study population, a clinic visit did not occur at  
 7 time  $k$ , then a subject's treatment does not change at  $k$ .

Suppose we did not wish to extrapolate to population  $G$  but rather wished to estimate the  
 expected utility  $E_{(G_x^{\top}, P_{\top})}(Y)$  in the study population  $G^{\top}$  when the treatment regime  $\overline{d}_x$  is followed,  
 where  $G_x^{\top}$  is defined like  $G_x$  but with  $g^{\top}$  instead of  $g$ . Then, without making any assumptions  
 whatsoever concerning the visit process  $\text{pr}_{G^{\top}}[T(k) = 1 | \overline{A}(k), \overline{T}(k-1), \overline{L}_{\overline{\mathcal{A}}}]$ ,  $E_{(G_x^{\top}, P_{\top})}(Y)$  is iden-  
 tified under the assumption that  $G^{\top}$  is TR- $\overline{\mathcal{O}}^{*,a}$ -SR and the positivity assumption that  $\text{pr}[A(k) =$   
 $d_{x,k}[\overline{A}(k-1), \overline{T}(k-1), \overline{H}^*(k)] | \overline{A}(k-1), \overline{R}(k-1), \overline{H}^*(k)] > 0$  for each  $k$  w.p.1. under  $(G^{\top}, P^{\top})$ .  
 Specifically,  $E_{(G_x^{\top}, P_{\top})}(Y)$  is identified and satisfies

$$E_{G_x^{\top}, P_{\top}}(Y) = E_{G^{\top}, P_{\top}}[\Delta_x(\overline{T})YW]$$

$$W = \left\{ \prod_{k=0}^K g^{\top}[A(k) | \overline{A}(k-1), \overline{R}(k-1), \overline{L}^*(k)] \right\}^{-1}$$

and

9 
$$\Delta_x(\overline{T}) = \prod_{k=0}^K I(A(k) = d_{x,k}[\overline{A}(k-1), \overline{T}(k-1), \overline{L}^*(k)])$$

11 In contrast, if we want to extrapolate to a population  $G$  with a different visit process and  
 estimate  $E_{(G_x, P_{\top})}[Y]$ , matters become more difficult. A conventional approach would be to assume  
 a nonignorable selection bias model visit process for  $G^{\top}$  such as the following. For  $k=0, \dots, K$ ,

13 
$$\text{pr}_{G^{\top}}[T(k) = 1 | \overline{A}(k) = \overline{a}(k), \overline{T}(k-1), \overline{L}^*(k), \overline{Y}_{\overline{a}}] = 1 / \{1 + \exp[-\{H_k^{\top}(\overline{a}) + Q_k^{\top}(\overline{a}, y)\}]\} \quad (33)$$

where  $H_k^{\top}(\overline{a}) = h_k^{\top}(\overline{a}, \overline{T}(k-1), \overline{L}^*(k))$  is an unspecified function and  $Q_k^{\top}(\overline{a}, \overline{Y}_{\overline{a}}) = q_k^{\top}(\overline{a}, \overline{T}(k-1),$   
 $\overline{L}^*(k), y)$  is a selection bias function that captures the association between the counterfactual  
 utility  $\overline{Y}_{\overline{a}}$  and  $T(k)$  that remains after conditioning on the observed past  $(\overline{\mathcal{O}}^{*,a}(k), A(k))$  and that  
 is assumed known for purposes of data analysis. In a sensitivity analysis, we would study how  
 our inferences concerning  $E_{(G_x, P_{\top})}[Y]$  change as we vary the selection bias function. If model  
 (33), the assumption that  $G^{\top}$  is TR- $\overline{\mathcal{O}}^{*,a}$ -SR, and an appropriate strong positivity assumption  
 all hold, then it follows from Section 7 of Robins *et al.* [15] that if we regard  $g[T(k) | \overline{A}(k) =$   
 $\overline{a}(k), \overline{T}(k-1), \overline{L}^*(k), \overline{Y}_{\overline{a}} = y]$  as a known function  $g^{\dagger}[\overline{T}(k), \overline{a}, \overline{L}^*(k), y]$ , say, then both  $H_k(\overline{A})$   
 and  $E_{G_x, P_{\top}}(Y)$  are identified with the identifying formula for  $H_k(\overline{A})$  given in Section 7 of

Robins *et al.* and

$$E_{G_x, P_T}(Y) = E_{G^\top, P_T}[\Delta_x(\bar{T})YWW^\dagger]$$

$$W^\dagger = \left\{ \prod_{k=0}^K \frac{g^\dagger[\bar{T}(k), \bar{A}, \bar{L}^*(k), Y]\{1 + \exp\{H_k^\top(\bar{A}) + Q_k^\top(\bar{A}, Y)\}\}}{\exp\{H_k^\top(\bar{A}) + Q_k^\top(\bar{A}, Y)\}^{T(k)}} \right\}^{-1}$$

1 In fact, in this context, the NDE assumption is often not required.

2 However, rather than taking the conventional approach, we shall instead choose to make no  
 3 assumptions whatsoever concerning the conditional visit probabilities  $\text{pr}_{G^\top}[T(k) = 1 | \bar{A}(k), \bar{T}(k-1), \bar{L}_{\mathcal{A}}]$  (which implies we also make no assumptions concerning  $\text{pr}_{G^\top}[T(k) = 1 | \bar{A}(k) =$   
 4  $\bar{a}(k), \bar{T}(k-1), \bar{L}^*(k), \bar{Y}_{\mathcal{A}}]$ ). Rather we will investigate what assumptions, in addition to those  
 5 needed to identify  $E_{G^\top, P_T}(Y)$ , are required to identify  $E_{(G_x, P_T)}[Y]$  in this setting. We shall see  
 6 that identification requires both the NDE assumption and an assumption that implies the visit rate  
 7 under  $G_x$  is less than the rate under  $G^\top$ .

8 Furthermore, our identifying assumptions will require that, unlike earlier, we consider the  
 9 joint distribution of the counterfactual variable  $\bar{T}_{(\bar{a}, G^\top)}$  and  $\bar{T}_{G_x}$  recording a subject's visit histo-  
 10 ries under regimes  $(\bar{a}, G^\top)$  and  $G_x$ , where the regime  $(\bar{a}, G^\top)$  denotes the regime with determin-  
 11 istic treatment history  $\bar{a}$  and random visit history determined by the visit process  $\text{pr}_{G^\top}[T(k) =$   
 12  $1 | \bar{A}(k), \bar{T}(k-1), \bar{L}_{\mathcal{A}}]$  of the observed data. For notational convenience, we shall let  $\bar{T}_{\bar{a}}$  denote  
 13  $\bar{T}_{\bar{a}, G^\top}$  and  $\bar{T}_{G_x}^\dagger$  denote  $\bar{T}_{G_x}$ . Further, we shall include  $T_{\bar{a}}(k)$  as a component of  $L_{\bar{a}}(k)$  and henceforth  
 14 denote the components of  $L_{\bar{a}}(k)$  other than  $T_{\bar{a}}(k)$  by  $H_{\bar{a}}(k) = H_{\bar{a}}(k-1)$ . It will also be notationally  
 15 useful to define  $H_{\bar{a}(k-1), \bar{T}^\dagger(k-1)}^{\dagger,*}(k) = H_{\bar{a}(k-1)}(k)t^\dagger(k-1)$  to distinguish it from  $H_{\bar{a}(k-1), \bar{T}^\dagger(k-1)}^*(k) \equiv$   
 16  $H_{\bar{a}(k-1)}(k)t_{\bar{a}(k-1)}(k-1)$ .

17 With these notational changes, each candidate's treatment regime  $\bar{d}_x$  is equal to a collection of  
 18 functions  $\{\bar{d}_{x,k}; k = 0, \dots, K\}$  where each  $\bar{d}_{x,k}$  maps the data  $(\bar{a}(k-1), \bar{T}^\dagger(k-1), \bar{h}_{\bar{a}(k-1), \bar{T}^\dagger(k-1)}^{\dagger,*}(k))$   
 19 that would be available at  $k$  under  $G_x$  to a treatment  $a(k)$ . That is,  $\bar{d}_{x,k}[\bar{a}(k-1), \bar{T}^\dagger(k-1),$   
 20  $\bar{h}_{\bar{a}(k-1), \bar{T}^\dagger(k-1)}^{\dagger,*}(k)] \in \mathcal{A}(k)$ . Furthermore, we assume

$$\bar{d}_{x,k}[\bar{a}(k-1), \bar{T}^\dagger(k-1), \bar{h}_{\bar{a}(k-1), \bar{T}^\dagger(k-1)}^{\dagger,*}(k)] = a(k-1) \quad \text{if } t^\dagger(k-1) = 0$$

21 to encode the assumption that treatment only changes at a visit. Further, by definition of  $G_x$  in  
 22 equations (14) and (15), there exists a known  $G$  such that, for all  $x$ 's,  $\text{pr}_{G_x}[T^\dagger(k) = 1 | \bar{A}(k-1),$   
 23  $\bar{T}^\dagger(k-1), \bar{L}_{\mathcal{A}}] \equiv \text{pr}_G[T^\dagger(k) = 1 | \bar{A}(k-1), \bar{T}^\dagger(k-1), \bar{L}_{\mathcal{A}}]$  whenever the density of the event  $(\bar{A}(k-1),$   
 24  $\bar{T}^\dagger(k-1), \bar{L}_{\mathcal{A}})$  is nonzero under  $(G_x, P_T)$ , where now  $\bar{L}_{\mathcal{A}} = (\bar{H}_{\mathcal{A}}, \bar{T}_{\mathcal{A}})$ . Our key identifying  
 25 assumption is the following.

26 *Visit process (VP) assumption:*

27 (i) For all  $k$ ,

$$\text{pr}_G[T^\dagger(k) = 1 | \bar{A}(k), \bar{T}^\dagger(k-1), \bar{L}_{\mathcal{A}}] = \text{pr}_G[T^\dagger(k) = 1 | \bar{A}(k), \bar{T}^\dagger(k-1), \bar{T}(k), \bar{H}^*(k)] \quad (34)$$

28 where  $\bar{T}(k) = \bar{T}_{\bar{A}(k)}(k)$  and  $\bar{H}^*(k) = \bar{H}_{\bar{A}(k-1), \bar{T}^\dagger(k-1)}^*(k)$ .

1 (ii) No new visit (NNV) assumption: With probability 1,

$$\text{pr}_G[T^\ddagger(k)=1|\bar{A}(k), \bar{T}^\ddagger(k-1), \bar{T}(k), \bar{H}^*(k)]=0 \quad \text{if } T(k)=0 \quad (35)$$

3 Assumption (34) states that the  $g$ -conditional density of  $T^\ddagger(k)$  given  $\bar{L}_{\mathcal{A}}$  and  $(\bar{A}(k), \bar{T}^\ddagger(k-1))$   
 5 depends on  $\bar{L}_{\mathcal{A}}$  through and only through the components  $(\bar{T}(k), \bar{H}^*(k))$  of  $\bar{L}_{\mathcal{A}}$  that would be  
 observed under the regime  $(\bar{a}, G^\top)$  with  $\bar{a}(k-1)=\bar{A}(k-1)$ .

Under the VP assumption, the expected utility  $E_{G_x, P^\top}[Y]$  of  $Y=y(\bar{A}, L(K+2))$  is mathematically well defined. Specifically, the expectation is w.r.t. to the density  $f_{G_x, P^\top}(\bar{T}^\ddagger, \bar{A}, \bar{L}_{\mathcal{A}})=g_x(\bar{T}^\ddagger, \bar{A}|\bar{L}_{\mathcal{A}})p^\top[\bar{L}_{\mathcal{A}}]$  with

$$g_x(\bar{T}^\ddagger, \bar{A}|\bar{L}_{\mathcal{A}}) \quad (36)$$

$$= \prod_{k=0}^K g[T^\ddagger(k)|\bar{A}(k), \bar{T}^\ddagger(k-1), \bar{T}(k), \bar{H}^*(k)] \quad (37)$$

$$\times \prod_{k=0}^K I(A(k)=d_{x,k}[\bar{A}(k-1), \bar{T}^\ddagger(k-1), \bar{H}^{\ddagger*}(k)]) \quad (38)$$

where  $\bar{H}^{\ddagger*}(k)$  has components  $H_{\bar{A}(m-1)}(m)T^\ddagger(m-1)$  for  $m \leq k$ .

7 Equation (35) formalizes the very strong sense in which the NNV assumption requires that  
 the visit rate under  $G$  is less than the visit rate under  $G^\top$ . Specifically, equation (35) states that  
 9 for any week  $k+1$  in which a subject with treatment history  $\bar{A}(k)$  would not have had a visit  
 under  $G^\top$ , he also would not have had a visit under  $G$ . The NNV assumption will essentially  
 11 never be precisely true, except in the special case in which all subjects made weekly visits under  
 $G^\top$  so  $T(k)$  is always 1 for all  $k$ 's. However, as discussed below, it cannot be weakened without  
 13 sacrificing the identifiability of  $E_{G_x, P^\top}[Y]$  from the data  $\bar{O}^*$  sampled from  $(G^\top, P^\top)$ . Identification  
 will additionally require the following positivity assumption.

15 *Restricted positivity (RP) assumption:* With  $(G_x, P^\top)$  probability 1, for  $k \leq K$ ,  $g^\top[a(k)|\bar{A}(k-1), \bar{T}(k-2), \bar{H}^*(k), T(k-1)=1] > 0$  for all  $a(k)$  in the support of  $\bar{A}(k)$  under the conditional law  
 17  $g_x(a(k)|\bar{A}(k-1), \bar{L}_{\mathcal{A}}, T(k-1)=1)$ , where we recall  $T(k-1)=T_{\bar{A}(k-1)}(k-1)$  and  $T_{\bar{a}(k-1)}(k-1) \in \bar{L}_{\mathcal{A}}$ .

19 Note the RP assumption only refers to the case  $T_{\bar{A}(k-1)}(k-1)=1$ . The case  $T_{\bar{A}(k-1)}(k-1)=0$  follows from the NNV assumption. That is, by assumption,  $g^\top[a(k)|\bar{A}(k-1), \bar{T}(k-2), \bar{H}^*(k), T(k-1)=0]=I(a(k)=A(k-1))$ . But, under the NNV assumption,  $g_x(a(k)|\bar{A}(k-1), \bar{L}_{\mathcal{A}}, T(k-1)=0)=I(a(k)=A(k-1))$  also holds.

23 Our main result is the following.

*Theorem 7.1*

25 Suppose  $G^\top$  is TR- $\bar{O}^{*,a}$ -SR, and for known  $g[T^\ddagger(k)|\bar{A}(k), \bar{T}^\ddagger(k-1), \bar{L}_{\mathcal{A}}]$  and  $\bar{d}_x$ , the NDE, the VP, the RP, and the C assumptions hold. Then,  $E_{G_x, P^\top}[Y]$  with  $Y=y(\bar{A}, L(K+2))$  is identified from data  $\bar{O}^*$  generated under  $(G^\top, P^\top)$  and equals  $E_{G^\top, P^\top}[U^\ddagger(g, g^\top)Y]$ , where  $U^\ddagger(g, g^\top)=u^\ddagger(\bar{O}^*$ ;

1  $g, g^\top$ ) with

$$U^\dagger(g, g^\top) = \frac{\sum_{\bar{t}^\dagger} \prod_{k=0}^K g[t^\dagger(k)|\bar{A}(k), \bar{t}^\dagger(k-1), \bar{T}(k), \bar{H}^*(k)] \Delta_x(\bar{t}^\dagger)}{\prod_{k=0}^K g^\top[A(k)|\bar{A}(k-1), \bar{T}(k-1), \bar{H}^*(k)]}$$

3 with  $\Delta_x(\bar{t}^\dagger) = \prod_{k=0}^K I(A(k) = d_{x,k}[\bar{A}(k-1), \bar{t}^\dagger(k-1), \bar{H}_{A(k-1), \bar{t}^\dagger(k-1)}^{\dagger,*}(k)])$ .

*Proof*

5 Under  $(G_x, P^\top)$  and  $(G^\top, P^\top)$ , respectively, the likelihood of an observation  $(\bar{A}, \bar{L}_{\mathcal{A}})$  is  $\sum_{\bar{t}^\dagger \in \mathcal{T}^\dagger} g(\bar{A}, \bar{t}^\dagger | \bar{L}_{\mathcal{A}}) p^\top(\bar{L}_{\mathcal{A}})$  and  $g^\top(\bar{A} | \bar{L}_{\mathcal{A}}) p^\top(\bar{L}_{\mathcal{A}})$ . Under our assumptions,  $\sum_{\bar{t}^\dagger \in \mathcal{T}^\dagger} g(\bar{A}, \bar{t}^\dagger | \bar{L}_{\mathcal{A}}) p^\top(\bar{L}_{\mathcal{A}})$  is absolutely continuous w.r.t.  $g^\top(\bar{A} | \bar{L}_{\mathcal{A}}) p^\top(\bar{L}_{\mathcal{A}})$  and the Radon-Nikodym derivative is  $U^\dagger(g, g^\top)$ . Thus,  $E_{G, P^\top}[Y] = E_{(G^\top, P^\top)}[U^\dagger(g, g^\top)Y]$ . Finally,  $U^\dagger(g, g^\top)$  and  $Y$  are functions of the observed data  $\bar{O}^*$ . □

The above proof of identifiability would have failed if the NNV assumption did not hold. First, absolute continuity would have failed because, the joint event  $A(k) \neq A(k-1)$  and  $T_{\bar{A}(k-1)}(k) = 0$ , which has probability zero under  $(G^\top, P^\top)$ , could then have nonzero probability under  $(G_x, P^\top)$ .

In addition, if the NNV assumption did not hold,  $\Delta_x(\bar{t}^\dagger)$  need not be a function of  $\bar{O}^*$ .

Recall that our final goal is to optimize  $E_{(G_x, P^\top)}[Y|V]$  over  $x \in \mathcal{X}$ . Suppose we specify an MSM  $E_{(G_x, P^\top)}[Y|V] = h(x, V, \psi^*)$  with  $h(x, V, \psi) = (r(x, V)^\top, r^*(V)^\top)\psi$ . Then, for a given  $q^*(x, V)$ , if the assumptions of Theorem 7.1 hold for all  $x \in \mathcal{X}$ , Theorem 7.1 implies the estimator  $\hat{\psi}$  solving (21) remains CAN when we replace the numerator of  $\hat{U}_x$  in (21) by the numerator of  $U^\dagger(g, g^\top)$  and the denominator by  $\prod_{k=0}^K g^\top[A(k)|\bar{A}(k-1), \bar{T}(k-1), \bar{H}^*(k); \hat{\alpha}]$ .

However, the estimator  $\hat{\psi}$  will often be computationally infeasible when  $K$  is large because the set  $\mathcal{T}^\dagger$  contains  $2^{K+1}$  elements. Therefore, we replace the previous expression with its unbiased simulation-based estimator  $S^{-1} \sum_{s=1}^S \Delta_x(\bar{t}_s^\dagger)$ , where, for  $s = 1, \dots, S$  and  $k = 0, \dots, K+1$ ,  $\bar{t}_s^\dagger(-1)$  is defined to be zero and  $\bar{t}_s^\dagger(k)$  is obtained recursively as a random draw from the (assumed known) Bernoulli density  $g[t^\dagger(k)|\bar{A}(k), \bar{t}^\dagger(k-1), \bar{H}_{\bar{A}(k-1), \bar{t}^\dagger(k-1)}^{\dagger,*}(k)]$  and  $\bar{t}_s^\dagger = \bar{t}_s^\dagger(K)$ . With this replacement, the solution  $\tilde{\psi}$  to the resulting estimating equation remains a CAN estimator of  $\psi^*$ , when the model  $g^\top[A(k)|\bar{A}(k-1), \bar{T}(k-1), \bar{H}^*(k); \alpha]$  is correct. Once we have obtained a CAN estimator of  $\psi^*$ , we can estimate  $x_{\text{opt}}(V) = x_{\text{opt}}(V, \psi^*)$  by  $x_{\text{opt}}(V, \tilde{\psi})$  as above.

In summary, the above development documents the very strong assumptions required to identify the  $E_{(G_x, P^\top)}[Y|V]$  from data generated under  $(G^\top, P^\top)$  in the presence of an arbitrary unmodelled nonignorable visit process  $G^\top$  that differs from the visit process of  $G_x$ . Two particular problems that we have yet to address are: How does one use one's limited knowledge of the population  $G$  to which we wish to extrapolate to choose the function  $g[t^\dagger(k)|\bar{A}(k), \bar{t}^\dagger(k-1), \bar{T}(k), \bar{H}^*(k)]$  needed to implement our estimator and how does one quantify the bias that results from imposing the NNV assumption when that assumption is incorrect. These are very difficult questions with no single 'correct' answer and any answer is lengthy. For this latter reason, we defer our answers to a future paper in which we will also consider in greater detail the alternative approach to the nonignorable visit process problem based on a nonignorable model such as equation (33).

1

APPENDIX A

In this appendix, we prove a general theorem that subsumes the special cases treated in Section 6.3. Let  $\tilde{c}(\bar{a}, \bar{t}, \bar{l})$  be a general function of  $(\bar{a}, \bar{t}, \bar{l})$ . We think of  $\tilde{c}(\bar{a}, \bar{t}, \bar{l})$  as the most general possible utility function. That is, the utility  $Y^*$  is given by  $Y^* = \tilde{c}(\bar{A}, \bar{T}, \bar{L})$ . Define  $u_{\tilde{c}}(k, \bar{a}, \bar{t}, \bar{l}) = 1$  if  $\tilde{c}(\bar{a}, \bar{t}, \bar{l})$ , as a function of  $\bar{l} = (\bar{z}, \bar{i})$ , depends nontrivially on the  $k+1$ th component  $i(k+1)$  of  $\bar{l}$  and define  $u_{\tilde{c}}(k, \bar{a}, \bar{t}, \bar{l}) = 0$ , otherwise. Given a function  $\tilde{c}(\bar{a}, \bar{t}, \bar{l})$  and a conditional law  $g^\top(\bar{t}|\bar{L}, \bar{A})$ , define the sets

$$\begin{aligned} \overline{\mathcal{B}}_{\tilde{c}}^*(\bar{l}, \bar{a}, \bar{t}^*) &= \{\bar{t}; t(k) \geq \max\{t^*(k), u_{\tilde{c}}(k, \bar{a}, \bar{t}^*, \bar{l})\} \text{ for } k=0, \dots, K+1\} \\ \overline{\mathcal{B}}_{\tilde{c}, g^\top}(\bar{l}, \bar{a}, \bar{t}^*) &= \{\bar{t} \in \overline{\mathcal{B}}_{\tilde{c}}^*(\bar{l}, \bar{a}, \bar{t}^*); g^\top(\bar{t}|\bar{l}, \bar{a}) > 0\} \end{aligned}$$

and

$$\mathcal{K}(\bar{a}, \bar{t}, \bar{l}) = \{k; t(k) + u_{\tilde{c}}(k, \bar{a}, \bar{t}, \bar{l}) > 0, 0 \leq k \leq K\}$$

*Theorem A.1*

5 Suppose  $G$  and  $G^\top$  are  $\overline{O}^{*a}$ -SR with the same marginal distribution  $P^\top$  for  $\overline{L}_{\mathcal{J}}$  and that the NDE assumption holds. Further, suppose that

$$\overline{\mathcal{B}}_{\tilde{c}, g^\top}(\overline{L}_{\mathcal{J}}, \bar{a}, \bar{t}^*) \text{ is nonempty for all } (\bar{a}, \bar{t}^*) \in \overline{\mathcal{J}}_g(\overline{L}_{\mathcal{J}}) \text{ w.p.1. under } P^\top \quad (\text{A1})$$

where  $\overline{\mathcal{J}}_g(\overline{L}_{\mathcal{J}})$  is the support of  $\overline{J} = (\overline{A}, \overline{T})$  under  $g(\bar{a}, \bar{t}^*|\overline{L}_{\mathcal{J}})$ . Then,

(a)  $E_{G, P^\top}[\tilde{c}(\overline{A}, \overline{T}, \overline{L})]$  is identified from data  $\overline{O}^*$  generated under  $(G^\top, P^\top)$  and it equals  $E_{G^\top, P^\top}[U(g, g^\top)]$  where  $U(g, g^\top) \equiv u(\overline{O}^*; g, g^\top)$  is defined as

$$\frac{\sum_{\bar{t}^* \in \overline{\mathcal{J}}_g(\overline{A}, \overline{L})} I(\overline{T} \in \overline{\mathcal{B}}_{\tilde{c}}(\overline{L}, \overline{A}, \bar{t}^*)) \tilde{c}(\overline{A}, \bar{t}^*, \overline{L}) \prod_{k=0}^K g[A(k), t^*(k)|\overline{A}(k-1), \bar{t}^*(k-1), \overline{L}_{\overline{T}^*}^*(k)]}{\prod_{k=0}^K g^\top[A(k)|\overline{A}(k-1), \overline{T}(k-1), \overline{L}^*(k)] \prod_{k \in \mathcal{K}(\overline{A}, \bar{t}^*, \overline{L})} g^\top[T(k)|\overline{A}(k), \overline{T}(k-1), \overline{L}^*(k)]} \quad (\text{A2})$$

9 with  $\overline{\mathcal{F}}_g(\overline{A}, \overline{L})$  the support of  $\overline{T}$  under  $g(\bar{t}|\overline{A}, \overline{L})$ , and  
 (b) the TPO\* assumption of equation (24) holds.

*Remark A.0*

Note that by  $G$  being  $\overline{O}^{*a}$ -SR, it holds that  $g(\bar{t}|\overline{A}, \overline{L}) = g(\bar{t}|\overline{A}, \overline{L}_{\mathcal{J}})$  and consequently,  $\overline{\mathcal{F}}_g(\overline{A}, \overline{L})$  is also the support of  $\overline{T}$  under  $g(\bar{t}|\overline{A}, \overline{L}_{\mathcal{J}})$ , which we denote by  $\overline{\mathcal{F}}_g(\overline{A}, \overline{L}_{\mathcal{J}})$ .

*Remark A.1*

15 Note  $\tilde{c}(\overline{A}, \bar{t}^*, \overline{L})$  and  $\overline{L}_{\overline{T}^*}^*(k)$  are both functions of  $\overline{O}^* = (\overline{A}, \overline{T}, \overline{L}_{\overline{T}^*}^*)$  whenever  $\overline{T} \in \overline{\mathcal{B}}_{\tilde{c}}(\overline{A}, \bar{t}^*, \overline{L})$ . It then follows as stated in the theorem that  $U(g, g^\top)$  is a function of  $\overline{O}^*$ .

*Corollary A.1*

17 If the suppositions of Theorem A.1 hold,  $G = G_x = \overline{\mathbf{d}}_{x=(x_a, x_t)}$ ,  $u_{\tilde{c}}(k, \bar{a}, \bar{t}, \bar{l})$  is the zero function,  
 19 then  $E_{G, P^\top}[\tilde{c}(\overline{A}, \overline{T}, \overline{L})]$  is equal to

$$E_{G^\top, P^\top} \left[ \left\{ \frac{\Delta(\overline{T}_{x_t}^*) \Delta_{x_a}(\overline{T}_{x_t}^*) \tilde{c}(\overline{A}, \overline{T}_{x_t}^*, \overline{L})}{\prod_{k=0}^K g^\top[A(k)|\overline{A}(k-1), \overline{T}(k-1), \overline{L}^*(k)] \prod_{k \in \mathcal{K}(\overline{A}, \overline{T}_{x_t}^*, \overline{L})} g^\top[T(k)|\overline{A}(k), \overline{T}(k-1), \overline{L}^*(k)]} \right\} \right]$$

1 Furthermore, equation (A1) is equivalent to the assumption that the set

$$\left\{ \bar{t}; t(k) \geq T_{G_x}(k) \text{ and } \prod_{k=0}^K g^\top [A_{G_x}(k), t(k) | \bar{A}_{G_x}(k-1), \bar{t}(k-1), \bar{L}_{\bar{A}_{G_x}(k-1), \bar{t}(k-1)}^*(k)] > 0 \right\}$$

3 is nonempty w.p.1. under  $P^\top$ .

*Corollary A.2*

5 If the assumptions of Theorem A.1 hold and  $G = G_{x_a}$ , with  $G_x$  as defined in equations (14) and (15), then  $E_{G, P^\top}[\tilde{c}(\bar{A}, \bar{T}, \bar{L})]$  is equal to

$$E_{G, G^\top, P^\top} \left[ \frac{1}{S} \sum_{s=1}^S \left[ \frac{I(\bar{T} \in \mathcal{B}_{\tilde{c}, g^\top}(\bar{L}, \bar{A}, \bar{T}_s^*)) \tilde{c}(\bar{A}, \bar{T}_s^*, \bar{L}) \delta_{x_a}(\bar{A}, \bar{T}_s^*, \bar{L})}{\prod_{k=0}^K g^\top [A(k) | \bar{A}(k-1), \bar{T}(k-1), \bar{L}^*(k)] \prod_{k \in \mathcal{X}(\bar{A}, \bar{T}_s^*, \bar{L})} g^\top [T(k) | \bar{A}(k), \bar{T}(k-1), \bar{L}^*(k)]} \right] \right]$$

7 with  $E_{G, G^\top, P^\top}$  the expectation taken under  $f_{G, G^\top, P^\top}(\bar{t}_1^*, \dots, \bar{t}_S^*, \bar{t}, \bar{a}, \bar{l}) \equiv \left\{ \prod_{s=1}^S \tilde{g}(\bar{t}_s^* | \bar{a}, \bar{l}, \bar{t}) \right\} f_{G^\top, P^\top}(\bar{a}, \bar{t}, \bar{l})$ , where  $\tilde{g}(\bar{t}_s^* | \bar{a}, \bar{l}, \bar{t}) \equiv \prod_{k=0}^K g[t^*(k) | \bar{a}(k), \bar{t}_s^*(k-1), \bar{L}_{\bar{t}_s^*(k-1)}^*(k)]$ .

*Proof of Theorem A.1*

Let  $\mathcal{A}_g(\bar{L}_{\mathcal{A}})$  denote the support of  $\bar{A}$  under  $g(\bar{a} | \bar{L}_{\mathcal{A}})$ . Then

$$\begin{aligned} & E_{G, P^\top}[\tilde{c}(\bar{A}, \bar{T}, \bar{L})] \\ &= E_{P^\top} \left[ \sum_{(\bar{a}, \bar{t}^*) \in \mathcal{F}_g(\bar{L}_{\mathcal{A}})} \tilde{c}(\bar{a}, \bar{t}^*, \bar{L}_{\bar{a}}) g(\bar{a}, \bar{t}^* | \bar{L}_{\mathcal{A}}) \right] \\ &= E_{P^\top} \left[ \sum_{(\bar{a}, \bar{t}^*) \in \mathcal{F}_g(\bar{L}_{\mathcal{A}})} \tilde{c}(\bar{a}, \bar{t}^*, \bar{L}_{\bar{a}}) \prod_{k=0}^K g[a(k), t^*(k) | \bar{a}(k-1), \bar{t}^*(k-1), \bar{L}_{\bar{a}(k-1), \bar{t}^*(k-1)}^*(k)] \right] \\ &= E_{P^\top} \left[ \sum_{(\bar{a}, \bar{t}^*) \in \mathcal{F}_g(\bar{L}_{\mathcal{A}})} \tilde{c}(\bar{a}, \bar{t}^*, \bar{L}_{\bar{a}}) \prod_{k=0}^K g[a(k), t^*(k) | \bar{a}(k-1), \bar{t}^*(k-1), \bar{L}_{\bar{a}(k-1), \bar{t}^*(k-1)}^*(k)] \right. \\ &\quad \left. \times \left\{ \sum_{\bar{t} \in \mathcal{B}_{\tilde{c}, g^\top}(\bar{L}_{\bar{a}}, \bar{a}, \bar{t}^*)} \prod_{\{k; t^*(k) = u(k, \bar{a}, \bar{t}^*, \bar{L}_{\bar{a}}) = 0\}} g^\top [t(k) | \bar{a}(k), \bar{t}(k-1), \bar{L}_{\bar{a}(k-1), \bar{t}^*(k-1)}^*(k)] \right\} \right] \\ &= E_{G^\top, P^\top} \left\{ \sum_{(\bar{a}, \bar{t}^*) \in \mathcal{F}_g(\bar{L}_{\mathcal{A}})} \sum_{\bar{t} \in \mathcal{B}_{\tilde{c}, g^\top}(\bar{a}, \bar{t}^*, \bar{L}_{\bar{a}})} \frac{I(\bar{A} = \bar{a}) I(\bar{T} = \bar{t})}{g^\top[\bar{a}, \bar{t} | \bar{L}_{\mathcal{A}}]} \right. \\ &\quad \times \prod_{\{k; t^*(k) = u(k, \bar{a}, \bar{t}^*, \bar{L}_{\bar{a}}) = 0\}} g^\top [t(k) | \bar{a}(k), \bar{t}(k-1), \bar{L}_{\bar{a}(k-1), \bar{t}^*(k-1)}^*(k)] \\ &\quad \left. \times \tilde{c}(\bar{a}, \bar{t}^*, \bar{L}_{\bar{a}}) \prod_{k=0}^K g[a(k), t^*(k) | \bar{a}(k-1), \bar{t}^*(k-1), \bar{L}_{\bar{a}(k-1), \bar{t}^*(k-1)}^*(k)] \right\} \end{aligned}$$

$$\begin{aligned}
 &= E_{G^\top, P^\top} \left\{ \sum_{\bar{t}^* \in \mathcal{F}_g(\bar{A}, \bar{L})} I[\bar{A} \in \overline{\mathcal{A}}_g(\bar{L}, \overline{\mathcal{A}})] \frac{I(\bar{T} \in \overline{\mathcal{B}}_{\tilde{c}}(\bar{L}, \bar{A}, \bar{t}^*))}{g^\top[\bar{A}, \bar{T} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}] } \right. \\
 &\quad \times \prod_{\{k; t^*(k)=u(k, \bar{A}, \bar{t}^*, \bar{L})=0\}} g^\top[T(k) | \bar{A}(k), \bar{T}(k-1), \bar{L}^*(k)] \\
 &\quad \left. \times \tilde{c}(\bar{A}, \bar{t}^*, \bar{L}) \prod_{k=0}^K g[A(k), t^*(k) | \bar{A}(k-1), \bar{t}^*(k-1), \bar{L}_{\bar{A}(k-1), \bar{t}^*(k-1)}^*(k)] \right\} \\
 &= E_{G^\top, P^\top} [u(\bar{O}^*; g, g^\top)]
 \end{aligned}$$

- 1 where the second equality follows because  $G$  is  $\bar{O}^{*a}$ -SR, the third follows because, by  
the definition of  $\overline{\mathcal{B}}_{\tilde{c}, g^\top}(\bar{L}, \bar{a}, \bar{t}^*)$ , and assumption (A1) the expression in set braces equals  
3  $\prod_{\{k; t^*(k)=u(k, \bar{a}, \bar{t}^*, \bar{L}, \bar{a})=0\}} [ \sum_{t(k)=0}^1 g^\top[t(k) | \bar{a}(k), \bar{t}(k-1), \bar{L}_{\bar{a}(k-1), \bar{t}^*(k-1)}^*(k)] ]$ , the fourth follows  
because

$$5 \quad E_{G^\top} \left[ \frac{I(\bar{A}=\bar{a}) I(\bar{T}=\bar{t})}{g^\top[\bar{a}, \bar{t} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}]} \middle| \overline{\mathcal{L}}_{\overline{\mathcal{A}}} \right] = E_{G^\top} \left[ \frac{I(\bar{A}=\bar{a})}{g^\top[\bar{a} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}]} \frac{I(\bar{T}=\bar{t})}{g^\top[\bar{t} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}, \bar{a}]} \middle| \overline{\mathcal{L}}_{\overline{\mathcal{A}}} \right] = 1$$

for  $\bar{t} \in \overline{\mathcal{B}}_{\tilde{c}, g^\top}(\bar{L}, \bar{a}, \bar{t}^*)$  by  $g^\top[\bar{a}, \bar{t} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}]$  being  $\bar{O}^{*a}$ -SR, part (b) of this theorem (to be shown  
next) and equation (A1), the fifth follows because  $I(\bar{T} \in \overline{\mathcal{B}}_{\tilde{c}, g^\top}(\bar{L}, \bar{A}, \bar{t}^*))=1$  is equivalent to  
 $I(\bar{T} \in \overline{\mathcal{B}}_{\tilde{c}}(\bar{L}, \bar{A}, \bar{t}^*))=1$  under  $G^\top$ , and the last equality follows because

$$\begin{aligned}
 &\prod_{\{k; t^*(k)=u(k, \bar{A}, \bar{t}^*, \bar{L})=0\}} g^\top[T(k) | \bar{A}(k), \bar{T}(k-1), \bar{L}^*(k)] / g^\top[\bar{A}, \bar{T} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}] \\
 &= \prod_{k=0}^K g^\top[A(k) | \bar{A}(k-1), \bar{T}(k-1), \bar{L}^*(k)] \prod_{\{k; t^*(k)+u(k, \bar{A}, \bar{t}^*, \bar{L})>0\}} g^\top[T(k) | \bar{A}(k), \bar{T}(k-1), \bar{L}^*(k)]
 \end{aligned}$$

by  $g^\top[\bar{A}, \bar{T} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}]$  being  $\bar{O}^{*a}$ -SR.

- 7 Finally, the TPO\* assumption of equation (24) holds because (i) by (A1) for all  $\bar{a}$  such  
that  $g(\bar{a} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}) > 0$ , there exists a  $\bar{t}$  such that  $g^\top(\bar{t} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}, \bar{a}) > 0$  and (ii) by  $G^\top$  being  $\bar{O}^{*a}$ -SR,  
9  $g^\top(\bar{t} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}, \bar{a}) > 0 \Rightarrow g_{\bar{A}, \bar{T} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}}^\top(\bar{a}, \bar{t} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}) = g^\top(\bar{a}, \bar{t} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}) > 0 \Rightarrow g^\top(\bar{a} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}) > 0$ . □

*Proof of Corollary A.1*

- 11 The numerator of equation (A2) equals  $\Delta(\bar{T}_{x_2}^*) \Delta_{x_1}(\bar{T}_{x_2}^*) \tilde{c}(\bar{A}, \bar{T}_{x_2}^*, \bar{L})$  when  $G = \bar{\mathbf{d}}_{x=(x_1, x_2)}$ .

Moreover, under regime  $G_x = \bar{\mathbf{d}}_{x=(x_a, x_t)}$  the support of  $(\bar{A}, \bar{T})$  under  $g(\bar{a}, \bar{t}^* | \overline{\mathcal{L}}_{\overline{\mathcal{A}}})$  is the singleton  
 $(\bar{A}_{G_x}, \bar{T}_{G_x})$ . However, arguing as in the proof of part (b) of the theorem

$$\begin{aligned}
 &g^\top(\bar{t} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}, \bar{a}) |_{\bar{a}=\bar{A}_{G_x}} > 0 \Leftrightarrow g_{\bar{A}, \bar{T} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}}^\top(\bar{a}, \bar{t} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}) |_{\bar{a}=\bar{A}_{G_x}} = g^\top(\bar{a}, \bar{t} | \overline{\mathcal{L}}_{\overline{\mathcal{A}}}) |_{\bar{a}=\bar{A}_{G_x}} \\
 &= \prod_{k=0}^K g^\top[a(k), t(k) | \bar{a}(k-1), \bar{t}(k-1), \bar{L}_{\bar{a}(k-1), \bar{t}(k-1)}^*(k)] |_{\bar{a}=\bar{A}_{G_x}} > 0 \quad \square
 \end{aligned}$$

*Proof of Corollary A.2*

Corollary A.2 follows at once from the observation that the numerator of equation (A2) equals

$$\sum_{\bar{t}^* \in \bar{\mathcal{T}}_g(\bar{A}, \bar{L})} \left\{ I(\bar{T} \in \bar{\mathcal{B}}_{\bar{c}, g \top} \bar{\mathcal{B}}_{\bar{c}, g \top}(\bar{L}, \bar{A}, \bar{T}^*)) \Delta_{x_a}(\bar{A}, \bar{t}^*, \bar{L}) \right. \\ \left. \times \tilde{c}(\bar{A}, \bar{t}^*, \bar{L}) \prod_{k=0}^K g[t^*(k) | \bar{A}(k), \bar{t}^*(k-1), \bar{L}_{\bar{T}^*(k-1)}^*(k)] \right\}$$

1 which can be written as  $E_{\tilde{g}}[\delta_{x_a}(\bar{A}, \bar{T}^*, \bar{L}) I(\bar{t} \in \bar{\mathcal{B}}_{\bar{c}, g \top}(\bar{L}, \bar{A}, \bar{T}^*)) \tilde{c}(\bar{A}, \bar{T}^*, \bar{L}) | \bar{A}, \bar{L}, \bar{T}]$ . □

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