K-179

UC Berkeley Biostatistics

Pill Box Organizers Are Associated with Improved HIV Antiretroviral Adherence and Viral Suppression: A Marginal Structural Model Analysis

Maya L Petersen[1], Yue Wang[1], Mark J. van der Laan[1], David Guzman[2], Elise Riley[2], and David R. Bangsberg[2,3]

1) Division of Biostatistics, UC Berkeley School of Public Health; 2) Epidemiology and Prevention Interventions Center, Division of Infectious Diseases, San Francisco General Hospital;
3) Positive Health Program, San Francisco General Hospital, UCSF

REACH

Introduction

- Incomplete adherence is a common cause of sub-optimal response to antiretroviral therapy (ART)
- Pill box organizers (medisets) are the least expensive and most widely used adherence aid
- Effect of pill box organizers on adherence to ART is unknown
- Because medisets are standard of care, randomized controlled trials to study the effect of medisets raise ethical concerns
- Marginal structural models (MSM) are a statistical methodology that aims to replicate the findings of a randomized controlled trial using observational data
  - •Different estimators rely on alternative models to control for confounding
- **Objective:** Estimate the effect of mediset use for a given month on adherence to ART and viral load the same month

Methods: Data

- **REACH Cohort:** Systematic sample of HIV-positive adults recruited from San Francisco homeless shelters, free meal programs, and low-income single-room-occupancy hotels between March 1998 and September 2005
- **Outcome (Y):** Adherence and viral load
  - **Y1:** Adherence assessed via unannounced pill count every 3-6 weeks at place of residence
  - **Y2:** Log viral load
  - **Y3:** Viral load <400 copies/ml
- **Intervention (A):** Mediset use assessed at first visit each month
- **Covariates (W):** Considered as potential confounders and controlled for in analyses
  - Current regimen: Classes used, once daily dosing, # drugs
  - Labs: CD4 count, nadir CD4 count, viral load
  - Recreational drug use: Alcohol, intravenous drugs (IDU), crack
  - Homelessness
  - Prior adherence
  - Treatment history: Drugs experienced, mono/dual nucleoside exposure, ARV-naive
  - Ethnicity, sex, age, sexual orientation
  - Time: Date (calendar time), months spent on current regimen

Results: Sample Characteristics

- 269 individuals followed for 3170 Person-Months (PM)
  - 237 individuals (2628 PM) had measurements of all confounders and mediset use
    - 237 (2504 PM) with adherence measurements
    - 194 (2227 PM) with viral load measurements
- Subject characteristics are described in **Table 1**
  - Majority people of color
  - High proportion injection drug users
  - Majority treated with PI-based therapy

Mediset Use

- 61% of subjects used medisets for at least one month (N=163)
- Multivariable logistic regression was used to predict mediset use given confounders
- Mediset use was associated with **(Table 2)** the following:
  - Higher prior adherence
  - Female sex
  - More recent calendar time
  - Not being homeless

Table 1: Patient and Treatment Characteristics

Characteristic (at baseline)	
Non-Caucasian (%)	153 (58%)
Male (%)	214 (80%)
Men who have Sex with Men (%)	157 (58%)
Median Age (IQR)	44 (IQR: 38,49)
Antiretroviral Treatment	
PI-based (%)	147 (55%)
NNRTI-based (%)	95 (35%)
PI-NNRTI based (%)	20 (7%)
RTI only (%)	8 (3%)
Once Daily Therapy (%)	35 (13%)
Median # ARV drugs in current regimen (IQR)	3 (IQR: 3, 4)
Median Months on Current Regimen (IQR)	6 (IQR: 3, 13)
Median # of ARV drugs experienced (IQR)	4 (IQR: 3, 6)
ARV Naïve (%)	107 (40%)
Mono or dual nucleoside exposure (%)	113 (42%)
Characteristic (over course of follow-up)	
Intravenous Drug Use (%)	83 (32%)
Crack Use (%)	86 (33%)
Slept on Street or in Shelter (%)	49 (19%)
Mean Days Alcohol Consumed (in past month)	3.6 (SD=7.6)
Median Nadir CD4/ml (IQR)	168 (IQR: 90, 342)
Median CD4/ml (IQR)	338 (IQR: 195, 532)
Person-Months with Mediset Use (%)	1371 (43%)
Person-Months with Viral Load < 400 cps/ml (%)	1431 (45%)
Median Viral Load log copies/ml (IQR)	2.3 (IQR: 1.0, 4.1)
Median PC Adherence (IQR)	86 (IQR=52, 98)

IQR= Inter-Quartile Range, SD=Standard deviation,

Results: Adherence

- Mean adherence was 73% (SD=30, Range=0-100)
- Prior to adjusting for confounding, mediset use was associated with 8.8% higher adherence (95% CI 4.0, 13.6)

Marginal (Unadjusted) Associations with Adherence (p<0.05)

- Adherence was lower among individuals with these attributes:
  - Lower prior adherence
  - Lower prior CD4 T cell count
  - Higher prior viral load
  - Higher alcohol use
  - Crack and intravenous drug users
  - Homeless
  - Women
  - African-Americans
- Adherence was higher with
  - Hispanics
  - More recent calendar date

Results: Viral Load

- One hundred thirty-nine subjects (72%) achieved a mean viral load of fewer than 400 copies/ml at least once during follow-up
- 58% of person-time was virologically suppressed
- Prior to adjusting for confounding, mediset use was associated with 1.2 log lower viral load (95% CI: 0.3, 2.0)

Adherence and Viral Load

- Mean adherence in those with fewer than 400 copies/ml was 28% lower than adherence among those with more than 400 copies/ml. (95% CI: 23, 32)
- 10% higher adherence was associated with a 0.25 lower log viral load (95% CI: 0.22, 0.29)

Table 2: Logistic Regression of Mediset on Confounders

Covariate	OR	95% CI
Once daily ART	0.61	(0.28, 1.33)
Adherence (per 10% adherence)	1.13	(1.05, 1.21)
CD4 count (per 100 cells)	1.10	(0.98, 1.24)
CD4 count (2 months prior) (per 100 cells)	0.99	(0.90, 1.09)
Nadir CD4 count (per 100 cells/ml)	0.53	(0.25, 1.12)
Nadir CD4 count (2 months prior) (per 100 cells)	1.38	(0.67, 2.84)
Viral Load (per 100,000 cps)	1.04	(0.87, 1.24)
Viral Load (2 months prior)) (per 100,000 cps)	1.03	(0.89, 1.18)
Calendar Month (per 30 days)	1.04	(1.02, 1.05)
Months on Current ART Regimen	0.99	(0.97, 1.00)
Age (per year)	0.99	(0.95, 1.03)
Number of Days Alcohol Consumed	0.98	(0.95, 1.02)
Intravenous Drug Use	1.29	(0.73, 2.29)
Slept on street or in shelter	0.47	(0.25, 0.90)
Crack use	1.22	(0.68, 2.18)
Woman	3.09	(1.19, 8.03)
Man who has Sex with Men	1.60	(0.71, 3.64)
Black/African-American1	1.03	(0.55, 1.93)
Hispanic/Latino[1]	1.63	(0.34, 7.96)
Other Ethnicity[1]	0.74	(0.24, 2.26)
Mono/Dual RT Experience	0.84	(0.40, 1.76)
ARV Naïve	0.50	(0.26, 0.97)
Un-boosted PI Regimen[2]	0.61	(0.34, 1.12)
PI/NNRTI Regimen[2]	1.37	(0.34, 5.53)
RT Only Regimen[2]	0.45	(4E-4,4E2)
Boosted PI Regimen[2]	0.69	(0.23, 2.12)
Number ARVs in Regimen	0.92	(0.55, 1.54)
Number ARVs Experienced	0.79	(0.66, 0.95)
Number Regimens Experienced	1.25	(0.70, 2.23)

1 White as Baseline
2 NNRTI Regimen as Baseline

Table 3: Regression of Adherence on Mediset & Confounders

Covariate	Coefficient	95% CI
Mediset Use	4.47	(1.98, 6.97)
Once daily ART	0.78	(-3.12, 4.68)
Adherence (per 10% adherence)	6.33	(5.81, 6.68)
CD4 count (per 100 cells)	-0.05	(-0.99, 0.90)
CD4 count (2 months prior) (per 100 cells)	0.25	(-0.83, 1.33)
Nadir CD4 count (per 100 cells)	-0.88	(-9.64, 7.87)
Nadir CD4 count (2 months prior) (per 100 cells)	1.69	(-6.81, 10.18)
Viral Load (per 100,000 cps)	-0.12	(-0.24, 0.01)
Viral Load (2 months prior) (per 100,000 cps)	-0.10	(-0.20, 0.01)
Calendar Month (per 30 days)	-0.03	(-0.07, 0.02)
Months on Current ART Regimen	0.04	(-0.03, 0.10)
Age (per year)	0.14	(0.01, 0.28)
Number Days Alcohol Consumed	-0.05	(-0.18, 0.08)
Intravenous Drug Use	-3.73	(-6.42, -1.03)
Slept on street or in shelter	-0.98	(-3.82, 1.87)
Crack use	-2.46	(-5.14, 0.22)
Woman	-2.89	(-5.86, 0.08)
Man who has Sex with Men	-0.03	(-2.66, 2.60)
Black/African-American[1]	-6.45	(-8.80, -4.10)
Hispanic/Latino[1]	-2.20	(-6.75, 2.36)
Other Ethnicity[1]	-4.42	(-10.91, 2.07)
Mono/Dual RT Experience	-1.45	(-5.45, 2.54)
ARV Naïve	0.70	(-2.13, 3.53)
Un-boosted PI Regimen[2]	-0.56	(-3.25, 2.13)
PI/NNRTI Regimen[2]	0.46	(-4.55, 5.47)
RT Only Regimen[2]	2.36	(-5.73, 10.45)
Boosted PI Regimen[2]	0.60	(-4.52, 5.72)
Number ARVs in Regimen	-0.38	(-2.22, 1.47)
Number ARVs Experienced	0.24	(-0.53, 1.01)
Number Regimens Experienced	0.25	(-2.32, 2.81)

1 White as Baseline
2 NNRTI Regimen as Baseline

Table 4: Regression of Log VL on Mediset & Confounders

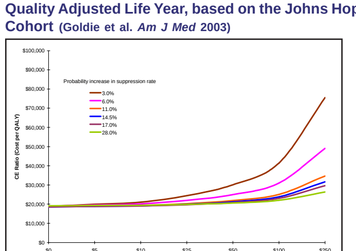
Covariate	Coefficient	95% CI
Mediset Use	-0.34	(-0.60, 0.08)
Once daily ART	0.27	(-0.54, 1.07)
Adherence (per 10% adherence)	-0.15	(-0.18, -0.12)
CD4 count (per 100 cells)	-0.10	(-0.15, -0.05)
CD4 count (2 months prior) (per 100 cells)	-0.05	(-0.10, 0.01)
Nadir CD4 count (per 100 cells)	-0.30	(-0.74, 0.13)
Nadir CD4 count (2 months prior) (per 100 cells)	0.33	(-0.10, 0.75)
Viral Load (per 100,000 cps)	0.24	(0.13, 0.35)
Viral Load (2 months prior)) (per 100,000 cps)	0.07	(0.01, 0.13)
Calendar Month (per 30 days)	0.00	(-0.01, 0.00)
Months on Current ART Regimen	0.00	(-0.01, 0.01)
Age (per year)	-0.04	(-0.05, -0.02)
Number Days Alcohol Consumed	-0.02	(-0.03, -0.01)
Intravenous Drug Use	0.20	(-0.07, 0.47)
Slept on street or in shelter	-0.13	(-0.45, 0.19)
Crack use	0.43	(0.17, 0.69)
Woman	-0.03	(-0.45, 0.38)
Man who has Sex with Men	0.10	(-0.22, 0.42)
Declined to report sexual orientation	0.42	(-0.08, 0.75)
Black/African-American[1]	0.02	(-0.45, 0.50)
Hispanic/Latino[1]	0.40	(-0.19, 0.99)
Other Ethnicity[1]	0.22	(-0.12, 0.55)
Declined to Report Ethnicity[1]	-0.25	(-0.58, 0.08)
Mono/Dual RT Experience	0.28	(-0.04, 0.60)
ARV Naïve	-0.22	(-0.79, 0.34)
Un-boosted PI Regimen[2]	-0.42	(-1.33, 0.50)
PI/NNRTI Regimen[2]	0.12	(-0.37, 0.61)
RT Only Regimen[2]	0.03	(-0.21, 0.27)
Boosted PI Regimen[2]	0.05	(-0.02, 0.12)
Number ARVs in Regimen	-0.17	(-0.42, 0.07)
Number ARVs Experienced	-0.34	(-0.55, -0.13)
Number Regimens Experienced	0.27	(-0.54, 1.07)

1 White as Baseline
2 NNRTI Regimen as Baseline

Table 5: MSM Estimates of Effect of Mediset on Adherence and Viral Load

Estimator	Difference in % Adherence	95% CI	Difference in Log VL	95% CI	OR VL<400	95% CI
G-Computation	4.5%	(2.0, 7.0)	-0.34	(0.08, 0.60)	1.81	(1.25, 2.62)
IPTW	4.1%	(0.0, 8.3)	-0.37	(0.05, 0.69)	1.91	(1.27, 2.90)
Double Robust	4.1%	(1.1, 7.1)	-0.36	(0.09, 0.63)	1.91	(1.27, 2.90)

Figure 1. Relationship between Percent Improvement in Viral Suppression, Cost of Intervention, and Cost per Quality Adjusted Life Year, based on the Johns Hopkins Cohort (Goldie et al. *Am J Med* 2003)



Methods: Statistics

Counterfactual Framework

- We can imagine the outcome that an individual would have had under two different interventions
  - $Y_{MediSet}$= Outcome with Mediset
  - Y_0 = Outcome without Mediset
  - "Counterfactual" because only one is observed
  - A missing data problem
- Causal effect of a treatment on an individual:
  - Individual Effect= $Y_{MediSet}$-Y_0
- Population level effect is the average of individual effects
  - Population Effect = $E[Y_{MediSet}-Y_0]$

Marginal Structural Models (MSM)

- Aim to mimic the results of a randomized controlled trial
- Assumption 1: No unmeasured confounders
- Assumption 2: Experimentation in treatment assignment (ETA assumption)
- Three MSM estimators:
  - I. Inverse Probability of Treatment Weighted
  - II. G-computation
  - III. Double Robust
  - Rely on distinct models to control for confounding
  - Improved robustness to model misspecification.

I. Inverse Probability of Treatment Weighting (IPTW) (Figure 1)

- Controls confounding by modeling the probability of using mediset given confounders
  - Fit multivariable logistic regression of mediset use on confounders (**Pr(A=a|W)=g(a|W)**)
  - This model is called the treatment mechanism (**Table 2**)
- This logistic regression model is used to assign weights inversely proportional to the subject's probability of receiving his observed treatment.
  - Corrects for non-random mediset use
  - E.g., Homeless individuals were less likely to use medisets (Homelessness was under-represented among mediset users). Thus, homeless individuals who used medisets receive larger weights.
- The causal effect of mediset use is estimated by fitting a weighted least squares regression of outcome on mediset use.

II. G-computation (Figure 1)

- Controls confounding using standard multivariable regression of outcome on mediset use and confounders
  - **E(Y|A,W) (Tables 3-4)**
- This regression model is used to predict each subject's counterfactual adherence in the presence and absence of mediset use, given her confounder values.
- The causal effect of mediset use is estimated by fitting a least squares regression of predicted counterfactual adherence on mediset use.
- When is G-computation equivalent to standard multivariable regression?
  - Single time point treatment
  - Exposure does not interact with any confounder
  - A linear model is used

III. Double Robust

- Uses
  1) Multivariable regression of outcome on mediset use and confounders (E(Y|A,W)) used in G-computation
  2) Multivariable logistic regression of mediset use on confounders (treatment mechanism) used in IPTW estimation
- Based on estimating function methodology
  - Maximally robust to model misspecification
  - Consistent if the model for either E(Y|A,W) or g(A|W) is correct

Model Selection for Multivariable Regressions

- All multivariable regressions (E(Y|A,W) and g(a|W)) fit using the Deletion/Substitution/Addition algorithm.
  - Data-adaptive regression
  - 5-fold cross validation
  - Considering a maximum of two-way interactions

Inference

- All standard errors were estimated using 200 non-parametric bootstrap samples.
  - To account for repeated measures, bootstrap sampling was based on patient rather than data-point

Confounders

- Time-lagged confounder measurements were used to ensure that confounders occurred before, and thus could not be influenced by, mediset use
  - All potential confounders were lagged by 1 month
  - Viral load, CD4 count, and nadir CD4 count were also lagged by 2 months
- Missing confounder values imputed by carrying the most recent observation forward
  - Missing values for mediset use and outcomes not imputed

Figure 1. Implementation of IPTW and G-computation

Sample data: Simplified Example

ID	Mediset (A)	Prior Adherence (W)	Adherence (Y)
1	1	1	0.7
2	0	0	0.8
3	1	1	0.4
4	1	0	1
5	0	1	0.4
6	0	0	0.7

Implementation of IPTW Estimator

1. Fit logistic regression model of mediset use given prior adherence

$$P(A=1|W)=\frac{1}{1+\exp(-(0.6931-1.3863\times W))}$$

2. Use this model to predict the probability of using medisets for subjects that used medisets, and the probability of not using medisets for subjects that did not use medisets.

P(A=1|W=1) = 0.67
P(A=0|W=1) = 1-0.67=0.33
P(A=1|W=0) = 0.33
P(A=0|W=0) = 1-0.33=0.67

ID	Mediset(A)	Adherence (Y)	Weights=1/predicted probability of observed intervention
1	1	0.7	1.5
2	0	0.8	1.5
3	1	0.4	1.5
4	1	1	3.0
5	0	0.4	3.0
6	0	0.7	1.5

3. Regress observed adherence on mediset, using weights.

Medisets improve adherence 20% $E(Y_1-Y_0)=0.20$

Implementation of G-computation Estimator

1. Fit linear regression model of observed adherence given mediset use and prior adherence

E(Y|A=1,W=1) = 0.55
E(Y|A=0,W=1)= 0.4
E(Y|A=1,W=0)= 1.0
E(Y|A=0,W=0)= 0.75

2. Use this linear regression model to predict counterfactual adherence for each subject in the presence and absence of mediset use.

$$E(Y\mid A,W)=0.75+0.25\mathrm{A}-0.35W-0.1AW$$

ID	Mediset (a)	Counterfactual adherence (Y_a)
1	0	0.4
2	0	0.75
3	0	0.4
4	0	0.75
5	0	0.4
6	0	0.75
1	1	0.55
2	1	1.0
3	1	0.55
4	1	1.0
5	1	0.55
6	1	1.0

3. Regress counterfactual adherence on mediset use in new dataset.

Medisets improve adherence 20% $E(Y_1-Y_0)=0.20$

Conclusions

- Marginal Structural Models were used to estimate the effect of pill box organizers (medisets) on adherence to ART and viral load **(Table 5)**
  - Three separate estimators were employed, which control for confounding using distinct multivariable regression models
- All estimators suggested that mediset use resulted in a significant 4% improvement in adherence
- All estimators supported a significant reduction in log viral load and increased probability of virologic success due to mediset use
- We estimate that pill box organizers may be associated with a cost of approximately $19,000 per quality-adjusted life year. Pill box organizers should be a standard intervention to improve adherence to antiretroviral therapy.

References: www.biostatsresearch.com

van der Laan MJ, Robins JM. *Unified methods for censored longitudinal data and causality* New York: Springer; 2002.
Sinisi S, van der Laan MJ. Deletion/Substitution/Addition algorithm in learning with applications in genomics. *Statistical Applications in Genetics and Molecular Biology*. 2004;3(1):Article 18.
Goldie SJ, Paltiel AD, Weinstein MC, et al. Projecting the cost-effectiveness of adherence interventions in persons with human immunodeficiency virus infection. *Am J Med*. 2003;115(8):632-41.

Funding

This study was funded by NIMH grants 54907 and 63011
Viral load kits were donated by Roche
ML Petersen is funded by a Pre-Doctoral Fellowship from Howard Hughes Medical Institute
MJ van der Laan is funded by NIH grant R01 GM071397
Dr. Bangsberg received additional funding from The Doris Duke Charitable Foundation

Contact:
David Bangsberg, MD,MPH
Associate Professor of Medicine
POB 1373 UCSF
San Francisco, CA 94143-1372
email: db@epi-center.ucsf.edu

University of California San Francisco
UCSF
AIDS Research Institute