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History-Adjusted Marginal Structural Models to Estimate Time-Varying Effect Modification

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Abstract

Much of epidemiology and clinical medicine is focused on the estimation of treatments or interventions administered over time. In such settings of longitudinal treatment, time-dependent confounding is often an important source of bias. Marginal structural models are a powerful tool for estimating the causal effect of a treatment using observational data, particularly when time-dependent confounding is present. Recent statistical work presented a generalization of marginal structural models, called history-adjusted marginal structural models. Unlike standard marginal structural models, history-adjusted marginal structural models can be used to estimate modification of treatment effects by time-varying covariates. Estimation of time-dependent causal effect modification is frequently of great practical relevance. For example, clinical researchers are often interested in how the prognostic significance of a biomarker for treatment response can change over time. This article provides a practical introduction to the implementation and interpretation of history-adjusted marginal structural models. The method is illustrated using a clinical question drawn from the treatment of HIV infection. Observational cohort data from San Francisco, California, collected between 2000 and 2004, are used to estimate the effect of time until switching antiretroviral therapy regimen among patients receiving a non-suppressive regimen, and how this effect differs depending on CD4 T cell count.

INTRODUCTION

Dynamic treatment regimens are decision rules for altering treatment in response to changes in patient or pathogen characteristics. Such dynamic decision-making is central to the practice of medicine; clinicians select a future treatment plan that is expected to optimize a patient's long-term outcome, then modify this treatment plan over time in response to changes in disease progression. For example, patient risk factors and sequential measurements of blood pressure inform when antihypertensive medication is initiated. Similarly, the dose of antidepressant medication is often modified in response to changes in patient symptoms and side effects. And, as will be described here, the decision to switch antiretroviral therapy regimen for an Human Immunodeficiency Virus (HIV)-infected patient is based on the virologic and immunologic response to treatment, as well as side effects and other factors.

Despite the crucial and ubiquitous role of dynamic decision making in medicine, rigorous identification of candidate dynamic treatment regimens and evaluation of their effectiveness remains relatively rare. Randomized controlled trials can be used to compare candidate dynamic treatment regimens; however these trials do not themselves identify the decision rules to be compared. We suggest that observational data provide a rich source for identifying dynamic treatment regimens expected to optimize patient outcome. We introduce a new methodology, history-adjusted marginal structural models (HA-MSM) (1), which directly identifies a specific type of optimal dynamic treatment regimen using observational data.

HA-MSM generalize marginal structural models (MSM), introduced by Robins, (2-4). MSM are a powerful statistical tool for causal inference. Epidemiological and clinical research often relies on longitudinal treatment status and covariate data. When treatment status changes over time, conventional analytic approaches (such as standard multivariable regression methods) often fail to provide valid causal inference about the effect of treatment. Marginal structural models address this well-recognized problem of time-dependent confounding.

While MSM address confounding by time-dependent covariates, to date they have been restricted to the estimation of effect modification by baseline covariates only. Thus it has been possible to use this methodology to address questions such as "What is the

effect of a treatment and how does it differ between study members with different covariate values at entry to the study?", but not "How does the effect of a treatment differ as a result of changing values of a covariate over the course of the study?". As a result, MSM have not been applied to identify optimal dynamic treatment regimens.

As will be outlined here, HA-MSM use the identical causal framework as standard MSM, but unlike MSM, can be used to identify a rule for making treatment decisions over time, based on time-varying covariates, that represents a specific type of optimal dynamic treatment regimen. This dynamic treatment regimen corresponds closely to the needs of clinical practitioners, in that it allows a practitioner to use a patient's most recent measured covariates to update, at each patient visit, the future treatment plan that will maximize the patient's expected long-term outcome.

This paper provides a practical introduction to HA-MSM; the formal statistical theory and assumptions are presented in (1). We illustrate our methodology with an example drawn from the treatment of HIV using antiretroviral therapy (ART).

ANTIRETOVIRAL THERAPY FOR THE TREQTMENT OF HIV INFECTION: WHEN TO SWITCH?

HIV evolves rapidly in the presence of a selective pressure. This leads to the accumulation of mutations that confer "resistance" to antiretroviral drugs. The optimal manner to avoid the rapid emergence of resistance-associated mutations is therefore to completely suppress viral replication. This can be achieved in many patients with standard three-drug combination regimens (5). However, a substantial proportion of treated patients fail to achieve complete viral suppression. Such patients are often switched to a new regimen, but this can lead to the use of all available therapeutic options. Since many patients with incomplete viral suppression continue to do well immunologically (and therefore clinically) (6-8), many clinicians choose not to switch to a new regimen as long as CD4 T cell counts remain elevated. Hence, clinicians are often faced with a dilemma in patients with detectable viremia on therapy: should they switch therapy as soon as possible, thereby risking using up all drugs quickly and exposing patients to increasingly complicated and potentially toxic regimens? Or should they maintain patients on a partially suppressive regimen as long as they are doing well

immunologically and clinically, even though this approach will allow the ongoing accumulation of drug-resistance mutations that can limit future therapeutic options? (For a review of this issue, see Deeks (9).)

In this paper, we estimate the effect of non-suppressive therapy on future CD4 T cell count, and estimate how this outcome differs depending on a patient's current CD4 T cell count, and time spent on non-suppressive therapy. Based on these estimates, we identify a rule for deciding when to switch to a new antiretroviral therapy that will maximize the patient's expected CD4 T cell count in the future. Data for these analyses are drawn from the Study on the Consequences of the Protease Inhibitor Era (SCOPE), an observational cohort of HIV-infected patients in San Francisco. Participants are seen at 4-month intervals. At each visit, they complete interviewer- and self-administered questionnaires examining domains including socioeconomic status (housing, income, employment), antiretroviral medication use and adherence, occurrence of opportunistic infection or malignancy, and recreational drug use. Plasma HIV RNA levels and CD4/CD8 T cell counts are measured at each visit, as well as between visits according to physician discretion. Importantly, decisions as to when and how to modify therapy are made by primary care providers based on standard of care.

For our current analysis, we retrospectively identified subjects from SCOPE who experienced virologic failure while being observed in this study. Subjects became eligible for our analyses ($t=0$) if they failed to achieve an undetectable HIV RNA levels (< 75 copies RNA/mL) by week 24 on a new regimen, or if they rebounded from an undetectable level. The exposure of interest was time until switching to a new therapy. This can be summarized as a binary variable at each time point, indicating whether or not a subject has switched off of his or her original non-suppressive ART regimen. We only allowed subjects to switch once in our analyses. The method can be easily extended, however, to encompass more complex treatment patterns.

In the sections which follow, we rely on this data structure to illustrate our methodology. In the final section, we present the results of our analyses.

THE COUNTERFACTUAL FRAMEWORK

The causal effect of a treatment on an individual can be defined as the difference in the individual's outcome with and without the treatment. Such outcomes are termed counterfactual because only one is observed for each individual. MSM are models of how the population distribution of these counterfactual outcomes changes as a result of changes in treatment.

We begin by introducing some standard notation. Treatment over the course of the study ($t=0,...,K$) is denoted $\bar{A}(K) = (A(0),..., A(K))$, and covariates are denoted $\bar{L}(K+1)$, where treatment occurs after covariates at a given time point, and K+1 is the end of follow-up. In our HIV example, $\bar{A}(K)$ is a vector of binary variables, consisting of one for each time point until a subject switches therapy, and zero thereafter. For each possible time until switching, $\bar{L}_{\bar{a}}(K+1)$ denotes the counterfactual CD4 T cell counts and other covariates over time that would have been observed if the subject had switched therapy at the time implied by $\bar{A} = \bar{a}$. The outcome for a given time point t is the counterfactual CD4 T cell count measured 8 months in the future under the switching time indicated by $\bar{a}$, denoted $Y_{\bar{a}}(t+8)$.

If we observed the counterfactual CD4 T cell counts for each individual under each possible switch time, we could estimate the causal effect of waiting to switch therapy by simply comparing the counterfactual outcomes under different switch times. However, we only observe the CD4 T cell counts for each individual under a single (*non-random*) switch time. As a result, in order to estimate the effect of time until switching therapy on CD4 T cell count using the observed data, we must assume that the covariates we measured are sufficient to control for confounding. For example, within strata defined by our measured confounders, there must be no unmeasured variables that predict, at any time point, both probability of switching treatment and also CD4 T cell count 8 months in the future.

Under this assumption, we could use standard MSM to ask: "At baseline (when virologic failure occurs), how does time until switching to a new regimen affect CD4 T cell count 8 months later? How does this effect differ depending on a patient's CD4 T cell count at baseline?" However, an MSM assumed at a single time point does not allow us

to estimate how the effect of future non-suppressive therapy may change as a result of changes in a patient's CD4 T cell count, or how this information should be used to decide when to switch a patient to a new ART regimen. HA-MSM directly address these questions.

HISTORY-ADJUSTED MARGINAL STRUCTURAL MODELS

HA-MSM rely on the identical causal framework as standard MSM, but estimate a different parameter of interest. HA-MSM assume a standard MSM at each time point during the study, which models counterfactual outcomes indexed by treatment that occurs after that time point, conditional on some subset of the observed history up till that time point. In addition, HA-MSM allow us to assume a common model across time points. In other words, HA-MSM model some parameter of the counterfactual outcome if the study population were to follow their observed treatment history up till time *j*, followed by a specified counterfactual future treatment history until outcome is measured, conditional on a subset of (possibly time-varying) covariates and/or treatment history measured before time *j*. In this article, we will focus on HA-MSM concerned with the mean of these counterfactual outcomes; however, the same framework can be readily adopted to model any other parameter.

We denote a future longitudinal treatment regimen, beginning at time *j* and continuing until the outcome is measured *m* time points later, as $\underline{a}(j, j+m-1) \equiv (a(j), a(j+1), \ldots a(j+m-1))$, for $j = 0, \ldots, K+1-m$. The effect modifiers of interest are denoted $V(j) \subset (\overline{L}(j), \overline{A}(j-1))$, a subset of a subject's treatment and covariate history up till time *j*. For each time point in the study for which the outcome *m* time points later is defined, HA-MSM model the expectation of the counterfactual outcome $Y_{\overline{A}(j-1),\underline{a}(j,j+m-1)}(j+m)$, conditional on *V(j)*, under each possible future treatment regimen. Thus, HA-MSM are concerned with estimation of the following parameter: $E(Y_{\overline{A}(j-1),\underline{a}(j,j+m-1)}(j+m) \mid V(j))$, where *j=0,…,K+1-m*.

Applied to our example, future antiretroviral treatment from time *j* until the outcome is measured, denoted $\underline{a}(j, j+m-1)$, consists of a vector of counterfactual treatment decisions *a(j),…a(j+m-1)* , where *a(t)=0* if a subject has switched treatment at

or before time *t*, and otherwise *a(t)=1*. This vector of future treatment decisions exists for each subject beginning at each time point *j=0,...,K+1-m*. We summarize $\underline{a}(j, j+m-1)$ as $c(j) \equiv \sum_{l=j}^{j+m-1} a(l)$, which represents the future time (beginning at time point *j*) that the subject will spend on his/her original failing therapy before either switching or the outcome is measured. The current CD4 T cell count at time *j* is denoted *CD4(j)=S(j),* a subset of the full covariate history measured over time, $\bar{L}(j)$. For each time point *j*, we are interested in the mean counterfactual CD4 T cell count *m=8* months later among individuals who have not yet switched therapy, if they were to switch therapy at a specified counterfactual time after *j*.

To address this question, we might assume the following model:

$$E(Y_{\bar{A}(j-1),c(j)}(j+8) \mid \bar{A}(j-1), CD4(j)) = I(A(j-1)=1) \times (\beta_0 + \beta_1 c(j) + \beta_2 CD4(j) + \beta_3 j + \beta_4 c(j) \times CD4(j) + \beta_5 c(j) \times j) \quad (1)$$

$j = 0,..., K+1-8$.

In other words, we might assume that, among individuals who have not yet switched treatment (*A(j-1)=1*), counterfactual CD4 T cell count 8 months later depends on additional time until switching (*c(j)*), but the magnitude of this effect differs depending on the duration a patient has already spent on non-suppressive therapy (*j*) and current CD4 T cell count (*CD4(j)*).

This model allows us to estimate the effect of each additional month until switching to a new therapy on CD4 T cell count 8 months later, among patients who have been on their current non-suppressive therapy for different durations and have different current CD4 T cell counts. For example, by testing whether $\beta_4 = 0$ we are testing the hypothesis that a subject's current CD4 T cell count modifies the effect of future time until switching.

INVERSE PROBABILTIY OF TREATMENT WEIGHTED ESTIMATION

Several HA-MSM estimators are available; here, we focus on the inverse probability of treatment weighted (IPTW) estimator, which can be implemented using standard software. The IPTW estimator can be understood as simply a weighted least squares estimator. For each time point *j* in the study, each subject receives a weight

which is informally the inverse of the subject's probability of receiving the treatment that he or she actually received, from time point *j* until the outcome is measured. If a subject has a longitudinal treatment regimen beginning at time point *j* that occurs frequently in the data among subjects with his covariate and treatment history, he receives a small *j*-specific weight. In contrast, if the subject has an unusual longitudinal treatment regimen given his covariates, the subject will receive a large weight. In our HIV example, patients whose CD4 T cell counts have recently declined are more likely to switch therapy. A subject that did not switch therapy despite a recent decline in CD4 T cell count would thus have a small predicted probability of receiving her observed treatment, and receive a large weight.

The first step in implementing the IPTW estimator is to model the treatment mechanism, or fit a predictive model of treatment at each time point *t*, given the observed past up till that time point: $g(A(t) \mid \bar{A}(t-1), \bar{L}(t))$, $t = 0,...,K$. For example, we model the treatment decision (switch therapy or not) made at every time point *t* using logistic regression. A simple model of the treatment mechanism might be:

$$\text{logit}(A(t) \mid A(t-1=1, CD4(t)) = \theta_0 + \theta_1 CD4(t),\ t = 0,...,K, \qquad (2)$$

where *CD4(t)* is CD4 T cell count at time *t*. Recall that once a subject switches, he/she is no longer at risk of switching in the future. Thus, when fitting our model of the probability of staying on therapy at a given time point (*A(t)=1*), we fit the model only among subjects who have not already switched before that time point (*A(t-1)=1*).

For the IPTW estimator to be consistent, the estimate of the treatment mechanism must be consistent and enough covariates must be included in the treatment model so that outcome is independent of treatment assignment conditional on the variables in the model (or in other words, there must not be additional confounders that do not appear in the model of the treatment mechanism).

For each time point *j=0,...,K+1-m*, the model of the treatment mechanism (equation 2) is used to estimate the denominator of the *j*-specific weight:

$$\prod_{l=j}^{j+m-1} g(A(l) \mid \bar{A}(l-1), \bar{L}(l))$$

For subjects who do not switch therapy before the outcome is measured *m* months later, the denominator of the *j*-specific weight is

$$\prod_{l=j}^{j+m-1} P(A(l)=1 \mid A(l-1)=1, CD4(l))$$

For subjects who have not switched therapy by time j, but who switch at some point $T=j+C(j)$ before the outcome is measured ($C(j)< m$), the denominator of the *j*-specific weight is

$$(1-P(A(T)=1 \mid A(T-1)=1, CD4(T)))\prod_{l=j}^{T-1} P(A(l)=1 \mid A(l-1)=1, CD4(l))$$

Recall that subjects who have already switched therapy by time *j* do not contribute to our counterfactuals of interest.

The weight is then calculated as the inverse of the denominator. Note that the same subject will have a separate weight for each time point *j* in the study, with denominators corresponding to the probability that the subject received his/her observed treatment from that time point *j* until the outcome is measured. Once each subject has been assigned a set of *K+1-m* weights, a weighted least squares regression is run using standard software, with each subject contributing *K+1-m* weighted lines of data.

THE HA-MSM DYNAMIC TREATMENT REGIMEN

For each time point during the study, HA-MSM identify the future static treatment regimen that will maximize the expectation of the outcome, given treatment history and covariates of interest up till that time point. Recall that a static treatment regimen allows treatment to change over time, but not in response to changing patient covariates. In our example, model 1 allows us to estimate how much longer subjects should remain on their current non-suppressive therapy in order to maximize their expected CD4 T cell count 8 months later, given how long they have already been on non-suppressive therapy and their current CD4 T cell count. Among individuals who have not already switched, the effect of each additional month waiting to switch therapy is $\beta_1 + \beta_4 CD4(j) + \beta_5 j$.

At any given time point, this expression provides an optimal static future treatment regimen. When this expression is negative, each additional month waiting to switch will lead to depletion of CD4 T cells, suggesting that an individual should be switched immediately. When the expression is positive, waiting to switch will result in a

gain in CD4 T-cells, suggesting that the patient should be maintained on his current regimen.

The optimal future static treatment regimen estimated by HA-MSM in turn suggests an interesting *dynamic* treatment regimen. Recall that a dynamic treatment regimen is a rule or function that gives a recommended treatment decision at each time point, based on patient characteristics measured up till the time point. The dynamic treatment regimen identified by HA-MSM consists of following, at each time point, the first action of an individual's optimal static future treatment regimen at that time point. At subsequent time points, the optimal static future treatment regimen can then be updated in response to changes in covariates and treatment history.

RESULTS: WHEN TO SWITCH ANTIRETROVIRAL THERAPY

In our example, we identified from SCOPE a total of 100 patients who experienced loss of viral suppression on antiretroviral therapy and who had a CD4 T cell count measured 8 months later. Since a patient could contribute more than one episode of loss of suppression, we evaluated a total of 116 unique treatment episodes. Most patients had been on multiple treatment regimens prior to inclusion in our analysis.
The median time to switch after onset of failure was 6 months. Tables 1 and 2 describe the sample at time of confirmed virologic failure.

Cross-validated data-adaptive logistic regression (using the Deletion/ Substitution/ Addition algorithm (10)) was used to model the probability of switching therapy at each time point (the treatment mechanism) based on 40 candidate covariates (this included all covariates in tables 1 and 2, the time elapsed since loss of suppression, and plasma HIV RNA levels, defined as below of above the assay limit). The resulting fit of the treatment mechanism is shown in table 3.

The following standard MSM were used to estimate:

1. The marginal effect of time until switching therapy (c) on CD4 T cell count 8 months after loss of suppression ($Y(8)$): $E(Y_c(8)) = \beta_0 + \beta_1 c$
2. The effect of time until switching therapy on CD4 T cell count 8 months after loss of suppression (baseline), conditional on CD4 T cell count at baseline ($CD4(0)$): $E(Y_c(8) \mid CD4(0)) = \beta_0 + \beta_1 c + \beta_2 CD4(0) + \beta_3 c \times CD4(0)$

Table 4 shows the estimates of causal effects based on these models, as well as the corresponding non-causal associations (unadjusted for confounding). The MSM results suggest that, while waiting to switch therapy is generally associated with a loss of CD4 T cells (9.9 cells/month), waiting to switch is not detrimental among patients with high CD4 T cell counts (> 218 cells) at the time of virologic failure. The discrepancy between the causal coefficients, as estimated using MSM, and the non-causal associations (-9.9 vs. 4.9, -13.1 vs. -9.5) suggests the presence of significant time-dependent confounding.

At each time point, HA-MSM were used to estimate the effect of additional time until switching therapy among patients who remained on their original therapy, conditional on current CD4 T cell count. Nineteen individuals achieved re-suppression of the virus during follow-up despite remaining on the same therapy (an indicator that virologic failure was not due to resistance). As we aimed to estimate the effect of waiting to switch therapy among individuals with loss of viral suppression due to the presence of resistant virus, HA-MSM were fit only among those individuals with no history of re-suppression (*I(Supp=0)*). Our HA-MSM aimed to replicate the results of a randomized trial in which individuals currently on a non-suppressive therapy regimen and with no history of re-suppression on this regimen were assigned to switch to a new therapy at a random time in the future.

Two sets of HA-MSM analyses were conducted. In the first, the following model was assumed, and separate coefficients were estimated for each time point *j*.

$$E(Y_{\bar{A}(j-1)c(j)}(j+8) \mid A(j-1)=1, CD4(j))$$
$$= I(A(j-1)=1 \times I(Supp=0) \times (\beta_0 + \beta_1 c(j) + \beta_2 CD4(j) + \beta_3 c(j) \times CD4(j))$$

Based on the resulting coefficient estimates for the first nine months (*j=0,..,8*), figure 1 plots the estimated effect of each additional month waiting to switch therapy for three current CD4 T cell counts.

Figure 1 suggests that the effect of additional time until switching differs depending on the amount of time an individual has already spent on non-suppressive therapy, as well as on the individual's current CD4 T cell count. Specifically, in the months immediately subsequent to loss of virologic suppression, waiting to switch therapy appears beneficial among individuals with high current CD4 T cell counts, but

detrimental in those with low CD4 T cell counts. In contrast, among the population that have already spent at least five months on their current non-suppressive therapy, additional time waiting to switch has a negligible effect on future CD4 T cell count, regardless of an individual's current CD4 T cell count. This effect modification may be due in part to the fact that the population remaining on non-suppressive therapy for at least five months is a different population than the original group failing therapy; they are likely to have remained on non-suppressive therapy precisely because they were better able to tolerate it.

In the second set of analyses, a single model was fit for the first nine time points (*j=0,..,8*), now assuming common parameters across time and including time spent on non-suppressive therapy as a covariate in the model:

$$E(Y_{\bar{A}(j-1),c(j)}(j+8) \mid (A(j-1)=1, CD4(j)) = I(A(j-1)=1) \times I(Supp=0) \times$$
$$(\beta_0 + \beta_1 c(j) + \beta_2 CD4(j) + \beta_4 c(j) \times CD4(j) + \beta_5 c(j) \times j + \beta_6 c(j) \times CD4(j) \times j)$$

Using this common model, the estimated effect of each additional month until switching therapy is

$$\beta_1 + \beta_4 CD4(j) + \beta_5 j + \beta_6 CD4(j) \times j$$
$$= -10.4 + 0.05 \times CD4(j) + 1.9 \times j - 0.01 \times CD4(j) \times j$$

Table 5 shows the estimates of causal effect of switching based on this model (plotted for three CD4 T cell values in figure 2). This fit provides us with a decision rule for when to switch therapy; when this expression is negative, switch therapy immediately. When this expression is positive, wait until the next month, then re-evaluate the expression based on current CD4 T cell count and elapsed time.

DISCUSSION

The HA-MSM presented in this paper represent an important generalization of MSM methodology. MSM are well-established as powerful tools for causal inference, particularly in the setting of longitudinal data. In this article we have introduced an extension of MSM to identify and estimate time-dependent causal effect modification. We have further illustrated how HA-MSM make possible the identification of a specific type of dynamic treatment regimen. The dynamic treatment regimens identified by HA-

MSM will be most appropriate as candidates for future clinical trials when they include all major effect modifiers of the exposure of interest (1).

Alternative statistical methods currently available for identifying and evaluating dynamic treatment regimens, such as Structural Nested Mean Models (SNMM) and G-computation (11-13), require substantial programming effort to implement, perhaps explaining the paucity of epidemiologic research aimed at estimating dynamic treatment regimens. In contrast, as illustrated in this paper, HA-MSM can be implemented using standard software. In addition, SNMM and G-computation both identify dynamic treatment regimens aimed at optimizing an outcome at a fixed time-point. In contrast, in the example presented, HA-MSM were used to identify a dynamic treatment regimen aimed at optimizing a continuously changing outcome (CD4 T cell count 8 months in the future). In many applications, optimizing such a "moving" outcome, rather than an outcome at a fixed time point, may indeed be the researchers' goal.

In conclusion, HA-MSM identify treatment decision rules based on time-dependent covariates that are expected to optimize patient outcome. Identification of such dynamic treatment regimens is a crucial application in the medical sciences, in addition to other fields that rely on dynamic decision-making. We anticipate that these models will prove a useful tool in multiple fields of applied research.

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TABLE 1. Characteristics of sample at time of failure (continuous variables).[1]

Characteristic	1st Quartile	Median	Mean	3rd Quartile	Missing
Plasma HIV RNA level	365.5	4317	34190	24940	0
CD4 T cell count	175.5	261.5	321	428.8	0
CD8 T cell count	726.8	1022	1168	1497	0
Percent Average Adherence (self report)	100	100	92.36	100	0
Year Diagnosed with HIV	1986	1989	1989	1993	2
Age	44.2	50.5	49.9	55.5	0
Year of first antiretroviral treatment	1991	1996	1995	1997	0
Peak HIV RNA level (lab records)	46020	177500	242300	381200	0
Nadir CD4 T cell count (lab records)	36.25	72.5	118.3	165	0
Number of PI[2] drugs experienced	2	3	3.241	4	0
Number of NRTI[3] drugs experienced	4	5	4.819	6	0
Number of NNRTI[4] drugs experienced	0	1	0.9138	1	0

[1]Among 100 individuals (116 episodes) with a know time of viral failure, and follow-up for at least 8 months following time of failure.
[2] Protease inhibitor
[3] Nucleoside reverse transcriptase inhibitor
[4] Non-nucleoside reverse transcriptase inhibitor

TABLE 2. Characteristics of sample at time of failure (Categorical Variables).[5]

Characteristc	N (%)	Missing
Treatment history		0
Enfuvurtide	8 (7%)	
Tenofovir	41 (35%)	
Lamivudine	115 (99%)	
Mono/dual ART[6]	57 (49%)	
Current Treatment		0
Protease inhibitor	87 (75%)	
Nucleoside reverse transcriptase inhibitor	113 (97%)	
Non-nucleoside reverse transcriptase inhibitor	22 (19%)	
Lab Frequency		0
Most Recent HIV RNA level > than one month prior	49 (42%)	
Most Recent CD4 T cell count > than one month prior	42 (36%	
Subject Characteristics		
History of intravenous drug use	43 (37%)	0
Male	100 (86%)	0
Sexual orientation "Man who has sex with men"	79 (69%)	1
Homeless within past year	6 (5%)	0
Current diagnosis with an opportunistic disease	25 (22%)	0
Self-identified HIV risk group		0
Man having sex with men	79 (68%)	
Intravenous drug use ever	22 (19%)	
Heterosexual Intercourse	8 (7%)	
Other	7 (6%)	
Race/ethnicity		0
White	51 (44%)	
African-American/Black	35 (30%)	
Latino/Hispanic/ Mexican-American	17 (15%)	
Other	13 (11%)	
Crack use (past 4 months)		1
Every day	3 (3%)	
Once a week	6 (5%)	
Once a month	3 (3%)	
Less than once a month	7 (6%)	
Never	96 (83%)	
Methamphetamine use (past 4 months)		1
Once a week	2 (2%)	
Once a month	4 (3%)	
Less than once a month	3 (3%)	
Never	106 (92%)	

[5] Among 100 individuals (116 episodes) with a know time of viral failure, and follow-up for at least 8 months following time of failure

[6] ART=Antiretroviral treatment

Alcohol Use (past 4 months)		1
At least once a day	10 (9%)	
Nearly every Day	6 (5%)	
3-4 times a week	7 (6%)	
1-2 times a week	26 (23%)	
2 or 3 times total	14 (12%)	
Once	12 (10%)	
Never	40 (35%)	
Education (highest year of school completed)		0
Grades 7-11	16 (14%)	
High School/GED	24 (21%)	
Some College	46 (40%)	
4 Years College/BS/BA	19 (16%)	
Some/Completed Graduate School	11 (9%)	
Income (yearly household)		0
<=$6000	5 (4%)	
$6001-$12,000	50 (43%)	
$12,001-$18,000	20 (17%)	
$18,001-$24,000	14 (12%)	
$24,001-$30,000	2 (2%)	
$30,001-$36,000	4 (3%)	
$36,001-$75,000	13 (11%)	
>$75,000	8 (7%)	

TABLE 3. Odds ratios for switching treatment based on data-adaptive fit of treatment mechanism.[7] [8]

Covariate	Odds Ratio
Current diagnosis with an opportunistic disease	1.22
Number of protease inhibitor drugs experienced	1.11
Most recent HIV RNA level undetectable	0.44
Percent average adherence (per 10%)	0.92
Most recent CD4 T cell count (per 100 CD4 T cells)	0.92
Nadir CD4 T cell count (per 100 CD4 T cells)	1.05
Most recent HIV RNA level more than one month prior	0.90
Age (per 5 years)	0.90

[7] Note: Variables for treatment mechanism selected among larger sample of non-suppressed in SCOPE cohort: 255 people, 368 episodes, including people with unknown loss of suppression time and missing outcome. The coefficients on the selected model (corresponding to the Odds Ratios reported here) were then refit on the population with known loss of suppression time.

[8] Note: Standard errors and P-values not shown, to emphasize that role of the treatment mechanism in construction of weights, rather than for the purposes of causal interpretation.

TABLE 4. Non-causal associations and estimated causal effects of time until switching therapy on CD4 T Cell Count 8 months after loss of suppression.[9] [10]

	Coefficient	95% CI[11] [12]
Associations for Each Additional Month Until Switching Therapy		
Unadjusted Association: $E(Y(8)\|C=c)$	4.9	-6.3, 16.8
Multivariable Regression:	-9.5	-17.7, -1.3
$E(Y(8)\|CD4(t=0),C=c)$	0.05 * CD4(t=0)	0.03, 0.08
Causal Effects of Each Additional Month Until Switching Therapy		
Standard MSM: $E(Y_c(8))$	- 9.9	-21.1, 2.9
Conditional Standard MSM:	-13.1 c	-22.5, -4.8
$E(Y_c(8)\|CD4(t=0))$	0.06 * CD4(t=0)	0.03, 0.09

[9] "C" and "c" denote, respectively, the observed and counterfactual number of months after baseline (viral failure) of exposure to original non-suppressive therapy

[10] CD4 (t=0) denotes observed CD4 T cell count at baseline (time of viral failure).

[11] Based on 100 Bootstrap samples

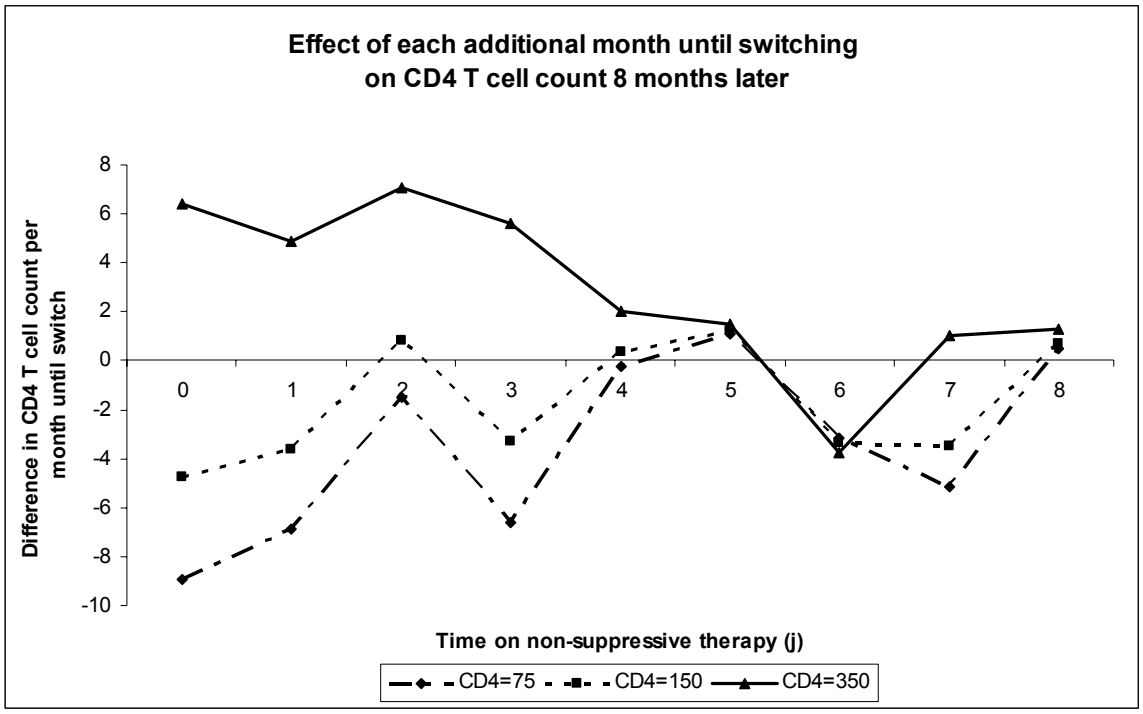
[12] CI=Confidence interval

TABLE 5. Coefficients from HA-MSM model for first 9 time points (j=0,..,8).[13] Estimated effect of each additional month until switching therapy, given current CD4 T cell count (CD4(j)) and elapsed time since failure occurred (j).

Coefficient	95% CI[14 15]
-10.4	-18.5, -4.0
0.05 x CD4(j)	0.03, 0.08
1.9 x j	-0.03, 3.4
- 0.01 x CD4(j) x j	-0.02, -0.003

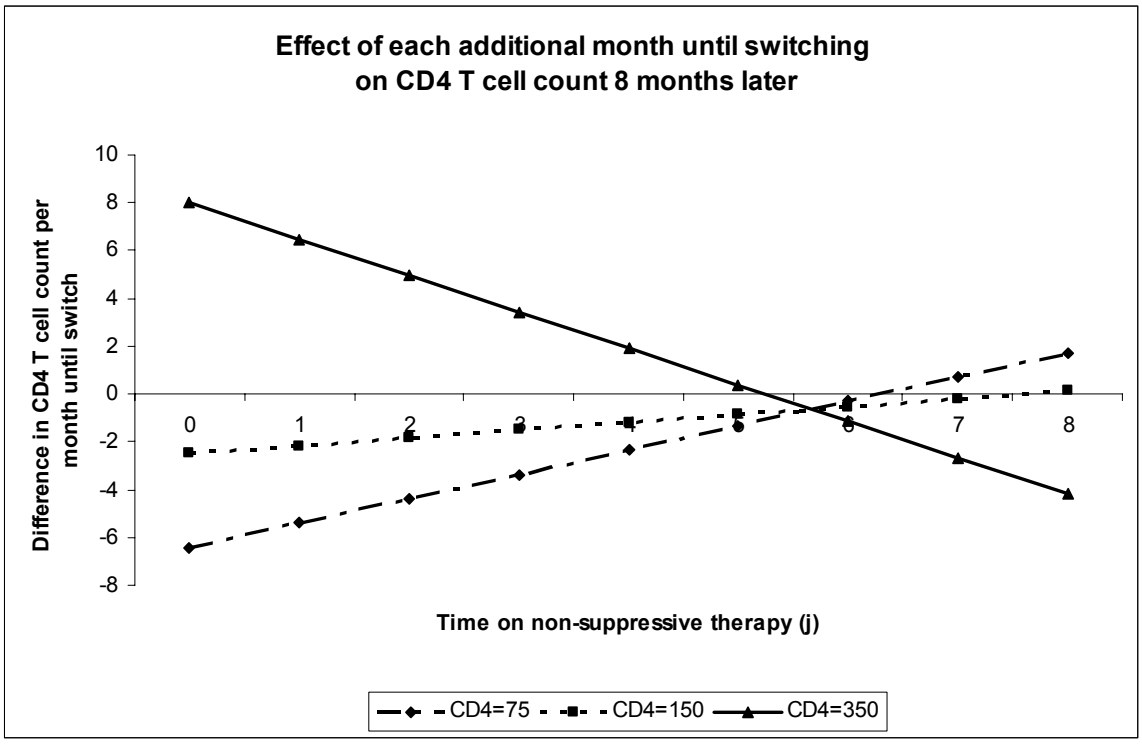
[13] Estimated among people who have not yet switched therapy and have not re-suppressed the virus.
[14] Based on 100 Bootstrap samples
[15] CI = Confidence Interval

FIGURE 1. Separate HA-MSM fit at each of first 9 time points.[16]



[16] Estimated among people who have not yet switched therapy and have not re-suppressed the virus.

FIGURE 2: Single HA-MSM fit for first 9 time points.[17]



[17] Estimated among people who have not yet switched therapy and have not re-suppressed the virus.