

Individualized treatment rules: Generating candidate clinical trials

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SUMMARY

Individualized treatment rules, or rules for altering treatments over time in response to changes in individual covariates, are of primary importance in the practice of clinical medicine. Several statistical methods aim to estimate the rule, termed an optimal dynamic treatment regime, which will result in the best expected outcome in a population. In this article, we discuss estimation of an alternative type of dynamic regime—the statically optimal treatment rule. History-adjusted marginal structural models (HA-MSM) estimate individualized treatment rules that assign, at each time point, the first action of the future static treatment plan that optimizes expected outcome given a patient's covariates. However, as we discuss here, HA-MSM-derived rules can depend on the way in which treatment was assigned in the data from which the rules were derived. We discuss the conditions sufficient for treatment rules identified by HA-MSM to be statically optimal, or in other words, to select the optimal future static treatment plan at each time point, regardless of the way in which past treatment was assigned. The resulting treatment rules form appropriate candidates for evaluation using randomized controlled trials. We demonstrate that a history-adjusted individualized treatment rule is statically optimal if it depends on a set of covariates that are sufficient to control for confounding of the effect of past treatment history on outcome. Methods and results are illustrated using an example drawn from the antiretroviral treatment of patients infected with HIV. Specifically, we focus on rules for deciding when to modify the treatment of patients infected with resistant virus. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS: causal inference; longitudinal data; dynamic treatment regime; adaptive treatment strategy; history-adjusted marginal structural model; human immunodeficiency virus

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1. INTRODUCTION

Many pressing clinical questions involve strategies or rules for deciding how treatments should be assigned and changed over time. To be effective, such strategies must be individualized. In other words, treatment must be assigned and modified in response to individual changes in disease progression, adverse effects, and other patient characteristics. Examples of such individualized treatment rules, known as dynamic treatment regimes in the statistical literature, include the decision to start anti-hypertensive medication in response to repeated measurements of hypertension and the decision to modify the dose of an antidepressant medication in response to adverse effects. Individualized treatment rules can be contrasted with static treatment regimens, in which treatment can change over time, but not in response to individual covariates.

Given a set of dynamic regimes or treatment rules of interest, there is a substantial literature on methods to estimate the expected counterfactual outcome under a specified treatment rule [1–7]. Of greater relevance to the current paper, prior research spanning multiple disciplines has focused on the estimation of *optimal* dynamic regimes. The optimal dynamic regime is the treatment rule that produces, on average, the best patient outcome at a given time point. Most approaches to estimation of such optimal rules have relied on dynamic programming and the assumption that the multivariate distribution of covariates and outcome over time is known or can be sampled [1]. Additional work has focused on the estimation of such rules using sequentially randomized trials (see, for example, [8–10]). Notably, Murphy and Robins have proposed alternative (related) approaches to the estimation of statically optimal dynamic regimes that avoid parametric assumptions on the entire multivariate data generating distribution [1, 3, 4, 11–13] and which can avoid the need for dynamic programming. For a more extensive review of the literature on the estimation of optimal dynamic treatment regimes and the links between the work of Murphy and Robins, see [1, 14].

In this article, we discuss estimation of a different type dynamic regime. Specifically, we focus on estimation of a treatment rule that assigns, at each time point, the first action of the future static treatment plan that optimizes expected outcome. Updating this optimal plan at subsequent time points based on a patient's covariates yields a dynamic treatment rule. The difference between such a 'statically optimal' treatment rule and an optimal dynamic treatment rule, as estimated by the methods of Murphy and Robins, can be understood by considering the respective randomized controlled trials to which the two parameters correspond.

Suppose that, at study entry, subjects are stratified by covariates thought to be important modifiers of treatment effect. Within each stratum subjects are randomized to follow one of several future treatment arms, and are then followed until the final outcome is observed. This classic randomized trial would identify the best static treatment plan (of those considered), beginning at baseline and given a subject's baseline covariates. Now suppose that the clock is somehow rewound, and an equivalent trial is then repeated beginning at the second time point after study entry, in which subjects are now randomized to treatment arms within strata defined by covariate values at time 2. The trial is then repeated for each time point in the study. Such a series of trials would identify, for each time point, the future treatment plan which provides the best expected outcome given a subject's current covariates. A statically optimal treatment rule corresponds with applying the results of such a series of clinical trials to the longitudinal assignment of treatment; given the time point and the patient's current characteristics, a patient's treatment is updated at each time point to the static plan that will result in the best expected outcome.

Statically optimal treatment rules can thus be understood as combining the results of a series of (hypothetical) randomized trials comparing static treatment plans into a more complex dynamic rule. In contrast, identifying the truly optimal dynamic rule corresponds to a trial in which subjects are randomized to treatment arms corresponding to all possible rules for assigning treatment in response to the evolution of subject covariates over time. Given the choice, the truly optimal rule will generally be preferable to the statically optimal rule. For example, in settings where a treatment is beneficial for some subjects, but, following the development of adverse effects, is fatal to others, the statically optimal rule can fail to identify the truly optimal rule, resulting in a lower mean outcome in the population. A simulation illustrating this example is provided van der Laan *et al.* [15].

While the truly optimal rule is generally preferable, consideration of the corresponding clinical trials demonstrates that it is also a much more ambitious parameter. As a result, it is expected that, in comparison to estimates of the statically optimal rule, estimates of the truly optimal rules should either be less precise (i.e. have larger confidence intervals), or rely on a greater degree of model-based extrapolation. The precision advantage provided by the statically optimal rule should be even greater in cases where time since baseline (e.g. study entry) is not itself meaningful and as a result estimates can be pooled across time points. By focusing on a series of static treatment effects that are relatively straightforward to estimate, and which can be estimated using standard software as a series of weighted multivariable regressions, statically optimal treatment rules are thus a practical alternative for estimation of dynamic regimes using finite data sets.

In summary then, while a truly optimal rule will be generally preferable to a statically optimal rule, there seem to be several practical advantages to the estimation of statically optimal treatment rules. Our goal in this article is to introduce statically optimal treatment rules as an interesting and novel type of dynamic treatment regime, one which is interpretable and has some clinically desirable characteristics, but which is not intended as a replacement for the truly optimal rule. We further aim to illustrate that statically optimal rules are relatively straightforward to estimate, and thus represent a useful tool for practical data analyses.

Like the methods of Murphy [1] and Robins [12, 13], our approach uses the concept of counterfactuals or potential outcomes [16, 17], and the counterfactual framework for causal inference [3, 11]. Our method employs history-adjusted marginal structural models (HA-MSM) [15, 18], a generalization of the marginal structural model (MSM) approach to causal inference [19–22]. HA-MSM estimate individualized treatment rules by identifying, at each time point, the future static treatment plan that optimizes expected outcome given individual covariates of interest. The first action of this static plan is then assigned, and the optimal future static plan recalculated at the subsequent time point. The resulting treatment regimen is a dynamic rule, in that the treatment assigned can change in response to individual covariates [15].

However, as we explain, the treatment rules identified by HA-MSM can depend on the way in which treatment was assigned in the study population (the treatment mechanism). As a result, if these rules were applied at a given time point to an identical population in which treatment up till that time point had been assigned differently, they would not necessarily identify the future treatment plan that would optimize expected outcome. In this paper, we present conditions sufficient to ensure that the treatment rule estimated by HA-MSM is truly ‘statically optimal’, or in other words, that the treatment rule identifies at each time point the first action of a static treatment regimen that is optimal *regardless* of treatment assignment up till that time point. Using the directed acyclic graph (DAG) framework [23], we illustrate that specific causal structures are sufficient to ensure static optimality. Finally, we show that HA-MSM can still be used to derive

statically optimal treatment rules when these conditions are not met, by incorporating a summary of patient history, such as that provided by the treatment mechanism or propensity score (PS), into the individualized rule.

Throughout the article, we rely for an example on a research question drawn from the treatment of HIV infection: When antiretroviral therapy (ART) fails to suppress viral replication, what treatment rule should be used to decide when to modify the drugs in a patient's regimen? In Section 2, we present some background on this clinical question and the data used to address it. (For a full description of the sample and corresponding HA-MSM models, see Petersen *et al.* [18].) Section 3 uses this data example to review HA-MSM, including key assumptions, the parameter of interest, and the resulting dynamic treatment regime. Section 4 discusses the dependence of the HA-MSM parameter on the observed treatment mechanism. Section 5 presents an equality under which HA-MSM-derived treatment rules are statically optimal (i.e. independent of the treatment mechanism) and gives a sufficient condition for the equality to hold. Section 6 shows how including in the HA-MSM model either (1) the entire observed history, or (2) a summary of the history provided by the treatment mechanism or PS, ensures this equality, and thus static optimality. Section 7 uses DAG theory to demonstrate that the necessary equality also holds under specific causal structures. Thus, in certain contexts, incorporation of the treatment mechanism may not be necessary. Section 8 presents examples of statically optimal treatment rules derived from the data example. The results illustrate the implementation of the treatment mechanism method to ensure static optimality, as well as a causal structure under which inclusion of the treatment mechanism as a covariate is not needed. Finally, we conclude with a discussion in Section 9.

2. HIV DATA EXAMPLE: WHEN TO SWITCH ANTIRETROVIRAL THERAPY?

Combination ART can successfully suppress viral replication in many HIV-infected individuals. As a result, the immune system recovers, CD4+ T cell counts increase, and clinical prognosis improves dramatically [24]. Unfortunately, HIV frequently develops resistance to the drugs being used to treat it, allowing the virus to resume replication and resulting in an increase in the amount of virus in the patient's blood (measured as plasma HIV RNA level or viral load). When this loss of virologic suppression occurs, clinicians are faced with an important treatment decision: how to decide when to modify the patient's antiretroviral regimen. Waiting too long to switch to a new regimen may result in the accumulation of additional resistance mutations in the virus. Also, increased levels of viral replication will generally lead over time to progressive loss of CD4+ T cell counts. However, switching regimens too early can deplete future treatment options, and may result in increased toxicity. (For a review of this issue, see Deeks [25].) Importantly, the decision as to 'when to switch' is often made by clinicians based in part on the number of previous treatment regimens (with fewer prior regimens leading to a desire to modify therapy earlier), and the rate at which patients appear to be progressing clinically. Hence, the optimal strategy for deciding when to switch is likely to be based on the evolution of patient and virologic characteristics over the course of non-suppressive therapy.

We used HA-MSM to estimate the effect of time until modifying ART regimen on CD4+ T cell count 8 months in the future ($m = 8$ in subsequent notation). Data were drawn from the Study on the Consequences of the Protease Inhibitor Era (SCOPE) cohort, an observational cohort of HIV-infected individuals followed between 2000 and 2004 in San Francisco, California. Data were collected on socioeconomic status (housing, income, employment), antiretroviral medication use

and adherence, occurrence of opportunistic infection and malignancy, recreational drug use, plasma HIV RNA levels, and CD4+/CD8+ T cell counts. All data were collected at 4 month scheduled intervals; in addition, laboratory data were collected between intervals at clinician discretion. Exact dates for all antiretroviral treatment changes were available. In analysing the data, a discrete monthly time scale was used, based on the approximate frequency with which new laboratory data were collected and treatment decisions made.

Subjects qualified for the current analysis ($t = 0$) if they experienced loss of virologic suppression on an antiretroviral regimen. Loss of virologic suppression ('virologic failure') was defined using either of the following criteria: (1) at least two detectable viral loads, and no undetectable viral loads in a 4 month period while on a stable antiretroviral regimen; or (2) at least two detectable viral loads and no undetectable viral loads within the first 6 months of starting a new regimen.

One hundred thirty-three subjects experiencing a total of 167 episodes of virologic failure were identified from the SCOPE cohort and contributed to the analyses described here. Of these, 116 episodes among 100 subjects were followed up for at least 8 months after failure; censoring occurred due to the end of follow-up (in 2004), loss to follow-up, and death (a total of three deaths were observed). For a full description of the sample and more complete details on censoring and death, see [18, 26].

The effect of additional time until treatment modification on CD4+ T cell count 8 months in the future was estimated for each of the first 8 months following loss of virologic suppression ($t = 0$). Thus, the full follow-up time for a given subject consisted of either 16 months following loss of suppression, or, if the subject switched regimens before 8 months, 8 months after the switch time; we denote this follow-up time $K + 1$.

The treatment of interest (time until modification of the antiretroviral regimen or 'switching') was defined using a vector of binary covariates $\bar{A}(K) = (A(0), \dots, A(K))$, where 0 denotes the time virologic failure occurred, and $K + 1$ denotes the end of follow-up. $A(t)$ remained equal to one as long as a patient remained on his original non-suppressive therapy, jumped to zero as soon as a subject switched therapy, and remained zero thereafter. Longitudinal covariates measured on a subject are denoted $\bar{L}(K + 1) = (L(0), \dots, L(K + 1))$, where $L(t)$ was measured before $A(t)$. The outcome of interest for a given baseline time point j was CD4+ T cell count $m = 8$ months in the future ($Y(j + m)$). The observed data for a given subject thus consisted of $O = (\bar{A}(K), \bar{L}(K + 1))$.

3. REVIEW OF HA-MSM

HA-MSM rely on the counterfactual framework for causal inference [3, 11], under which each individual has a set of counterfactual covariate processes corresponding to the paths each covariate would have followed under each possible treatment history. This set of counterfactuals is the full data: $X^{\text{Full}} = (\bar{L}(K + 1)_{\bar{a}}, \bar{a} \in \mathbf{A})$, where \mathbf{A} denotes the set of possible treatment regimens, and $\bar{L}(K + 1)_{\bar{a}}$ denotes the counterfactual covariates that would have been observed over the course of follow-up if an individual had followed treatment regimen $\bar{A}(K) = \bar{a}(K)$; the counterfactual outcome $Y_{\bar{a}}$ is contained in $\bar{L}(K + 1)_{\bar{a}}$. Under the counterfactual framework, a set of counterfactual CD4+ T cell counts (and other covariates) exist for each individual under each possible switch time.

The observed covariate values for an individual are assumed to be equal to the individual's counterfactual covariate values under her observed treatment history (the consistency assumption):

$$O = (\bar{A}(K), \bar{L}(K + 1)_{\bar{A}}) \quad (1)$$

Under this assumption (1), the distribution of the observed data is indexed by (1) the distribution of the full data (F_X), and (2) the distribution of the treatment history given the full data ($g(\bar{a}|X^{\text{Full}}) = g$): $O \sim P_{F_X, g}$, where $g(\bar{a}|X^{\text{Full}}) = P(\bar{A} = \bar{a}|X^{\text{Full}})$ is the treatment mechanism, which acts as a missingness variable.

HA-MSM further assume the existence of no unmeasured confounders (the sequential randomization assumption or SRA)

$$A(t) \prod_{\tau=0}^{t-1} X^{\text{Full}} \Big| \bar{A}(t-1), \bar{L}(t) \quad \text{for } t=0, \dots, K \quad (2)$$

In the HIV application, the SRA (2) assumes that measured variables are sufficient to control confounding of the effect of switching on future CD4+ T cell count. Under the SRA, the treatment mechanism can be written as

$$g(\bar{A}|X^{\text{Full}}) = \prod_{t=0}^K P(A(t)|\bar{L}(t), \bar{A}(t-1)) \quad (3)$$

Standard MSM model the expectation (or some other parameter) of the counterfactual outcome, conditional on baseline covariates of interest: $E(Y(m)_{\bar{a}}|V)$, where V denotes the values of effect modifiers of interest at baseline ($t=0$). HA-MSM can be understood as fitting, at each time point during follow-up, a standard MSM that models the counterfactual outcome indexed by treatment after that time point conditional on a subset of observed treatment and covariate history up till that time point. As an alternative to fitting a separate model at each time point, a common model can be fit across time points.

Let $\underline{a}(j)$ denote a future treatment regimen beginning at time point j and continuing until the outcome is measured m time points later ($\underline{a}(j) = a(j), \dots, a(j+m-1)$). In general, HA-MSM are concerned with the counterfactual outcome indexed by the observed treatment up till time $(j-1)$ and a specified future treatment regimen from time j until the outcome is measured: $Y(j+m)_{\bar{A}(j-1)\underline{a}(j)}$. HA-MSM model the mean (or some other parameter) of these counterfactuals, conditional on $V(j)$, a subset of the observed past up till time j ($V(j) \subset (\bar{L}(j), \bar{A}(j-1))$):

$$E[Y(j+m)_{\bar{A}(j-1)\underline{a}(j)}|V(j)] \quad (4)$$

Typically, $V(j) = (\bar{A}(j-1), \bar{S}(j))$, where $\bar{S}(j) \subset \bar{L}(j)$ denotes the covariates conditioned on, or the effect modifiers of interest.

We applied this method among individuals who had experienced loss of virologic expression and who remained on their original therapy to estimate the effect of additional time until switching therapy on CD4+ T cell count 8 months later. These counterfactual outcomes were denoted $Y(j+m)_{\bar{A}(j-1)c(j)}$, where $c(j)$ denoted the counterfactual future time (after time j) until a subject either switched treatment or the outcome was measured at time $j+m$. Note that $c(j)$ is a summary of the counterfactual treatment regimen beginning at time j (i.e. $c(j)$ is a summary of $\underline{a}(j)$). HA-MSM were used to estimate the following history-adjusted mean:

$$E[Y(j+m)_{\bar{A}(j-1)c(j)}|\bar{A}(j-1), \bar{S}(j)] \quad (5)$$

Models were fit only among those individuals who had not already switched therapy ($\bar{A}(j-1) = 1$), and only among those individuals who had not experienced re-suppression of the virus while on the same therapy ($\text{Sup}(j) = 0$). (The latter criterion allowed us to focus on subjects experiencing virologic failure due to viral resistance rather than poor adherence.) In two sets of analyses, the additional effect modifiers of interest were CD4+ T cell count at time j ($\text{CD4}(j)$), and the

presence of an opportunistic disease at time j ($OD(j)$). Thus initially $\bar{S}(j) = (CD4(j), Sup(j))$, and subsequently $\bar{S}(j) = (OD(j), Sup(j))$. In other words, among individuals who had not yet switched therapy or been re-suppressed by time point j , HA-MSM were used to model the mean counterfactual future CD4+ T cell counts that would have been observed if this entire subpopulation (or a random sample) had switched therapy $c(j)$ months after time j , and how these expected counterfactual outcomes differed depending on time elapsed since loss of suppression occurred (j), and on either a patient's CD4+ T cell count at time j ($CD4(j)$) or the presence of opportunistic disease ($OD(j)$) at time j .

The HA-MSM parameter identifies an interesting dynamic treatment regime, or rule for assigning treatment over time in response to individual changes in covariates. In the HIV analyses, the history-adjusted mean estimates, at each time point j , the effect of additional time until switching therapy on future CD4+ T cell count among individuals who have not yet switched, conditional on covariates of interest. For example, the effect of an additional month until switching can be estimated as

$$E(Y(j+m)_{\bar{A}(j-1)c(j)+1} | \bar{A}(j-1)=1, \bar{S}(j)) - E(Y(j+m)_{\bar{A}(j-1)c(j)} | \bar{A}(j-1)=1, \bar{S}(j))$$

This suggests the following treatment rule: when additional time waiting to switch decreases expected future CD4+ T cell count, switch immediately; when additional time waiting increases expected future CD4+ T cell count, wait until the next time point to switch, and then re-evaluate the estimated effect of additional waiting time. More generally, the treatment rule identified by HA-MSM consists of following, at each time point, the first action of the future static treatment plan that optimizes expected outcome. This treatment plan is updated at each time point in response to changes in patient covariates. Thus, the HA-MSM dynamic treatment rule can be defined as follows:

$$\begin{aligned} \underline{a}^*(j|V(j)) &\equiv \arg \max_{\underline{a}(j)} E(Y(j+m)_{\bar{A}(j-1)\underline{a}(j)} | \bar{A}(j-1)=\bar{a}(j-1), \bar{S}(j)) \\ d(j|V(j)) &\equiv \underline{a}^*(j|V(j))(1), \quad j=0, \dots, K+1-m \end{aligned}$$

where $d(j|V(j))$ is the treatment decision at time j and $\underline{a}^*(j|V(j))(1)$ refers to the first action of $\underline{a}^*(j|V(j))$.

4. MOTIVATION FOR STATICALLY OPTIMAL TREATMENT RULES

The history-adjusted mean (4) is a parameter of both the full data and the treatment mechanism in the observed data [15]. To see this, consider that assignment of treatment up to time j affects $V(j)$ values at time j (i.e. membership in the subpopulations, or strata, of interest at time j). Thus, the observed treatment up till time j can affect the counterfactual mean within the strata of interest.

In other words, if treatment up till time j had been assigned differently (for example, if treatment up till time j had been assigned randomly), members of a given subpopulation of interest at time j (individuals for whom $V(j) = v(j)$) would not necessarily be exchangeable with the corresponding subpopulation in the observed data. Specifically, the two groups would differ as a result of differences in the covariates used to assign treatment. To the extent that these covariates also affect outcome, estimates of the effect of future treatment could also differ between the two groups. As a result, the optimal future treatment plan identified for a given stratum of $V(j)$ in the

observed data can fail to optimize outcome if applied to the corresponding stratum in an experiment where treatment was assigned differently.

The dynamic treatment regime estimated by HA-MSM depends on the observed treatment mechanism; thus, a treatment rule estimated from an observational cohort might not remain statically optimal if applied to an identical cohort with a different treatment mechanism. This is particularly troubling, in the sense that the rule itself is a treatment mechanism. Thus, if a HA-MSM-derived treatment rule were applied to an identical population beginning at time 0 (the start of follow-up), at later time points the rule might no longer continue to select the optimal treatment plan.

In the HIV analyses, HA-MSM were used to identify the best future treatment plan (switch immediately or wait to switch) among the subpopulation who had not yet switched therapy. Membership in the subpopulation of individuals who remained on their non-suppressive therapy changed over time, as a result of the process for deciding when to switch therapy (the treatment mechanism). For example, estimation of the treatment mechanism (discussed at greater length below) revealed that individuals were more likely to switch therapy if they had lower CD4+ T cell counts. As a result, the population that remained on non-suppressive therapy at a given time point, among whom the best future treatment plan was estimated, contained a disproportionate number of individuals who had maintained high CD4+ T cell counts up till that time point.

The subpopulation that remained on non-suppressive therapy over time would have differed if the decision process for switching treatment had differed. For example, if treatment had been assigned randomly, the subpopulation remaining on non-suppressive therapy at a given time point would have included more individuals with low prior CD4+ T cell counts than were present in this subpopulation in the observed data. To the extent that past CD4+ T cell count affects future CD4+ T cell count, the expected future CD4+ T cell count would differ between the two subpopulations, and thus the optimal treatment decision could differ.

In other words, since membership in a given stratum of interest can depend on the way that treatment was assigned, the effect of future treatment decisions and thus the optimal treatment plan for the stratum can depend on the observed treatment mechanism. Our goal, however, is to identify stratum-specific future treatment plans that are expected to optimize future outcome *regardless* of the way in which past treatment was assigned. The resulting statically optimal individualized treatment rules will then continue to identify the optimal future plan at each time point if applied to a comparable population beginning at any time point during follow-up. For example, a statically optimal rule for deciding when to switch therapy would choose the best treatment plan (switch or not) among people remaining on their non-suppressive regimen at a given time point, regardless of how the decision to switch was made up till that time point. Thus, a statically optimal rule would identify the optimal treatment plan at each time point if applied in the context of a clinical trial (where the rule of interest has been applied since time 0), or alternatively, if applied in the context of clinical practice (where some other decision process, possibly unknown, has been applied since time 0).

5. STATICALLY OPTIMAL TREATMENT RULES

HA-MSM identify statically optimal individualized treatment rules when the history-adjusted mean no longer depends on the observed treatment mechanism, or in other words, when the observed history-adjusted mean equals the counterfactual history-adjusted mean:

$$E(Y(j+m)_{\bar{A}(j-1)\underline{a}(j)} | \bar{A}(j-1) = \bar{a}(j-1), \bar{S}(j)) = E(Y(j+m)_{\bar{a}(j-1)\underline{a}(j)} | \bar{S}(j)_{\bar{a}(j-1)}) \quad (6)$$

When equality (6) holds for all j , then the optimal future treatment plan at each time point j estimated by HA-MSM will be the same as the optimal future treatment plan at each time point j under *any* fixed treatment history up till that time point:

$$\begin{aligned} \underline{a}^*(j|V(j)) &\equiv \arg \max_{\underline{a}(j)} E(Y(j+m)_{\bar{A}(j-1)\underline{a}(j)} | \bar{A}(j-1) = \bar{a}(j-1), \bar{S}(j)) \\ &= \arg \max_{\underline{a}(j)} E(Y(j+m)_{\bar{a}(j-1)\underline{a}(j)} | \bar{S}(j)_{\bar{a}(j-1)}) \end{aligned}$$

Note that, given the covariates on which the statically optimal rule is based ($\bar{S}(j)$), the treatment history that corresponds to following the statically optimal rule itself is simply one of these possible fixed treatment histories. Thus, when equality (6) holds, the optimal future treatment plan at a given time point as estimated by HA-MSM will identify the optimal future treatment plan if the study population had been following the statically optimal rule (or any other treatment mechanism) up till that time point.

The following theorem presents an equality that is sufficient for identity (6) to hold, and thus to ensure that the rules estimated by HA-MSM are statically optimal.

Theorem 1

If

$$\begin{aligned} P(\bar{A}(j-1) = \bar{a}(j-1) | \bar{Y}(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \\ = P(\bar{A}(j-1) = \bar{a}(j-1) | \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \end{aligned} \quad (7)$$

then $E(Y(j+m)_{\bar{A}(j-1)\underline{a}(j)} | \bar{A}(j-1) = \bar{a}(j-1), \bar{S}(j)) = E(Y(j+m)_{\bar{a}(j-1)\underline{a}(j)} | \bar{S}(j)_{\bar{a}(j-1)})$ and the HA-MSM-derived rule is statically optimal.

The proof of Theorem 1 is presented in Appendix A. Here, we present the intuition behind the theorem, which further provides insight into the conditions, discussed below, for the identity (7) to hold.

Non-identity between the observed history-adjusted mean and the counterfactual history-adjusted mean can be seen as a problem of confounding. Consider the case where the goal is to estimate a simple counterfactual mean under treatment history $\bar{a} : E(Y_{\bar{a}})$. Clearly, unless the entire study population, or a random sample, received treatment history \bar{a} , $E(Y_{\bar{a}})$ is not necessarily equal to the mean outcome among people who received treatment history \bar{a} in the observed data ($E(Y_{\bar{a}}) \neq E(Y_{\bar{A}} | \bar{A} = \bar{a})$). This is a classic example of confounding; the two parameters will differ to the extent there are covariates that affect both treatment assignment and outcome, making treatment assignment dependent on counterfactual outcome ($P(\bar{A} = \bar{a} | Y_{\bar{a}}) \neq P(\bar{A} = \bar{a})$). Next, consider the case where the goal is to estimate a counterfactual mean under treatment history \bar{a} , given baseline covariates of interest $S : E(Y_{\bar{a}} | S)$. We say that S is sufficient to control for confounding if, once we condition on S , treatment assignment no longer depends on counterfactual outcome (within strata of S , treatment is randomized): $P(\bar{A} = \bar{a} | S, Y_{\bar{a}}) = P(\bar{A} = \bar{a} | S)$. In this case, within strata of S , the mean outcome among people who received treatment history \bar{a} in the observed data is equivalent to the mean counterfactual outcome under treatment $\bar{a} : E(Y_{\bar{A}} | \bar{A} = \bar{a}, S) = E(Y_{\bar{a}} | S)$. This concept is the motivation for the use of stratification and multivariable regression for causal inference.

The same concept can be extended to the current situation, only now considering the equivalence of mean outcomes indexed by observed vs counterfactual treatment *through time* $j - 1$. In order for equality (6) to hold, the covariates $\bar{S}(j)$, on which the treatment rule is to be based, must be sufficient to control for confounding of treatment assignment through time $j - 1$ on counterfactual outcome $Y_{\bar{A}(j-1)\underline{a}(j)}$. In other words, if treatment assignment through time $j - 1$ is independent of counterfactual outcome, given covariates $\bar{S}(j)$ (equality (7)), then the counterfactual history-adjusted mean will equal the observed history-adjusted mean (equality (6)).

If equality (7) holds, then the HA-MSM parameter is no longer dependent on the treatment mechanism. In the following two sections, we discuss choices of $\bar{S}(j)$ sufficient for equality (7) to hold, and thus sufficient to ensure that the HA-MSM-derived treatment rule is statically optimal.

6. INCORPORATING COVARIATE HISTORY TO ENSURE STATIC OPTIMALITY

As we show in this section, inclusion in $\bar{S}(j)$ of either the entire covariate history up till time $(j - 1)$, or a particular summary of the covariates that affect treatment assignment up till time $(j - 1)$, is sufficient for equality (7) to hold. The intuitive motivation for this approach again relies on confounding. We know from Section 5 that if $\bar{S}(j)$ is sufficient to control for confounding of $\bar{A}(j - 1)$ on counterfactual outcome $Y_{\bar{A}(j-1)\underline{a}(j)}$, then equality (7) will hold. We further know that confounding arises as a result of covariates that affect both treatment assignment and outcome. Thus, by including in $\bar{S}(j)$ all covariates that affect treatment assignment, we ensure that the HA-MSM-derived treatment rules are statically optimal. We present this result as a lemma, below (the proof is provided in Appendix B).

Lemma 1

If $P(\bar{A}(j - 1) = \bar{a}(j - 1) | X^{\text{Full}} = x)$ is only a function of $\bar{S}(j - 1)_{\bar{a}} \subset \bar{S}(j)_{\bar{a}}$, then $P(\bar{A}(j - 1) = \bar{a}(j - 1) | Y(j + m)_{\bar{a}} = y(j + m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) = P(\bar{A}(j - 1) = \bar{a}(j - 1) | \bar{S}(j)_{\bar{a}} = \bar{s}(j))$ and (by Theorem 1) the HA-MSM-derived rule is statically optimal.

Several choices of $\bar{S}(j)$ are sufficient to ensure that $P(\bar{A}(j - 1) = \bar{a}(j - 1) | X^{\text{Full}} = x)$ is only a function of $\bar{S}(j - 1)_{\bar{a}} \subset \bar{S}(j)_{\bar{a}}$, and thus that the HA-MSM-derived individualized treatment rule is statically optimal. For example, this is true if the HA-MSM parameter conditions on the entire covariate history in addition to covariates on which the investigator wishes to base the treatment rule. Under the SRA (2), $V(j) = (\bar{S}(j), \bar{A}(j - 1))$ then includes all covariates which affect treatment assignment up till time j .

Sufficient condition 1: $\bar{S}(j) = (\bar{L}(j - 1), \bar{S}^*(j))$, where $\bar{S}^*(j)$ denotes the initial set of covariates on which the investigator wishes to base the treatment rule.

Including the entire covariate history in the HA-MSM model removes the dependency of the resulting parameter on the treatment mechanism. However, when several covariates are measured over multiple time points, the covariate history $\bar{L}(j)$ can become very high dimensional. Specifying a reasonable HA-MSM model for $E[Y(j + m)_{\bar{A}(j-1)\underline{a}(j)} | V(j)]$ can thus become challenging or unfeasible.

An alternative to conditioning on the entire covariate history is to condition only those covariates that affect treatment assignment up till time $j - 1$. The covariates affecting treatment assignment

can be summarized by including the treatment mechanism itself (through time $j - 1$) as a covariate in $\bar{S}(j)$.

Sufficient condition 2: $\bar{S}(j) = (g(\bar{A}(j - 1)|X^{\text{Full}}), \bar{S}^*(j))$, where $\bar{S}^*(j)$ denotes the initial set of covariates on which the investigator wishes to base the treatment rule.

Alternatively, the covariates affecting treatment assignment up till time $j - 1$ can be summarized using PSs. PSs [27, 28] summarize the way in which treatment was assigned at each time point during a study based on a subject's observed past until that time point. Specifically, the PS at time j is defined as follows: $\text{PS}(j) = P(A(j) = a(j)|\bar{A}(j - 1) = \bar{a}(j - 1), \bar{L}(j))$. Inclusion of the product of the j -specific PSs up till time $j - 1$ in $\bar{S}(j)$ is also sufficient under the SRA (2) to ensure that $P(\bar{A}(j - 1) = \bar{a}(j - 1)|X^{\text{Full}} = x)$ is only a function of $\bar{S}(j - 1)_{\bar{a}} \subset \bar{S}(j)_{\bar{a}}$.

Sufficient condition 3: $\bar{S}(j) = (\prod_{l=0}^{j-1} \text{PS}(l), \bar{S}^*(j))$, where $\bar{S}^*(j)$ denotes the initial set of covariates on which the investigator wishes to base the treatment rule.

When the treatment mechanism (or PS) interacts with the exposure of interest, the statically optimal treatment rule will incorporate the treatment mechanism or PS up till time j . In this setting, implementing the resulting rule in practice will require measuring not only the covariates on which the investigator wished to base the treatment rule ($\bar{S}^*(j)$), but also all other covariates that contribute to the treatment mechanism.

7. CAUSAL STRUCTURES SUFFICIENT TO ENSURE STATIC OPTIMALITY

The previous section showed how conditioning the HA-MSM parameter on *all* covariates that affect treatment assignment can remove dependency on the observed treatment mechanism and permit estimation of a statically optimal treatment rule. In many cases, however, a treatment rule based on all such covariates may be neither practical nor desirable. Pearl's causal graph theory [29] provides a tool for identifying a minimal set of covariates sufficient to ensure static optimality of the HA-MSM-derived rule. In this section, we apply the concept of *d-separation* from DAG methodology to introduce an alternative condition for $\bar{S}(j)$ sufficient to ensure static optimality. Specifically, we show that, under certain causal structures, $\bar{S}(j)$ need not include all covariates that affect treatment assignment in order to ensure the static optimality of the treatment rule estimated. These results introduce greater flexibility in the choice of sufficient $\bar{S}(j)$, and provide a graphical tool to identify sufficient alternatives.

Pearl defines the graphical criteria for *d-separation* as follows (Definition 1.2.3):

Definition of d-separation

'A path p is said to be *d-separated* (or blocked) by a set of nodes Z if and only if

1. p contains a chain $i \rightarrow m \rightarrow j$ or a fork $i \leftarrow m \rightarrow j$ such that the middle node m is in Z , or
2. p contains an inverted fork (or collider) $i \rightarrow m \leftarrow j$ such that the middle node m is not in Z and such that no descendent of m is in Z .

A set Z is said to *d-separated* X from Y if and only if Z blocks every path from a node in X to a node in Y .

Pearl shows (Theorem 1.2.4) that ‘If sets X and Y are d -separated by Z in a DAG G , then X is independent of Y conditional on Z in every distribution compatible with G .’ Thus, d -separation of X and Y by Z (written $(X \perp\!\!\!\perp Y|Z)_G$) implies that X is conditionally independent of Y given Z (written $(X \perp\!\!\!\perp Y|Z)_P$), and thus that $P(X = x|Y = y, Z = z) = P(X = x|Z = z)$. This theorem provides us with a graphical criterion (presented as a Lemma) for evaluating the sufficiency of $\bar{S}(j)$ for equality (7) to hold.

Lemma 2

If $\bar{S}_a(j)$ d -separates $\bar{A}(j - 1)$ from $Y(j + m)_a$, then $\bar{S}(j)$ is sufficient to ensure that $P(\bar{A}(j - 1) = \bar{a}(j - 1)|Y(j + m)_a = y(j + m), \bar{S}(j)_a = \bar{s}(j)) = P(\bar{A}(j - 1) = \bar{a}(j - 1)|\bar{S}(j)_a = \bar{s}(j))$ and thus (by Theorem 1) that the HA-MSM-derived rule is statically optimal.

In applying the graphical criterion of d -separation, a DAG must first be converted from a graph showing causal relationships in the observed data to a graph showing causal relationships between the observed treatment and the counterfactual covariate processes. This process involves two steps (illustrated in Figure 1). First, replace the observed covariates $\bar{L}(K + 1)$ by their counterfactual counterparts $\bar{L}(K + 1)_a$. Second, erase all arrows from $\bar{A}(K)$ to $\bar{L}(K + 1)_a$ (the observed treatment does not affect the counterfactual values of covariates under a specified treatment). The resulting causal graph (Figure 1(B)) now shows the causal relations between the observed treatment history and the counterfactual values of covariates if treatment history had been set at \bar{a} .

The d -separation criterion of Lemma 2 suggests an alternative graph-based proof to Lemma 1. In the causal graph corresponding to the observed treatment history and counterfactual covariate

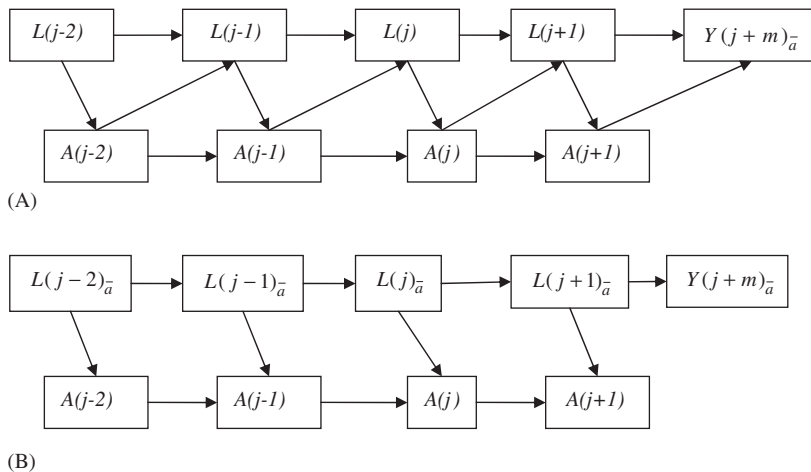


Figure 1. Illustration of DAG manipulation required prior to evaluation of d -separation in order to test whether a given $\bar{S}(j)$ is sufficient to ensure static optimality: (A) causal relationships in the observed data and (B) causal relationships between observed treatment and counterfactual covariates. The figure presents one possible basic causal structure for longitudinal data. For readability, we present a situation where $j = 2$, $K = 3$, and $Y(j + m) = Y(j + 2)$. Similar reasoning can be used for larger j , K , and m .

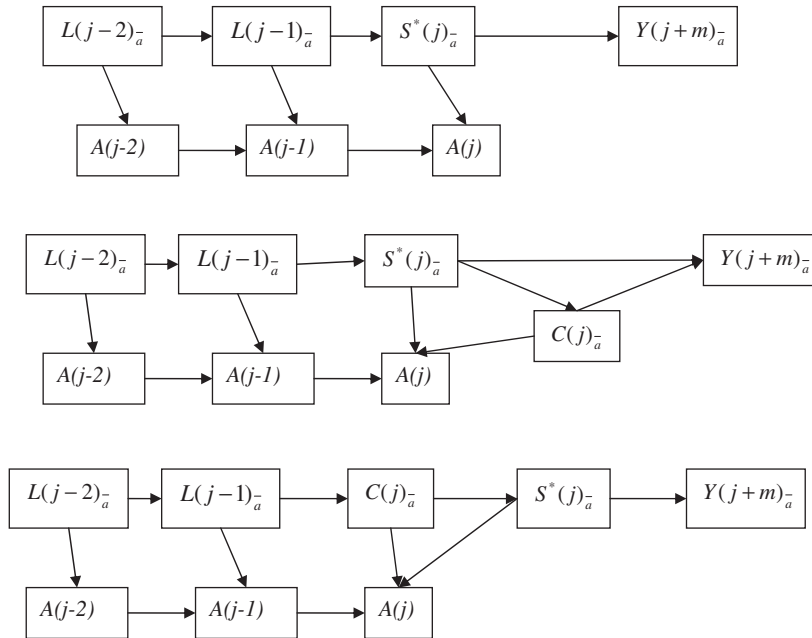


Figure 2. DAG-based examples of specific causal settings where $\overline{S}(j)_{\bar{a}} = S^*(j)_{\bar{a}}$ is sufficient to d -separate $\overline{A}(j-1)$ from $Y(j+m)_{\bar{a}}$. For readability, we use $j=2$, $K=3$, and $Y(j+m) = Y(j+2)$, and covariates and treatment occurring after time j are not shown.

values (Figure 1(B)), all paths from treatment $\overline{A}(K)$ to counterfactual covariates $\overline{L}(K+1)_{\bar{a}}$ are deleted. Thus, the only possible paths connecting $\overline{A}(j-1)$ to $Y(j+m)_{\bar{a}}$ are ‘backdoor paths’ (i.e. paths from $\overline{A}(j-1)$ to $Y(j+m)_{\bar{a}}$ via arrows into $\overline{A}(j-1)$). Graphically, Lemma 1 states that $\overline{S}(j)$ is sufficient for equality (7) and hence static optimality to hold if $\overline{S}(j-1)_{\bar{a}} \subset \overline{S}(j)_{\bar{a}}$ includes all covariates with causal arrows into $\overline{A}(j-1)$. But if $\overline{S}_{\bar{a}}(j)$ includes all covariates with arrows into $\overline{A}(j-1)$, then $\overline{S}_{\bar{a}}(j)$ must block all backdoor paths, and thus all paths, from $\overline{A}(j-1)$ to $Y(j+m)_{\bar{a}}$, and thus ensure their d -separation. As result, by Lemma 2, equation (7) must hold and $\overline{S}(j)$ is sufficient to ensure static optimality.

The graphical criterion of d -separation provides a minimal condition for $\overline{S}(j)$ to be sufficient. As shown, if $\overline{S}(j)_{\bar{a}}$ includes all covariates with causal arrows into $\overline{A}(j-1)$ (as required by Lemma 1), then d -separation holds. In addition, d -separation holds under many causal structures where $\overline{S}(j)_{\bar{a}}$ does not include all covariates with causal arrows into $\overline{A}(j-1)$, and thus where neither Sufficient Conditions 1 nor 2 are met (Figure 2).

Given a DAG, Lemma 2 provides a graphical tool for suggesting alternative choices of $\overline{S}(j)$, and for evaluating their sufficiency. Figures 2 and 3 present several sample causal graphs, illustrating examples of $\overline{S}(j)$ sufficient and insufficient to ensure static optimality. Note, however, that the sufficiency of a particular choice of $\overline{S}(j)$, other than a choice fulfilling Lemma 1, will depend on the specific causal structure of the data. Specifying this causal structure becomes more challenging as the number of covariates and time points increases.

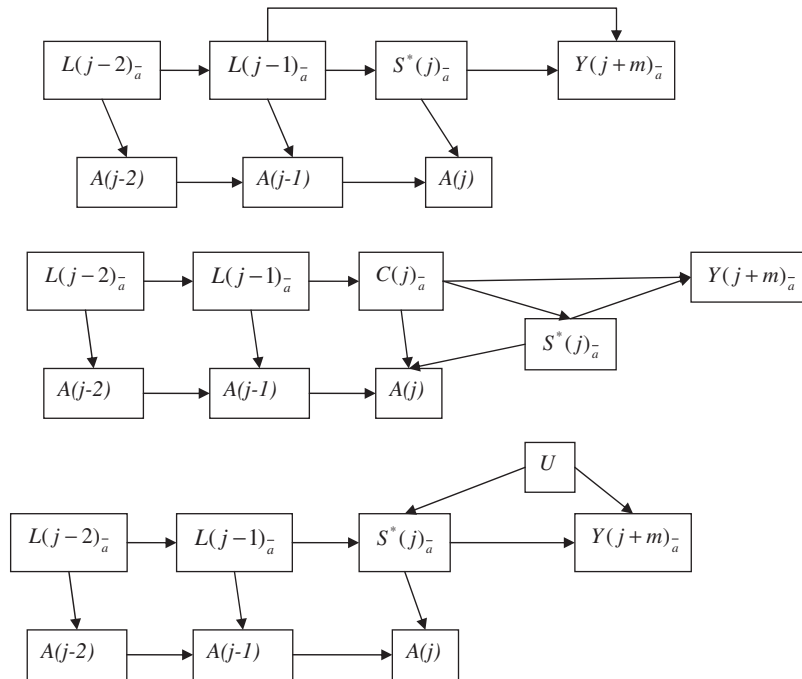


Figure 3. DAG-based examples of specific causal settings where $\bar{S}(j)_a = S^*(j)_a$ not sufficient to *d-separate* $\bar{A}(j-1)$ from $Y(j+m)_a$. For readability, we use $j=2$, $K=3$, and $Y(j+m) = Y(j+2)$, and covariates and treatment occurring after time j are not shown.

8. RESULTS: STATICALLY OPTIMAL TREATMENT RULES FOR DECIDING WHEN TO SWITCH THERAPY

Two sets of analyses were performed, aimed at estimating switching rules (among individuals who remained on their original therapy and had not re-suppressed the virus) based, respectively, on two covariates of interest: (1) CD4+ T cell count at time j ($\bar{S}^*(j) = (\text{Sup}(j) = 0, \text{CD4}(j))$); and (2) diagnosis with an opportunistic disease at time j ($\bar{S}^*(j) = (\text{Sup}(j) = 0, \text{OD}(j))$). All HA-MSM models were fit using the inverse probability of treatment weighted (IPTW) estimator [15, 18]. The resulting estimates of statically optimal rules thus rely on the following assumptions needed for the consistency of the IPTW estimator: (1) the measured covariates are sufficient to control for confounding of the effect of switching therapy on future CD4+ T cell count (SRA, assumption (2)); (2) the treatment mechanism (probability of switching given the past) was estimated consistently; and (3) the decision to switch was not made deterministically based on a subject's observed past; or in other words, sufficient experimentation in switching existed in the data for the parameter to be identifiable.

The treatment mechanism was fit data adaptively using the deletion/substitution/addition algorithm and 5-fold cross validation [30]. Specifically, the algorithm was used to search among linear combinations of polynomial powers of 40 candidate covariates, with cross-validation used to select

the number of terms and degree of interactions providing the optimal bias-variance tradeoff on independent data. The following covariates were considered by the algorithm: most recent laboratory values (CD4+ T cell count, CD8+ T cell count, and plasma HIV RNA level); self-reported adherence to antiretroviral drugs; year of HIV diagnosis and year of first antiretroviral treatment; peak HIV RNA level and nadir CD4+ T cell count; drug and class-specific measures of past treatment history and current regimen; HIV risk group; recreational drug use; diagnosis with an opportunistic disease; and demographic data including age, sex, race, income, and education. The final model selected contained eight main terms, and included the following covariates: current diagnosis with an opportunistic disease, most recent CD4+ T cell count and HIV RNA level, number of protease inhibitor drugs experienced, antiretroviral adherence, nadir CD4+ T cell count, age, and elapsed time since most recent HIV RNA level measurement. A full description of the candidate covariates and the estimated mechanism is provided in [18].

Confidence intervals for model coefficients were based on 100 non-parametric bootstrap samples, respecting the subject rather than the episode of failure as the experimental unit. Potentially informative censoring was addressed by inverse probability of censoring weighting [19, 31]. Details on the application of this approach to the current data example are available in [26].

8.1. Analysis 1: treatment rules based on opportunistic disease

In the first set of analyses, we first estimated an individualized treatment rule based on the following model (Model 1) of the effect of additional time until switching therapy $c(j)$ on future CD4+ T cell count (at $m = 8$ months in the future) among individuals who had not yet switched therapy ($\bar{A}(j - 1) = 1$) or been re-suppressed ($\text{Sup}(j) = 0$), given elapsed time since virologic failure occurred (j) and current diagnosis with an AIDS-defining opportunistic disease ($\text{OD}(j)$):

$$\begin{aligned} E(Y(j + m)_{\bar{A}(j-1)c(j)} | \bar{A}(j - 1) = 1, \text{Sup}(j) = 0, \text{OD}(j)) \\ = \beta_0 + \beta_1 c(j) + \beta_2 j + \beta_3 j \times c(j) + \beta_4 \text{OD}(j) + \beta_5 \text{OD}(j) \times c(j) \end{aligned}$$

The corresponding estimate of the effect of waiting to switch (Table I) yielded the following treatment rule: in individuals with a current diagnosis of an opportunistic disease, stay on the same therapy and re-evaluate the following month. In individuals without such a diagnosis, switch therapy immediately if less than 8 months have elapsed since loss of suppression occurred, otherwise wait to switch.

In the absence of an explicit causal structure, there is no guarantee that this treatment rule would continue to optimize outcome if it were applied to an identical population, beginning when loss of suppression occurred. In order to estimate a statically optimal treatment rule, the treatment mechanism through time $j - 1$ was incorporated into the HA-MSM model (Model 2):

$$\begin{aligned} E(Y(j + m)_{\bar{A}(j-1)c(j)} | \bar{A}(j - 1) = 1, \text{Sup}(j) = 0, \text{OD}(j)) \\ = \beta_0 + \beta_1 c(j) + \beta_2 j + \beta_3 j \times c(j) + \beta_4 \text{OD}(j) + \beta_5 \text{OD}(j) \times c(j) \\ + \beta_6 \prod_{l=0}^{j-1} g(A(l) | \bar{A}(l - 1), \bar{L}(l)) \end{aligned}$$

Table I. Individualized treatment rule for Analysis 1, based on Model 1 (without treatment mechanism as covariate).

Coefficient	95% CI ^{*,†}
$\beta_1 = -4.0$	-15.1, 7.1
$\beta_3 = 0.56 \times j$	-1.9, 3.1
$\beta_5 = 6.4 \times \text{OD}(j)$	-12.4, 25.2

$$d_j = I[(\beta_1 + \beta_3 \times j + \beta_5 \times \text{OD}(j)) < 0]$$

Treatment rule: $d_j = 1$: Switch at time j
 $d_j = 0$: Wait at time j

*Based on 100 bootstrap samples.

†CI = confidence interval.

Table II. Individualized treatment rule for Analysis 1, based on Model 2 (incorporating treatment mechanism as covariate).

Coefficient	95% CI ^{*,†}
$\beta_1 = -2.6$	-13.1, 7.9
$\beta_3 = -0.28 \times j$	-2.3, 1.8
$\beta_5 = 0.83 \times \text{OD}(j)$	-15.7, 17.2

$$d_j = I[(\beta_1 + \beta_3 \times j + \beta_5 \times \text{OD}(j)) < 0]$$

Treatment rule: $d_j = 1$: Switch at time j
 $d_j = 0$: Wait at time j

*Based on 100 bootstrap samples.

†CI = confidence interval.

Alternatively, the treatment mechanism could have been incorporated using an interaction term with the exposure of interest $c(j)$ and/or the other covariates. However, we found no evidence of interactions between the treatment mechanism and time until switching therapy.

The estimated statically optimal rule for deciding when to switch given current opportunistic disease and elapsed time (Table II) states that, regardless of diagnosis with an opportunistic disease and time elapsed since loss of suppression occurred, treatment should be switched immediately. The latter rule, rather than the former, would be expected to optimize patient outcome if applied to a comparable population in a clinical trial. In fact, such a rule makes more clinical sense than the former, non-statically optimal, rule in that waiting to switch therapy is unlikely to be more beneficial among those who have a current opportunistic disease.

8.2. Analysis 2: treatment rules based on CD4+ T cell count

In the second set of analyses, we estimated an individualized treatment rule based on the following model (Model 3) of the effect of future time until switching ($c(j)$) on future CD4+ T cell count (at $m = 8$ months in the future) among individuals who had not yet switched therapy or been re-suppressed, given current CD4+ T cell count ($\text{CD4}(j)$) and elapsed

Table III. Individualized treatment rule for Analysis 2, based on Model 3 (without treatment mechanism as covariate).

Coefficient	95% CI ^{*,†}
$\beta_1 = -9.2$	-17.6, -7.6
$\beta_4 = 0.05 \times \text{CD4}(j)$	0.02, 0.08
$\beta_5 = 1.5 \times j$	-0.4, 3.4
$\beta_7 = -0.009 \times \text{CD4}(j) \times j$	-0.02, -0.004

$d_j = I[(\beta_1 + \beta_4 \times \text{CD4}(j) + \beta_5 \times j + \beta_7 \times \text{CD4}(j) \times j) < 0]$

Treatment rule: $d_j = 1$: Switch at time j
 $d_j = 0$: Wait at time j

*Based on 100 bootstrap samples.

†CI = confidence interval.

time (j):

$$\begin{aligned}
 E(Y(j+m)_{\bar{A}(j-1)c(j)} | \bar{A}(j-1) = 1, \text{Sup}(j) = 0, \text{CD4}(j)) \\
 = \beta_0 + \beta_1 c(j) + \beta_2 \text{CD4}(j) + \beta_3 j + \beta_4 c(j) \times \text{CD4}(j) + \beta_5 c(j) \times j \\
 + \beta_6 \text{CD4}(j) \times j + \beta_7 c(j) \times \text{CD4}(j) \times j
 \end{aligned}$$

The resulting rule is reported in Table III.

In order to estimate a statically optimal individualized treatment rule, we then fit an additional HA-MSM, now including the treatment mechanism as a covariate. After considering potential multi-way interactions, our final HA-MSM model included the treatment mechanism as a main term only (Model 4):

$$\begin{aligned}
 E(Y(j+m)_{\bar{A}(j-1)c(j)} | \bar{A}(j-1) = 1, \text{Sup}(j) = 0, \text{CD4}(j)) \\
 = \beta_0 + \beta_1 c(j) + \beta_2 \text{CD4}(j) + \beta_3 j + \beta_4 c(j) \times \text{CD4}(j) + \beta_5 c(j) \times j \\
 + \beta_6 \text{CD4}(j) \times j + \beta_7 c(j) \times \text{CD4}(j) \times j + \beta_8 \prod_{l=0}^{j-1} g(A(l) | \bar{A}(l-1), \bar{L}(l))
 \end{aligned}$$

The resulting effect estimates yielded the following statically optimal treatment rule (Table IV):

$$\begin{aligned}
 d_j &= I[(-9.0 + 0.05 \times \text{CD4}(j) + 1.2 \times j - 0.009 \times \text{CD4}(j) \times j) < 0] \\
 d_j &= 1: \text{ Switch at time } j \\
 d_j &= 0: \text{ Wait at time } j
 \end{aligned}$$

In other words, when the expected effect of waiting to switch is negative, switch the patient immediately; when the expected effect is positive, wait to switch and re-evaluate at the subsequent visit.

Ninety-five per cent confidence intervals for each of the coefficients in this rule, based on 100 non-parametric bootstrap samples, are presented in Table IV. Alternatively, bootstrap re-sampling can be used to estimate variability in the treatment decision itself by plotting the proportion of bootstrap samples in which the statically optimal treatment rule indicates a switch for each of a range of CD4+ T cell counts and elapsed times since loss of suppression. Such an analysis

Table IV. Individualized treatment rule for Analysis 2, based on Model 4 (incorporating treatment mechanism as covariate).

Coefficient	95% CI ^{*,†}
$\beta_1 = -9.0$	-17.5, -0.5
$\beta_4 = 0.05 \times \text{CD4}(j)$	0.02, 0.08
$\beta_5 = 1.2 \times j$	-0.7, 3.1
$\beta_7 = -0.009 \times \text{CD4}(j) \times j$	-0.02, -0.003

$$d_j = I[(\beta_1 + \beta_4 \times \text{CD4}(j) + \beta_5 \times j + \beta_7 \times \text{CD4}(j) \times j) < 0]$$

Treatment rule: $d_j = 1$: Switch at time j
 $d_j = 0$: Wait at time j

*Based on 100 bootstrap samples.

†CI = confidence interval.

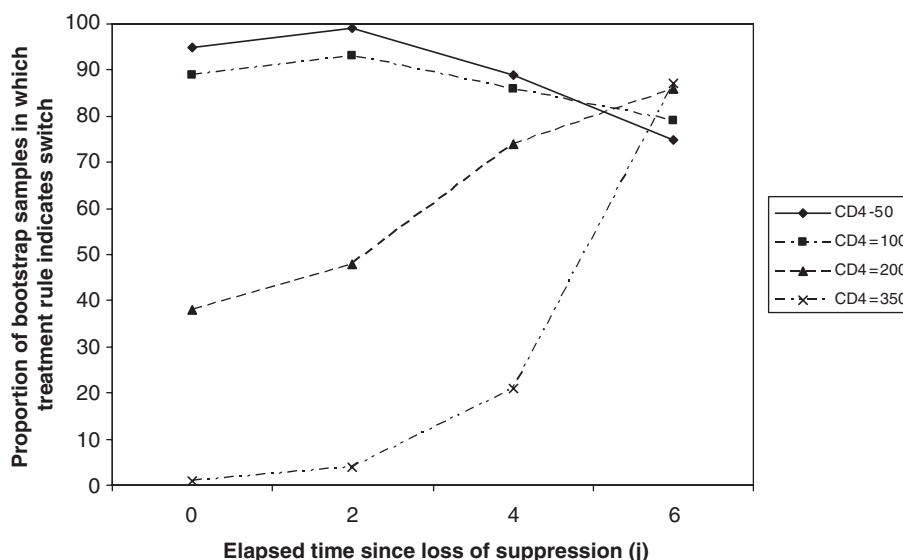


Figure 4. Data example: variability in treatment decision indicated by statically optimal treatment rule, according to CD4⁺ T cell count and elapsed time since loss of suppression occurred.

(Figure 4) suggests that, early after loss of suppression occurs, there is relatively strong evidence that patients with low CD4⁺ T cell count should be switched to a new regimen, while patients with high CD4⁺ T-cell counts can afford to wait. In contrast, among patients who have already spent 5 months on non-suppressive therapy, variability in the decision to switch depends less on current CD4⁺ T cell count, suggesting that the decision to switch for these patients should perhaps be based on other factors.

Interestingly, the initial HA-MSM (Model 3), which included only current CD4⁺ T cell count and elapsed time, and the HA-MSM that also adjusted for the treatment mechanism (Model 4) provided very similar estimates of the effect of future time until switching and the modification of this effect by current CD4⁺ T cell count and elapsed time (Table III vs Table IV, respectively). As a

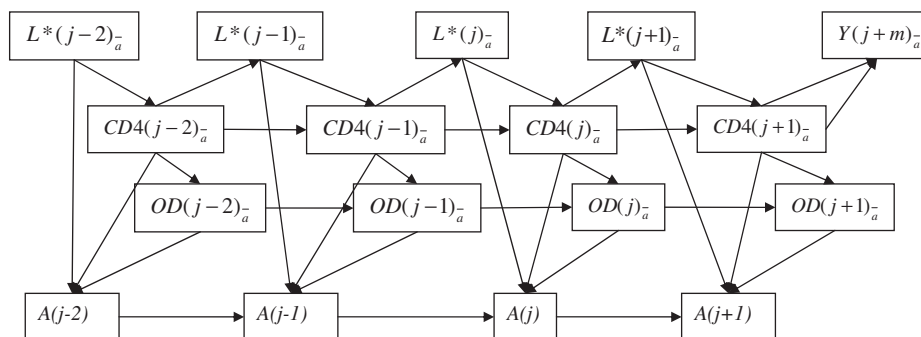


Figure 5. Possible DAG for HIV data example. $\bar{S}(j) = CD4(j)$, but not $\bar{S}(j) = OD(j)$, sufficient for static optimality. To simplify presentation, we use $j=2$, $K=3$, $Y(j+m) = Y(j+2)$. $L^*(j)_{\bar{a}}$ = additional components of the treatment mechanism, other than opportunistic disease and CD4+ T cell count (e.g. adherence).

result, the two approaches yielded very similar individualized treatment rules. The small change in coefficients in the CD4+ T cell-based treatment rule after adjusting for the treatment mechanism could be explained by the causal structure of the data (such as the postulated causal structure presented in Figure 5). The DAG shown in Figure 5 would also explain why the opportunistic disease-based treatment rule was altered by incorporation of the treatment mechanism. In this DAG, CD4+ T cell count at time j , but not opportunistic disease diagnosis at time j , is sufficient to d -separate treatment history prior to time j from CD4+ T cell count m months in the future.

Several limitations to these results should be acknowledged, due in large part to decisions to simplify the analyses in order to accommodate the small sample size and to provide a clear pedagogical example. First, treatment modification was defined broadly as any change to a subject's failing antiretroviral regimen. Thus, modification in this analysis included both substitution of a single drug and treatment interruption. A more clinically relevant analysis would define modification as initiation of a new regimen containing at least two new drugs and aimed at viral re-suppression; implementing such an analysis is significantly more complex, however, as it requires the use of multiple treatment mechanisms to address treatment interruption and partial modification. Second, the use of a linear model of the dependence of the counterfactual outcome on switching time may have failed to capture important time-dependent dynamics. Third, as we discuss further below, the relatively short-term immunologic outcome used may have limitations as a surrogate for outcomes of greater clinical relevance such as long-term mortality. As a result, the current data analysis should be interpreted primarily as an illustration of the estimation of a statically optimal rule, rather than as a guide to clinical practice. Analyses aimed at providing a more clinically relevant answer to a similar research question using data from several larger cohorts are currently underway.

9. DISCUSSION

In summary, HA-MSM estimate modification of causal effects by time-varying variables, and thus can be used to identify individualized treatment rules for modifying treatment in response to a patient's changing covariates. However, the dependence of the HA-MSM parameter on the observed treatment mechanism, or the way in which the assignment of treatment at each time

point depended on a subject's past, means that such rules would not necessarily remain statically optimal if applied in a clinical trial. As we have illustrated, treatment rules which are statically optimal, or in other words, which no longer depend on the treatment mechanism, can be estimated using HA-MSM given that the covariates on which the rule depends are sufficient to control for confounding of the effect of past treatment on outcome. As a result, by selecting the correct covariates, HA-MSM can be applied to observational data to identify individualized treatment rules appropriate for evaluation in a clinical trial, or for use in clinical practice.

Causal graphs can be used to identify whether a candidate set of covariates is sufficient to control confounding and thus ensure static optimality, as well as to suggest alternative sets of sufficient covariates. This approach does not rely on consistent estimation of the treatment mechanism, thus the double robust HA-MSM estimator [15] will remain consistent if either the treatment mechanism or data-generating distribution are correctly estimated. This approach does, however, rely on use of a DAG that accurately represents the causal relations in the data, and thus relies heavily on the background knowledge of the researcher. As Figure 4 illustrates, the causal relationships in longitudinal data are often complex, and their correct specification may be unpractical.

Inclusion of the entire covariate history, or alternatively, of the treatment mechanism or PS, in the HA-MSM model also ensures static optimality, regardless of the specific causal context. Under this approach, the static optimality of the dynamic treatment rule depends on consistent estimation of the treatment mechanism. As a result, the double robust HA-MSM estimator [15] will not protect against misspecification of the treatment mechanism when deriving candidate treatment rules, although it may provide gains in efficiency. The treatment mechanism- (or PS-) based approach has the advantage of generally requiring a much lower dimensional HA-MSM model than the approach which adjusts for the entire covariate history. The reliance of the former approach on consistent estimation of the treatment mechanism also implies that in settings where the treatment mechanism is known (such as in the context of sequentially randomized trials) HA-MSM can estimate statically optimal treatment rules without any assumptions beyond the HA-MSM model itself.

Expert knowledge has a central role to play in defining the HA-MSM parameter of interest, and thus in determining the estimated statically optimal treatment rule. The rules identified will clearly depend on the covariates on which treatment decisions are to be based; subject matter knowledge is needed to determine which covariates are appropriate for consideration in a given application. Subject matter knowledge is further needed to define appropriate outcomes to be optimized. Available data are often not sufficient to estimate true long-term outcomes of interest (such, as for example, survival time for chronic diseases), and short-term outcomes based on biomarkers often must be used instead. For example, the use of CD4+ T cell count 8 months in the future, as used in the HIV data example, may not reflect the true long-term cost (in terms of additional resistance mutations) or benefit (in terms of new drug availability) of waiting to switch regimens. Rules derived to optimize long-term survival may indeed differ from those which aim to optimize 8 month CD4+ count; however, sufficient data to estimate the former outcome were not available. Definition of surrogate outcomes which remain clinically relevant is an important practical issue in data analyses aimed at deriving statically optimal treatment rules, as well as in many analyses based on clinical cohorts.

Notably, treatment rules require a definition of possible times at which treatment can be changed. As noted explicitly by Murphy, use of a discrete time scale assumes that treatment decisions are essentially made on every subject in every interval [1]. Thus, choice of a time scale must depend on knowledge about treatment decisions in the underlying cohort.

The statically optimal rules presented in this paper are generally expected to be superior to static treatments that cannot change in response to the evolution of the patient and disease process. As mentioned in the Introduction, however, we do not suggest that the statically optimal rules discussed here will be superior to truly optimal dynamic regimes; rather, they represent a less ambitious alternative parameter that may prove more feasible to estimate. Further, the idea of history-adjusted parameters is itself quite general, and could be applied to optimal dynamic regimes such as those estimated by Murphy and Robins [1, 12]. For example, multiple optimal dynamic regimes could be estimated, in which successive time points are each in turn treated as the baseline; to the extent that time elapsed since baseline is not itself meaningful and pooling across time points is possible, this history-adjusted approach should make possible improved precision in the estimation of optimal dynamic regimes.

APPENDIX A

Proof of Theorem 1: An equality sufficient to ensure that the HA-MSM-derived rule is statically optimal.

Theorem 1

If

$$\begin{aligned} P(\bar{A}(j-1) = \bar{a}(j-1) | \bar{Y}(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \\ = P(\bar{A}(j-1) = \bar{a}(j-1) | \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \end{aligned} \quad (\text{A1})$$

then $E(Y(j+m)_{\bar{A}(j-1)\underline{a}(j)} | \bar{A}(j-1) = \bar{a}(j-1), \bar{S}(j)) = E(Y(j+m)_{\bar{a}(j-1)\underline{a}(j)} | \bar{S}(j)_{\bar{a}(j-1)})$.

Proof

Note that

$$\begin{aligned} E(Y(j+m)_{\bar{A}(j-1)\underline{a}(j)} | \bar{A}(j-1) = \bar{a}(j-1), \bar{S}(j) = \bar{s}(j)) \\ = E(Y(j+m)_{\bar{a}} | \bar{A}(j-1) = \bar{a}(j-1), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \\ = \sum_y y(j+m) P(Y(j+m)_{\bar{a}} = y(j+m) | \bar{A}(j-1) = \bar{a}(j-1), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \end{aligned}$$

and

$$\begin{aligned} P(Y(j+m)_{\bar{a}} = y(j+m) | \bar{A}(j-1) = \bar{a}(j-1), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \\ = \frac{P(Y(j+m)_{\bar{a}} = y(j+m), \bar{A}(j-1) = \bar{a}(j-1), \bar{S}(j)_{\bar{a}} = \bar{s}(j))}{P(\bar{A}(j-1) = \bar{a}(j-1), \bar{S}(j)_{\bar{a}} = \bar{s}(j))} \\ = \frac{P(\bar{A}(j-1) = \bar{a}(j-1) | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) P(Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j))}{P(\bar{A}(j-1) = \bar{a}(j-1) | \bar{S}(j)_{\bar{a}} = \bar{s}(j)) P(\bar{S}(j)_{\bar{a}} = \bar{s}(j))} \end{aligned}$$

Now note that

$$\frac{P(Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j))}{P(\bar{S}(j)_{\bar{a}} = \bar{s}(j))}$$

is only an F_X parameter (i.e. a parameter of the full data), so it remains to show that the ratio

$$\frac{P(\bar{A}(j-1) = \bar{a}(j-1) | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j))}{P(\bar{A}(j-1) = \bar{a}(j-1) | \bar{S}(j)_{\bar{a}} = \bar{s}(j))}$$

does not depend on g . Specifically, if this ratio = 1, or $P(\bar{A}(j-1) = \bar{a}(j-1) | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) = P(\bar{A}(j-1) = \bar{a}(j-1) | \bar{S}(j)_{\bar{a}} = \bar{s}(j))$ then this is true. \square

APPENDIX B

Proof of Lemma 1: A sufficient condition for equality (7) to hold, and thus for the HA-MSM-derived rule to be statically optimal.

Lemma 1

If $P(\bar{A}(j-1) = \bar{a}(j-1) | X^{\text{Full}} = x)$ is only a function of $\bar{S}(j-1)_{\bar{a}} \subset \bar{S}(j)_{\bar{a}}$, then

$$\begin{aligned} P(\bar{A}(j-1) = \bar{a}(j-1) | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \\ = P(\bar{A}(j-1) = \bar{a}(j-1) | \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \end{aligned}$$

and (by Theorem 1) the HA-MSM parameter is statically optimal.

Proof

Note that $P(\cdot | Y, S) = E(P(\cdot | X, Y, S) | Y, S)$, so

$$\begin{aligned} P(\bar{A}(j-1) = \bar{a}(j-1) | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \\ = E(P(\bar{A}(j-1) = \bar{a}(j-1) | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j), \\ X^{\text{Full}} = x) | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \end{aligned}$$

Since $Y(j+m)_{\bar{a}}$ and $\bar{S}(j)_{\bar{a}}$ are included in X^{Full} ,

$$\begin{aligned} P(\bar{A}(j-1) = \bar{a}(j-1) | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}, X^{\text{Full}} = x) \\ = P(\bar{A}(j-1) = \bar{a}(j-1) | X^{\text{Full}} = x) \end{aligned}$$

which is the treatment mechanism up till time $(j-1)$.

So,

$$\begin{aligned} P(\bar{A}(j-1) = \bar{a}(j-1) | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \\ = E(P(\bar{A}(j-1) = \bar{a}(j-1) | X^{\text{Full}} = x) | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \\ = \sum_x P(\bar{A}(j-1) = \bar{a}(j-1) | X^{\text{Full}} = x) P(X^{\text{Full}} = x | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \end{aligned}$$

If now $\bar{S}(j)_{\bar{a}}$ is such that the treatment probability $P(\bar{A}(j-1) = \bar{a}(j-1) | X^{\text{Full}} = x)$ is only a function of $\bar{S}(j-1)_{\bar{a}} \subset \bar{S}(j)_{\bar{a}}$ then it follows that, given $Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)$,

$P(\bar{A}(j-1) = \bar{a}(j-1) | X^{\text{Full}} = x)$ is a constant, and thus

$$\begin{aligned} & \sum_x P(\bar{A}(j-1) = \bar{a}(j-1) | X^{\text{Full}} = x) P(X^{\text{Full}} = x | Y(j+m)_{\bar{a}} = y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) \\ &= P(\bar{A}(j-1) = \bar{a}(j-1) | X^{\text{Full}} = x) \sum_x P(X^{\text{Full}} = x | Y(j+m)_{\bar{a}} \\ &= y(j+m), \bar{S}(j)_{\bar{a}} = \bar{s}(j)) = P(\bar{A}(j-1) = \bar{a}(j-1) | X^{\text{Full}} = x) \end{aligned}$$

The same approach to the right-hand side shows the two are equal and completes the proof. \square

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