



Defining the Immunologic Consequences of Early vs. Delayed Treatment Modifications Using Marginal Structural Models



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Introduction

- Observational cohort studies have consistently demonstrated that the rate of CD4+ T cell declines is slower in patients with multi-drug resistant HIV compared to historic controls of untreated patients with wild-type HIV.
- These studies have been used to justify waiting to modify therapy in patients with virologic failure, particularly if the options for complete viral suppression are limited.
- These prior observational studies may have been confounded by the likelihood that treated patients who were doing well were less likely to modify therapy than those not doing well.
- Marginal structure models are a statistical methodology that can address these issues.

Objectives

- To demonstrate the need for marginal structural models in the analysis of HIV cohort data
- To estimate the effect of time until treatment modification on future CD4 T cell count among patients virologically failing antiretroviral therapy
- To estimate modification of this effect by
 - CD4 T cell count at time of failure and over the course of non-suppressive therapy
 - Elapsed time since virologic failure occurred

Methods: Subject Selection

- We identified all episodes of virologic failure among patients followed between 2000 and 2004 as part of SCOPE, a clinical San Francisco-based cohort.
- Virologic failure** ($t=0$) was defined as $>= 2$ detectable and no undetectable plasma HIV RNA levels
 - In the first 6 months after starting a new regimen
 - Over a 4 month period on a stable regimen
- Outcome**= CD4 T cell count 8 months in the future
- Exposure**= Time until treatment modification (switch)
- Treatment modification** = change or interruption of at least 1 drug

Methods: Statistics

Marginal Structural Models (MSM)

- Mimic a RCT where subjects are enrolled at time of failure and assigned a random switch time
- Model counterfactual CD4 count 8 months after failure if a subject were assigned to switch treatment after c months: $Y_c(8)$

History-Adjusted MSM (HA-MSM)

- Mimic a RCT where subjects who have not yet switched therapy are enrolled at various times after failure and assigned a random future switch time
- At each time point after failure (j), model the counterfactual CD4 count 8 months later if a subject were assigned to switch treatment after c additional months: $Y_c(j+8)$
 - Fit among individuals who have not modified therapy and have not achieved re-suppression

Inverse Probability of Treatment Weighting (IPTW)

- Controls confounding by modeling the probability of switching treatment given covariates
 - This model is called the **treatment mechanism**
- Weights are inversely proportional to the probability of a patient receiving his observed treatment
 - E.g. Patients whose clinical status declines after failure are more likely to modify treatment early. Thus, patients whose clinical status declines but who modify treatment late get larger weights.
- Unlike multivariable regression, IPTW controls for confounding by covariates affected by past treatment

Treatment Mechanism

- Probability of modifying treatment given the observed past modeled using logistic regression (Table 3)
- Data-adaptively fit with cross-validation and aggressive search algorithm
- 40 candidate covariates (Table 1)

Inference

- MSM and HA-MSM: non-parametric bootstrap
- Treatment mechanism: robust s.e. from GEE

Table 1: Candidate confounders evaluated

Covariate	Age
Current treatment (PI/NRTI/NNRTI)	Gender
Plasma HIV RNA level	Sexual orientation
CD4 T cell count	Homeless within past year
CD8 T cell count	Diagnosis with opportunistic disease
Lab frequency	Education
Self-Reported Adherence	Yearly Income
Year HIV diagnosed	Self-identified HIV risk group
Drug experience: T20, TDF, 3TC	Race/ethnicity
Drug experience: #PIs, #NRTIs, #NNRTIs	Crack (past 4 months)
Past Mono/Dual therapy	Methamphetamine (past 4 months)
Year first treated with ART	Alcohol (past 4 months)
Peak HIV RNA Level	Intravenous drug use
Nadir CD4 T cell count	

Table 2: Subject characteristics at time of failure

Characteristic (continuous)	Median	Quartiles (1 st , 3 rd)
Plasma HIV RNA level	4317	(365,24940)
CD4 T cell count	261.5	(176,429)
CD8 T cell count	1022	(727,1497)
Percent Average Adherence (self report)	100	(100,100)
Year Diagnosed with HIV	1989	(1986,1993)
Age	50.5	(44,56)
Year of first antiretroviral treatment	1996	(1991,1997)
Peak HIV RNA level (lab records)	177500	(46020,381200)
Nadir CD4 T cell count (lab records)	72.5	(36,165)
Number of PI drugs experienced	3	(2, 4)
Number of NRTI drugs experienced	5	(4, 6)
Number of NNRTI drugs experienced	1	(0, 1)
Characteristic (categorical)	Frequency	%
ART Pre-1996	57	49%
Current treatment with PI	87	75%
Current Treatment with Enfuvirtide	7	6%
Male	100	86%
White	51	44%
Man who has sex with Men	79	69%

Table 3: Treatment Mechanism

Variables contributing to the probability of treatment modification. Fit using cross-validated data adaptive regression based on covariates in Table 1.

Covariate	Adjusted OR	95% CI
Current diagnosis with opportunistic disease	1.21	0.69, 2.14
Number of PI drugs experienced	1.11	0.99, 1.25
Most Recent Viral Load Undetectable	0.45	0.18, 1.10
Percent Average Adherence (per 10%)	0.92	0.92, 0.93
CD4 T cell count (per 100 CD4 T cells)	0.92	0.92, 0.92
Nadir CD4 T cell count (100 CD4 T cells)	1.06	1.05, 1.06
Most Recent Viral load > 1 month prior	0.90	0.57, 1.44
Age (per 5 years)	0.89	0.87, 0.91

Results

- 100 subjects (116 episodes of failure) were evaluated
- Median time to switch was 6 months (IQR=4,11)

Marginal Structural Models (MSM)

Effect of time until switching (c) on CD4 count 8 months later, given CD4 count at failure ($CD4(0)$):
 $E[Y_c(8) | CD4(0)] = \beta_0 + \beta_c + \beta_c CD4(0) + \beta_c \times CD4(0)$
 $\beta_c = -13.1$ 95% CI: (-22.5, -4.8)
 $\beta_c = 0.06$ 95% CI: (0.03, 0.09)

- In other words, the effect of waiting to switch depends on CD4 count at time of failure
 - For individuals with a CD4 count < 234 at time of failure, waiting resulted in a lower CD4 count 8 months later.
 - For individuals with a CD4 count of >234, waiting to switch resulted in a higher CD4 count 8 months later

Table 4: MSM vs. Standard Regression

Analytic approach	Estimated effect of each additional month until switching on CD4 count 8 months later
Crude association (unadjusted)	4.9
MSM (adjusted for confounding)	-9.9
Multivariable Regression (adjusted for CD4 at failure)	-9.5+0.051 c^* CD4(0)
MSM (adjusted for confounding)	-13.1+0.056 c^* CD4(0)

History-Adjusted MSM (HA-MSM)

- Single model across time points
- Effect of time until switching (c) on CD4 count 8 months later, given current CD4 count ($CD4(j)$) and time since failure (j):

$$E[Y_c(j+8) | CD4(j)] = \beta_0 + \beta_c + \beta_c CD4(j) + \beta_j + \beta_j \times CD4(j) + \beta_c \times j + \beta_{jc} \times CD4(j) \times j$$

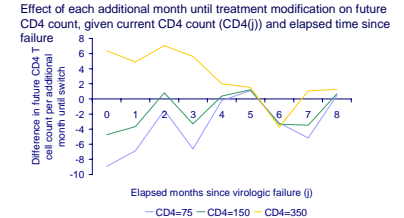
$$\beta_j = -10.4 \quad 95\% \text{ CI: } (-16.8, -3.3)$$

$$\beta_c = 0.05 \quad 95\% \text{ CI: } (0.02, 0.08)$$

$$\beta_j = 1.7 \quad 95\% \text{ CI: } (0.2, 3.2)$$

$$\beta_{jc} = -0.01 \quad 95\% \text{ CI: } (-0.01, -0.003)$$

Figure 1: HA-MSM, separate model for each time point



Conclusions

Statistical

- MSM analyses suggest that standard multivariable regression underestimates the immunologic harm due to delayed treatment modification
 - This may be due to the fact that CD4 T cell count is both the outcome and is used to decide when to modify therapy
- HA-MSM allow estimation of effect modification by time-varying covariates

Clinical

- Younger patients with higher nadir CD4 counts and lower current CD4 counts were more likely to switch
- Delayed treatment modification was associated with lower future CD4 count in patients with low, but not high, CD4 count at time of failure
- Over time, the effect of additional delay until switching waned, irrespective of current CD4 count

References: www.bepress.com

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