Constructing Inverse Probability Weights for Static Interventions

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Acknowledgement

- Slides contributed by Miguel Hernán or adapted from *Causal Inference* (Chapman & Hall/CRC, 2017) by Miguel Hernán and Jamie Robins
  - Any mistakes are my own
  - Chapters of book and SAS, STATA, and R code freely available at http://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/
  - You can "like" Causal Inference at https://www.facebook.com/causalinference

Case Study

Long-Term Effectiveness of Highly Active Antiretroviral Therapy on the Survival of Children and Adolescents with HIV Infection: A 10-Year Follow-Up Study

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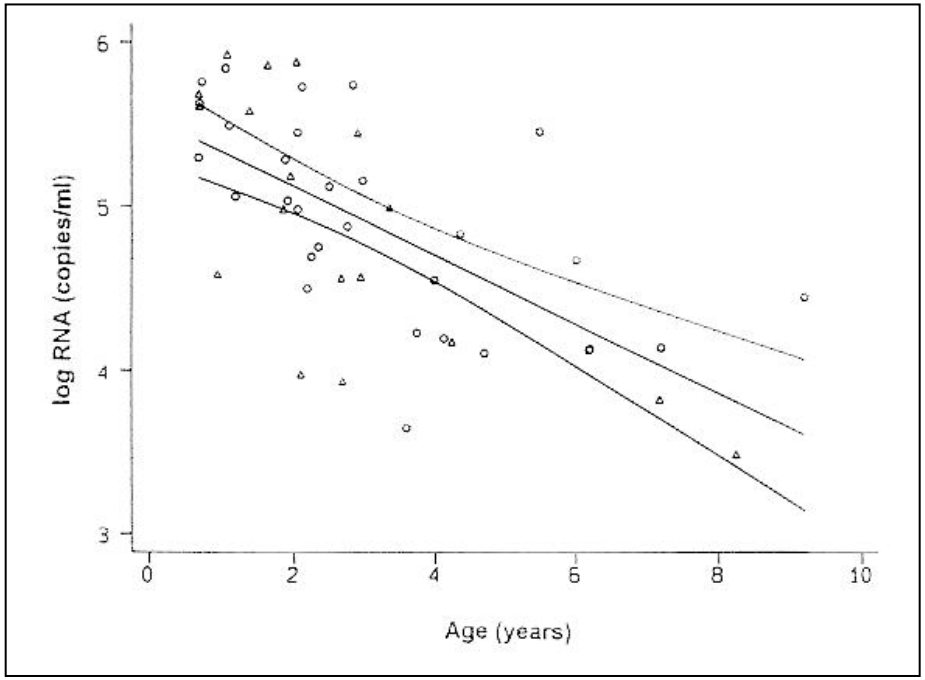
Introduction/Background

- Randomized controlled trials (RCTs) in HIV-infected adults have shown HAART to be highly effective in reducing the risk of mortality
- Natural progression of HIV infection in children is different from adults:
  - HIV RNA levels remain persistently higher than adults for first 2-3 years of life, decreasing to steady state levels in adults after approximately five-years
  - Generalizability of adult trial results?



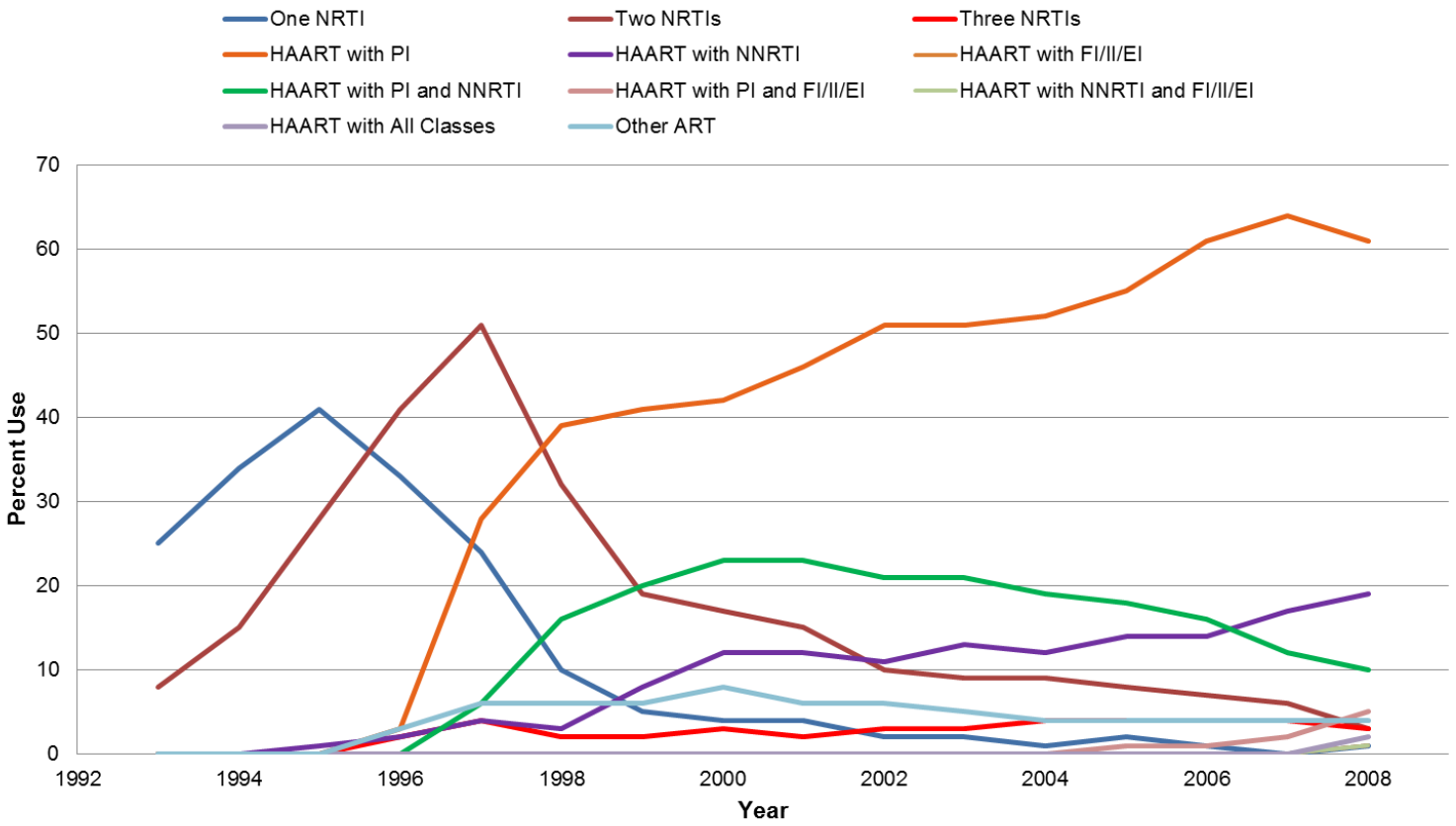
Pediatric Infectious Disease Journal. 15(12):1087-1091, December 1996.

Studies of HAART in Children

- RCTs of HAART in children have focused on intermediate immunologic and virologic endpoints
- Long-term studies of HAART on mortality reliant on observational studies:
  - Italian cohort study: triple combination therapy vs. no therapy – HR=0.29 (0.13-0.67) *(De Martino et al. 2000)*
  - PACTG 219 study: combination therapy with PI vs. therapy without PI – HR=0.33 (0.19-0.58) *(Gortmaker et al. 2000)*

Need to Re-Evaluate Effect of HAART on Mortality

- Previous studies ended follow-up in 1999:
  - Use of new antiretroviral drugs has increased
  - Changes in initial HAART regimens over time



Van Dyke et al. JAIDS 2011; 57:165-173

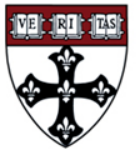
Study question

- What is the effect of HAART on *mortality* among perinatally HIV-infected children?

- Is this a good study question?

Formulation of a well-defined study question ★

- Well-defined causal inference questions can be mapped into a target trial
  - Case example: What is the effect of *initiating* HAART on mortality among perinatally HIV-infected children?
- Specify the protocol of the target trial including:
  - Eligibility criteria
  - Treatment strategies
  - Randomized treatment assignment
  - Follow-up period
  - Outcome
  - Causal contrast of interest
  - Analysis Plan



Hernan, Robins Am J Epidemiol. 2016;183(8):758–764

Pediatric AIDS Clinical Trials Group (PACTG) Protocols 219 & 219C

- Prospective cohort studies of HIV-exposed children (infected and uninfected) from more than 80 study sites in the US
  - Assess the long-term effects of HIV infection and in-utero and postnatal exposure to antiretroviral therapy
    - PACTG 219: April 1993-September 2000
    - PACTG 219C: September 2000-2006
- Extensive clinical, neuropsychological, and laboratory evaluations

Study Population, Exposure, Follow-up

- 1,236 perinatally HIV-infected children enrolled in PACTG 219 and 219C between January 1, 1996 and June 30, 2006
  - Excludes those with previous or current use of HAART at time of study entry
- HAART defined as the use of at least 3 drugs from at least 2 different classes of HIV therapy (NRTIs, NNRTIs, or PIs)
  - Once subjects initiated HAART they were assumed to remain on HAART for the duration of their follow-up
- Follow-up for a maximum of ten years to the last visit at which subject was seen alive or the last visit before June 30, 2006 (i.e. "completion of study")

Classification of treatment strategies according to their time course ★

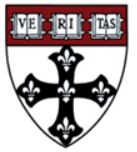
- **Point** interventions
  - Intervention occurs at a single time
  - Examples: one-dose vaccination, short-lived traumatic event, surgery…
    - Intention-to-treat effects in RCTs are about point interventions
- **Sustained** strategies
  - Interventions occur at several times
  - Examples: medical treatments, lifestyle, environmental exposures…
  - Many (most?) questions are about sustained exposures

Classification of sustained treatment strategies ★

- **Static**
  - **a fixed strategy for everyone**
  - **Example: treat with 150mg of daily aspirin during 5 years**
  - **Case example: initiate HAART**
- Dynamic
  - a strategy that assigns different values to different individuals as a function of their evolving characteristics
  - Example: start aspirin treatment if coronary heart disease, stop if stroke
  - Case example: initiate HAART if CD4 drops below 500 cells/mm^3

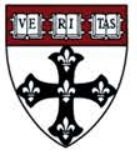
Randomized treatment assignment

- Causal inference methods are methods that emulate randomization
- Why is randomization important?

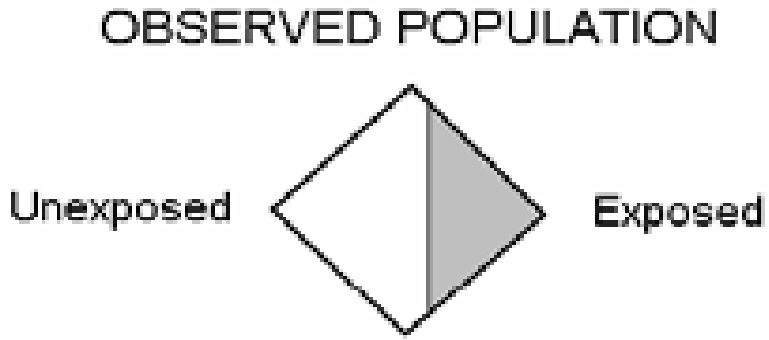


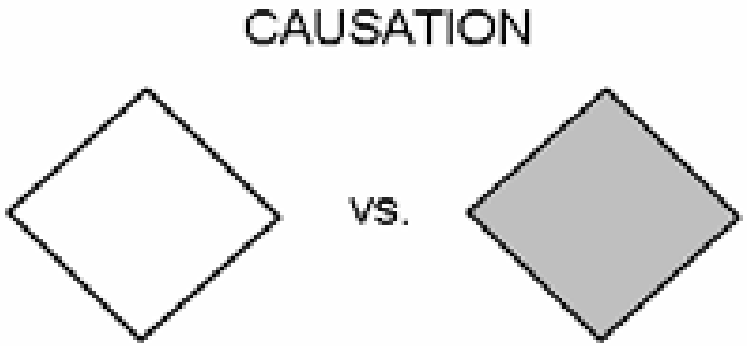
Definition of an average causal effect

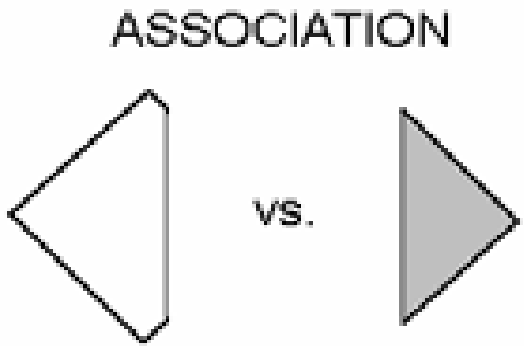
- Each person has two counterfactual outcomes:
  - Outcome Y if treated - $Y_{i,\ a=1}$
  - Outcome Y if untreated – $Y_{i,\ a=0}$
- Individual causal effect:
  - $Y_{i,\ a=1} \neq Y_{i,\ a=0}$
  - Cannot be determined except under extremely strong assumptions
- Average (population) causal effect:
  - $E[Y_{a=1} = 1] \neq E[Y_{a=0} = 1]$
  - Can be estimated under:
    - No assumptions (ideal randomized experiments)
    - Strong assumptions (observational studies)



Causation versus Association







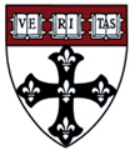
$\Pr[Y_{a=0}=1]$ $\Pr[Y_{a=1}=1]$ $\Pr[Y=1 \mid A=0]$ $\Pr[Y=1 \mid A=1]$

Causation versus Association

- $\Pr[Y_a=1]$
  - proportion of subjects that would have developed the outcome *Y* had all subjects in the population received exposure value *a*
  - (Counterfactual) risk of Y_a
  - Unconditional of marginal probability – "calculated" using data from the whole population
  - Causation: $\Pr[Y_{a=1}=1] \neq \Pr[Y_{a=0} = 1]$
- $\Pr[Y=1 \mid A=a]$
  - Proportion of subjects that developed outcome *Y* among those that received exposure value *a* in the population
  - Risk of Y among those exposed/unexposed
  - Conditional probability – calculated by using data from a subset of the population
  - Association: $\Pr[Y=1 \mid A=1] \neq \Pr[Y=1 \mid A=0]$

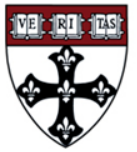
Ideal Randomized Experiment

- Large (near-infinite) population
- No loss to follow-up
- Full compliance (adherence) to assigned exposure or treatment
- Double blind assignment



Randomization (I)

- Assume two exposure groups (treated and untreated)
- Membership in each group is randomly assigned
  - e.g., by a flip of a coin
- First option:
  - Treat subjects in group 1, don't treat subjects in group 2
  - Pr[Y=1 | A=1] is, say, 0.57
- Second option:
  - Treat subjects in group 2, don't treat subjects in group 1
  - What is the risk? Pr[Y=1 | A=1] is 0.57



Randomization (II)

- When group membership is randomly assigned, risks are the same
- Both groups are comparable or **exchangeable**
- Exchangeability is the consequence of randomization

Exchangeability

- Subjects in group 1 would have had the same risk as those in group 2 had they received the treatment of those in group 2
- The counterfactual risk among the treated equals the counterfactual risk among the untreated under the same exposure level
- $\Pr[Y_a=1 \mid A=1] = \Pr[Y_a=1 \mid A=0] \Leftrightarrow A \perp\!\!\!\perp Y_a \Leftrightarrow Y_a \perp\!\!\!\perp A$
- Implies lack of confounding

In ideal randomized experiments

- Pr[Y=1 | A=1] is equal to Pr[$Y_{a=1}$=1]
- Pr[Y=1 | A=0] is equal to Pr[$Y_{a=0}$=1]

- Therefore the associational risk ratio
  - Pr[Y=1 | A=1]/ Pr[Y=1 | A=0]

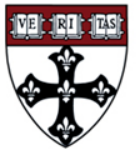
  is equal to the causal risk ratio
  - Pr[$Y_{a=1}$=1]/ Pr[$Y_{a=0}$=1]

Why is Pr[Y=1/A=1] is equal to Pr[$Y_{a=1}$=1]

- A two step proof:

1. Pr[Y=1 | A=1] = Pr[$Y_{a=1}$=1 | A=1]
   - by definition of a counterfactual variable (i.e., consistency)
2. Pr[$Y_{a=1}$=1 | A=1] = Pr[$Y_{a=1}$=1 | A=0] = Pr[$Y_{a=1}$=1]
   - by randomization – (i.e., exchangeability)

- Step 2 not generally true in the absence of randomization

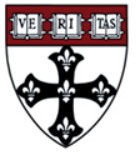


In an ideal randomized experiment

- Association *is* causation
  - Because randomization produced exchangeability

- We have a method for causal inference!
  - No need for adjustments of any sort
  - Assumption-free!

….However, real randomized experiments are not ideal randomized experiments….No clear-cut separation between real randomized experiments and observational studies…



Dead end?

- Exchangeability (a consequence of randomization) is a condition for causal inference
- Exchangeability is not generally an acceptable assumption in observational studies
  - Exposed and unexposed generally not comparable
    - Individuals who receive a heart transplant may have more severe disease
    - Case example: children who initiate HAART may have more severe disease than those who don't (i.e., confounding by indication)
- A condition weaker than exchangeability is needed for causal inference from observational data

Hope

- Consider only individuals with the same pre-exposure prognostic factors
- Then the exposed and unexposed may be exchangeable
  - e.g., among individuals with an ejection fraction of 10%, those who do and do not receive a heart transplant may be comparable
  - e.g., among individuals with CD4 count <100, those who do and do not receive antiretroviral therapy may be comparable
- This is often reasonable
  - Especially if conditioning on many pre-exposure covariates L

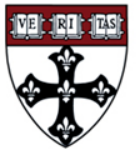
Conditional Exchangeability

- Within levels of the covariates, L, exposed subjects would have had the same risk as unexposed subjects had they been unexposed, and vice versa
- Counterfactual risk is the same in the exposed and the unexposed with the same level of L
- $\Pr[Y_a=1 \mid A=1, L=l] = \Pr[Y_a=1 \mid A=0, L=l] \Leftrightarrow A \perp\!\!\!\perp Y_a \mid L=l \Leftrightarrow Y_a \perp\!\!\!\perp A \mid L=l$
- Equivalent to randomization within levels of L
- Implies no unmeasured (residual) confounding within levels of the measured covariates L

In an observational study

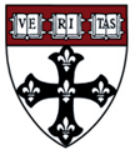
- Association is causation within levels of the covariates
  - Under the **assumption** of conditional exchangeability

- We have a method for causal inference from observational data that is not assumption-free
  - But the need to rely on this assumption is not THE problem



THE problem

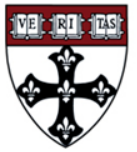
- The assumption of conditional exchangeability is **untestable**
  - Even if there is conditional exchangeability, there is no way we can know it with certainty
- This is why causal inference from observational data is controversial
  - We can use expert knowledge to enhance plausibility of the assumption
    - Measure as many relevant pre-exposure covariates as possible
  - Can only hope that the assumption is approximately true (i.e., there may be confounding due to unmeasured factors)



Methods to compute causal effects

- Stratification
- Regression
- Matching
- Standardization
- Inverse probability weighting

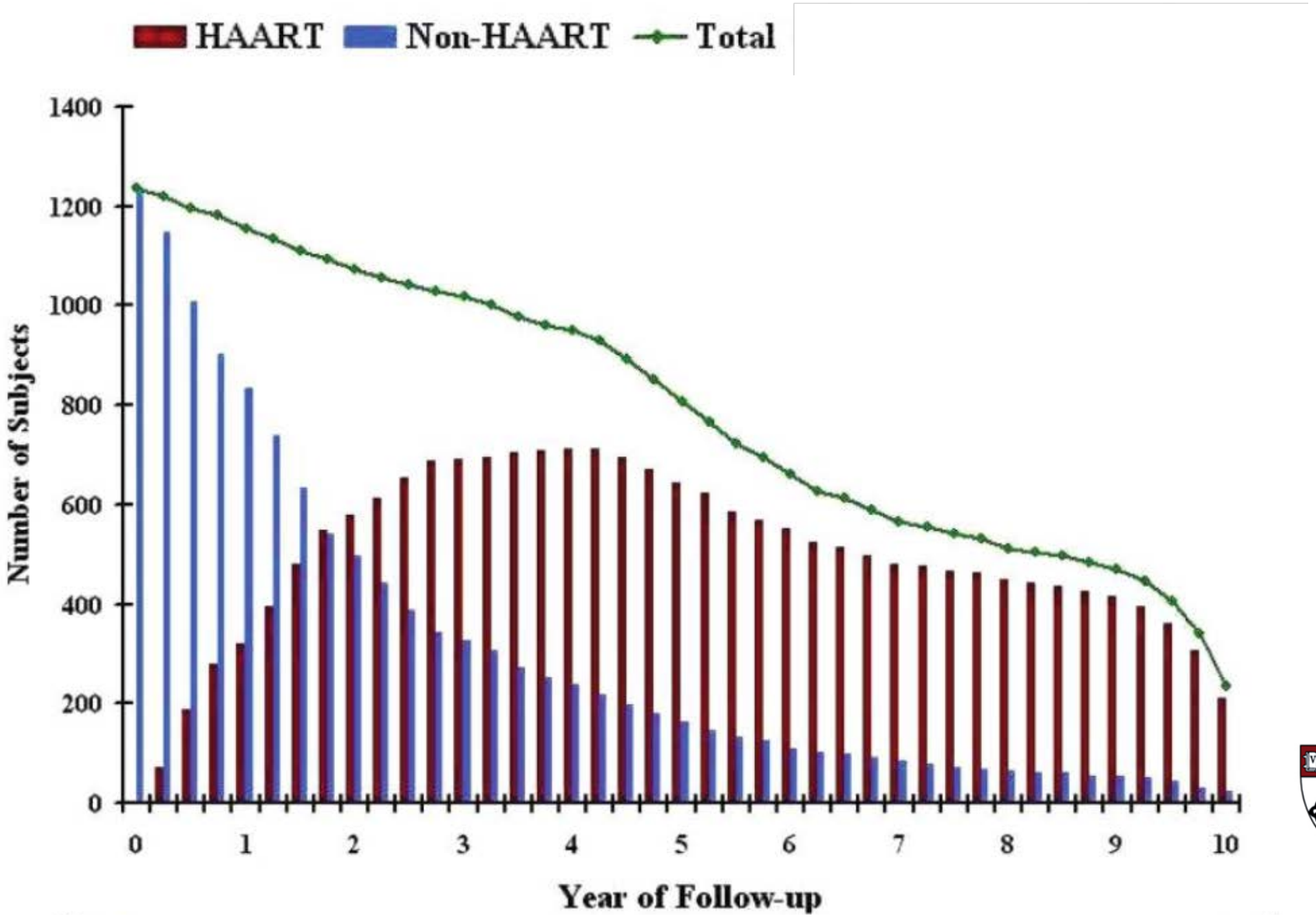
⇨ALL assuming conditional exchangeability



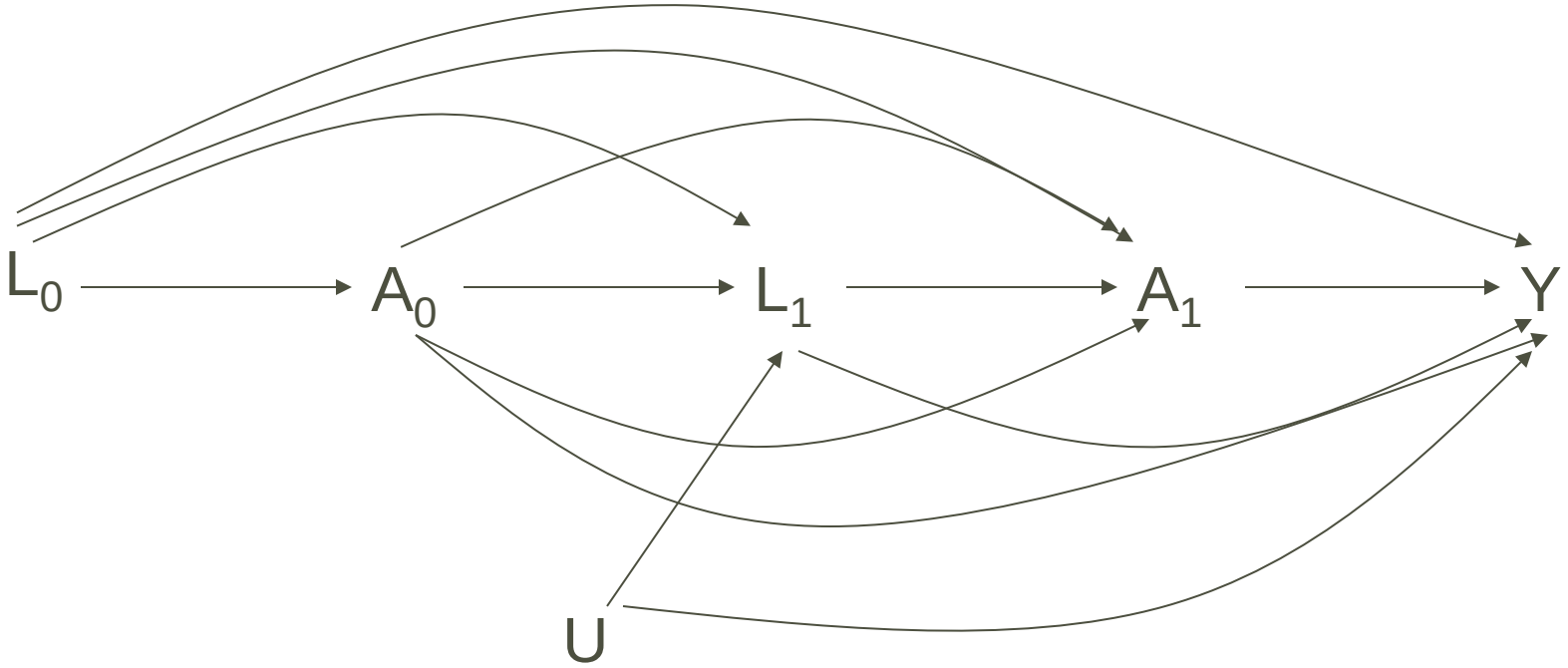
Choice of method depends on type of strategies

- Comparison of strategies involving point interventions only
  - All methods work
  - if all baseline confounders are measured
- Comparison of sustained strategies
  - Generally only causal inference methods work
  - Time-varying treatments imply time-varying confounders
    - possible treatment-confounder feedback
  - Conventional methods may introduce bias even when sufficient data are available on time-varying treatments and time-varying confounders

Case example: HAART initiation over time



Case Example: Directed Acyclic Graph



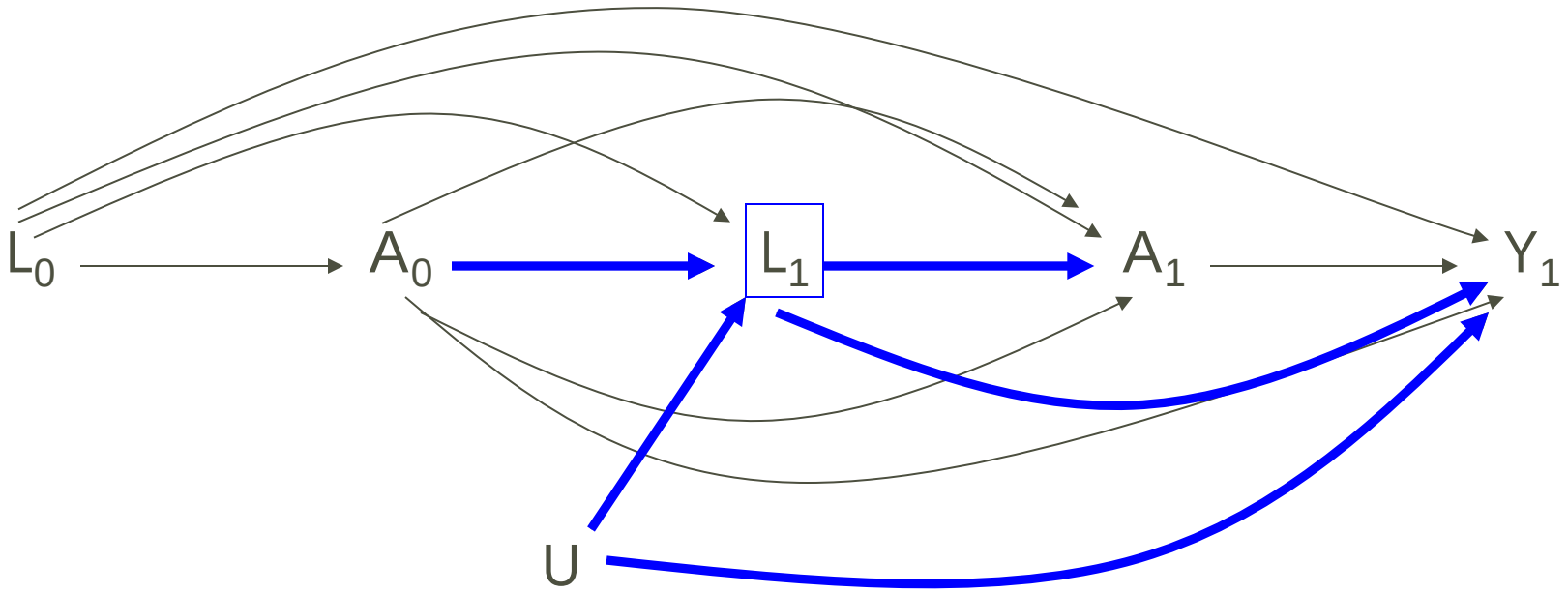
Where Li = confounder (CD4, viral load, etc) information at time i,

Ai = treatment (HAART) information at time i, and

Y = outcome (mortality) information at time i.

U = unmeasured covariate

Problem with Stratified Analytic Approach ★



- Interested in the cumulative effect of treatment.
- L_1 is affected by A_0 – if we adjust for L_1 then A_0 effect is confounded.
- Also could induce selection bias (collider).

Inverse probability weighting

- YOU will compute the causal risk ratio using inverse probability weighting (IPW) in an observational study

  - i.e., you will compute $\Pr[Y_{a=1}=1]/\Pr[Y_{a=0}=1]$ under conditional exchangeability

A simplified observational study

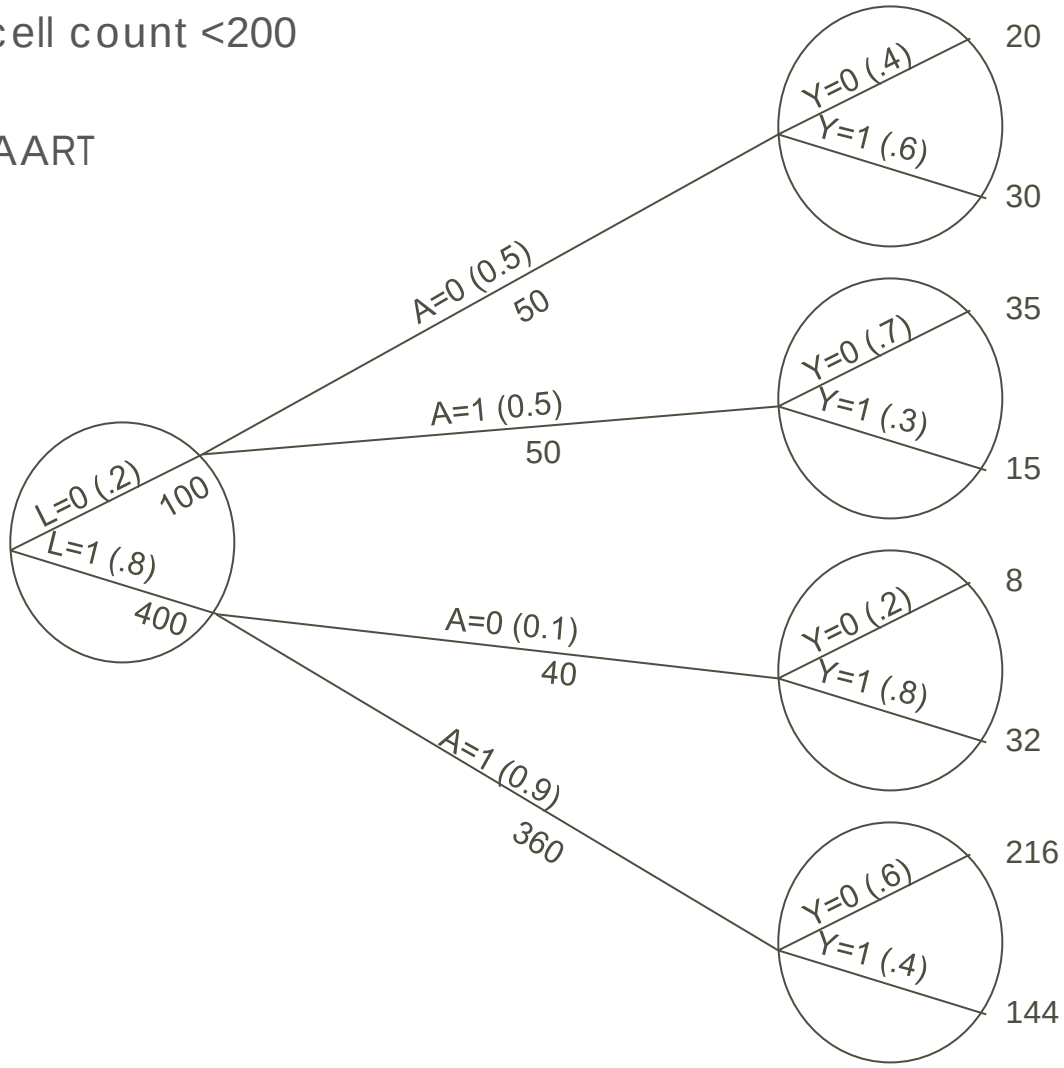
- 500 HIV-infected adults
- Variables:
  - *L=1:* CD4 cell count <200 cells/mm^3
  - *A=1:* on highly active antiretroviral therapy (HAART)
  - *Y=1:* AIDS
- Treatment status is decided after looking at CD4 cell count
- No loss to follow-up

The data summarized in a table

	L=0		*L=1*	
	Y=1	*Y=0*	*Y=1*	*Y=0*
A=1	15	35	144	216
A=0	30	20	32	8

The data summarized in a tree

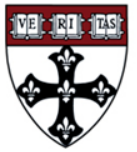
- *L=1:* CD4 cell count <200 cells/mm^3
- *A=1:* on HAART
- *Y=1:* AIDS



Your goal

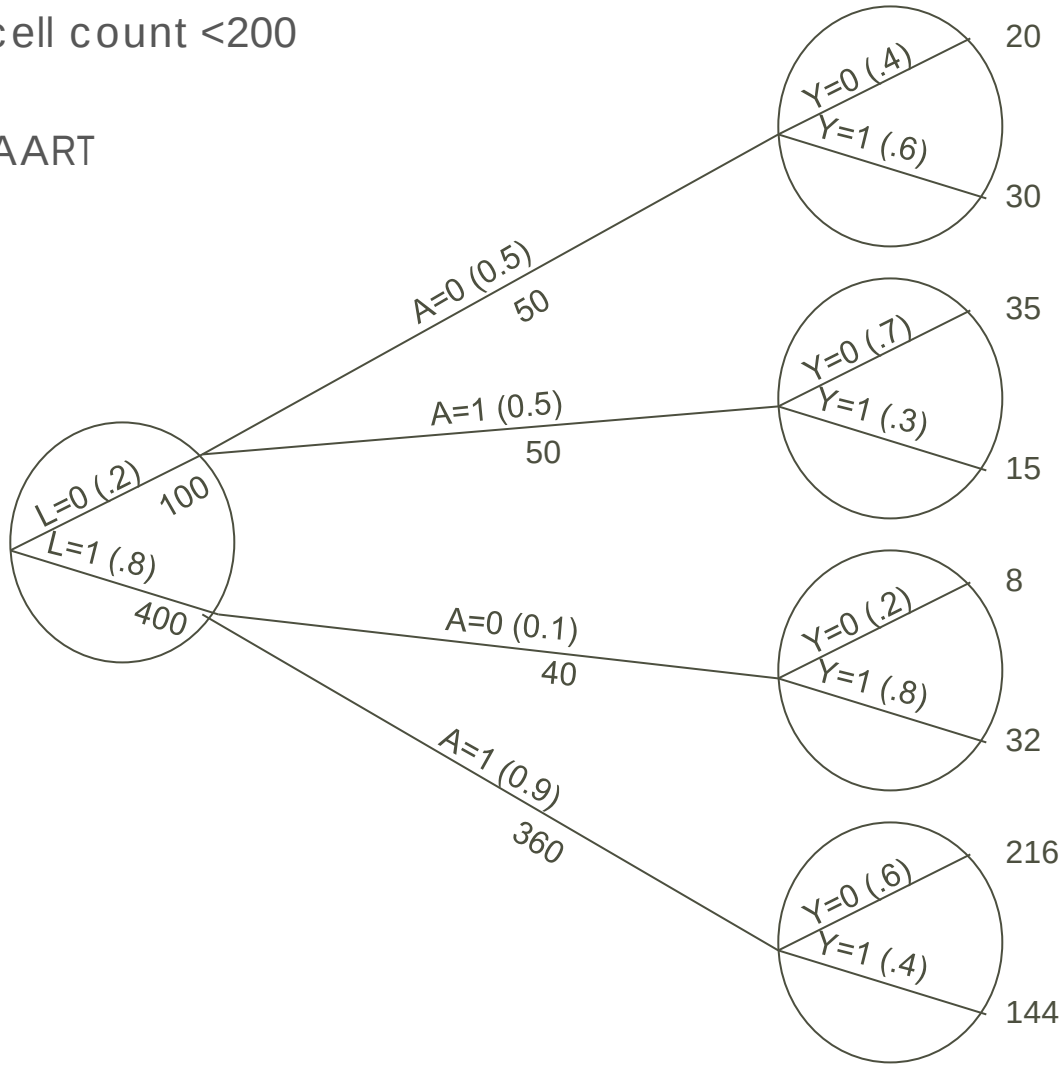
- To compute the effect of HAART on the risk of AIDS on the causal risk ratio scale
  - $\Pr[Y_{a=1}=1]/\Pr[Y_{a=0}=1]$
  - Assuming conditional exchangeability within levels of L

- First, compute $\Pr[Y_{a=0}=1]$
- Second, compute $\Pr[Y_{a=1}=1]$



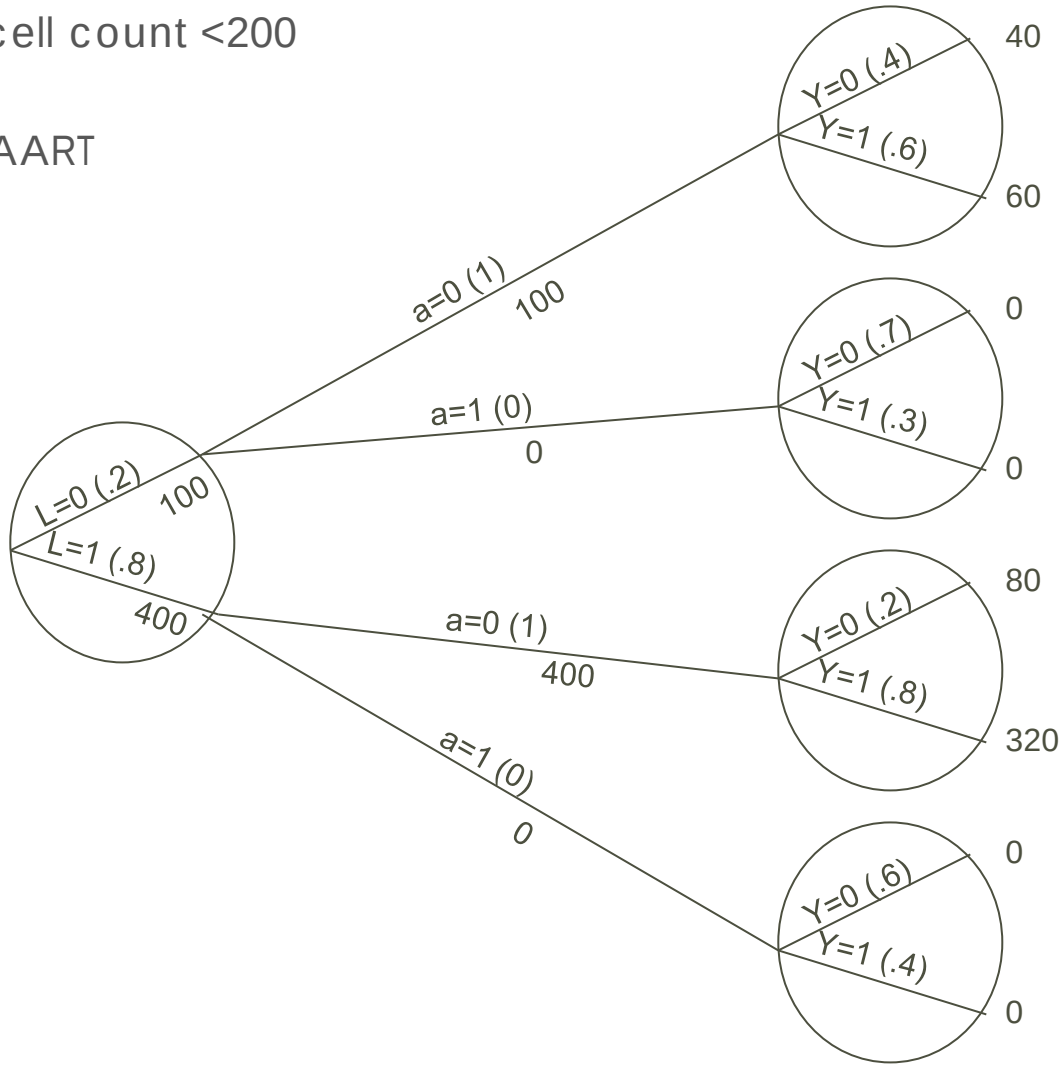
Original data

- *L=1:* CD4 cell count <200 cells/mm^3
- *A=1:* on HAART
- *Y=1:* AIDS



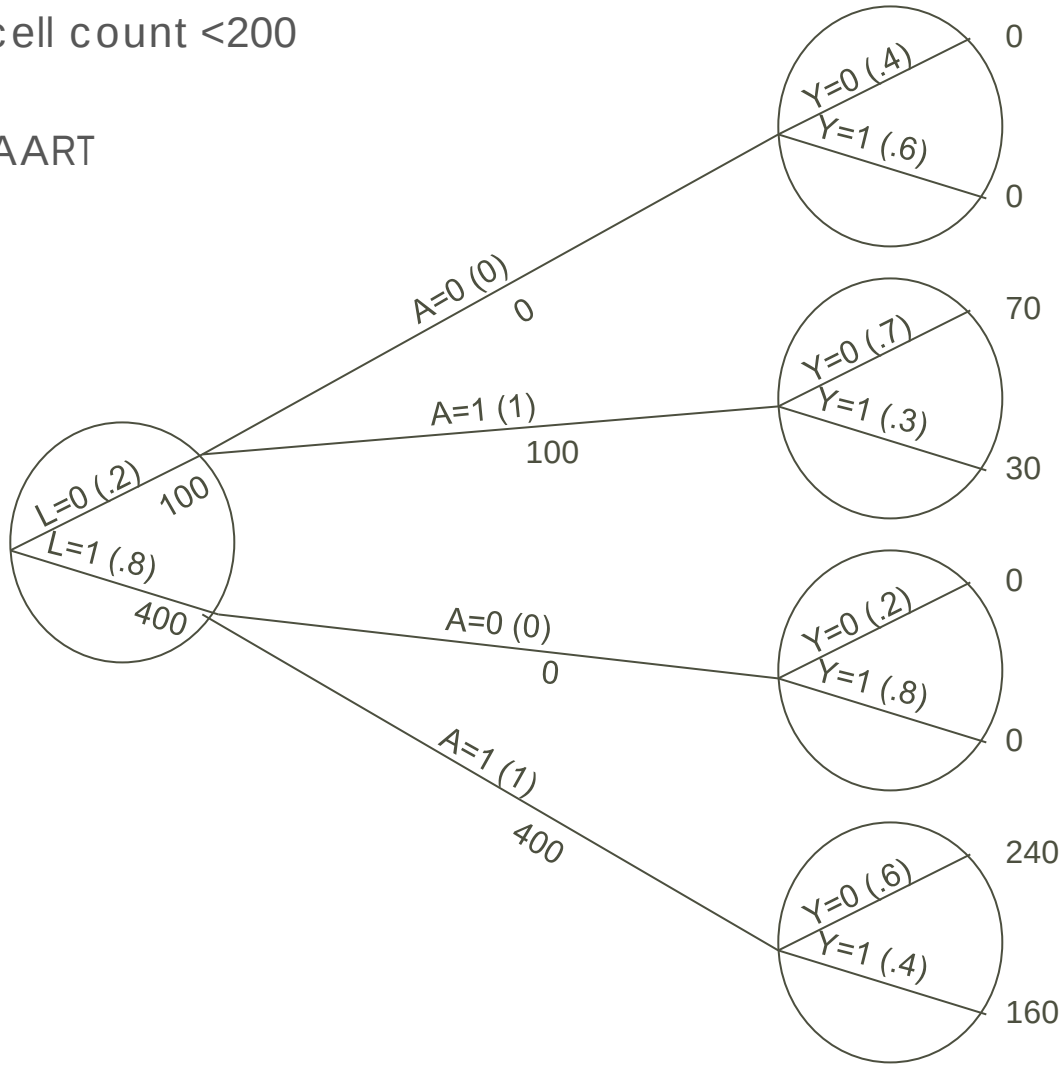
Data had everyone been untreated

- *L=1:* CD4 cell count <200 cells/mm^3
- *A=1:* on HAART
- *Y=1:* AIDS



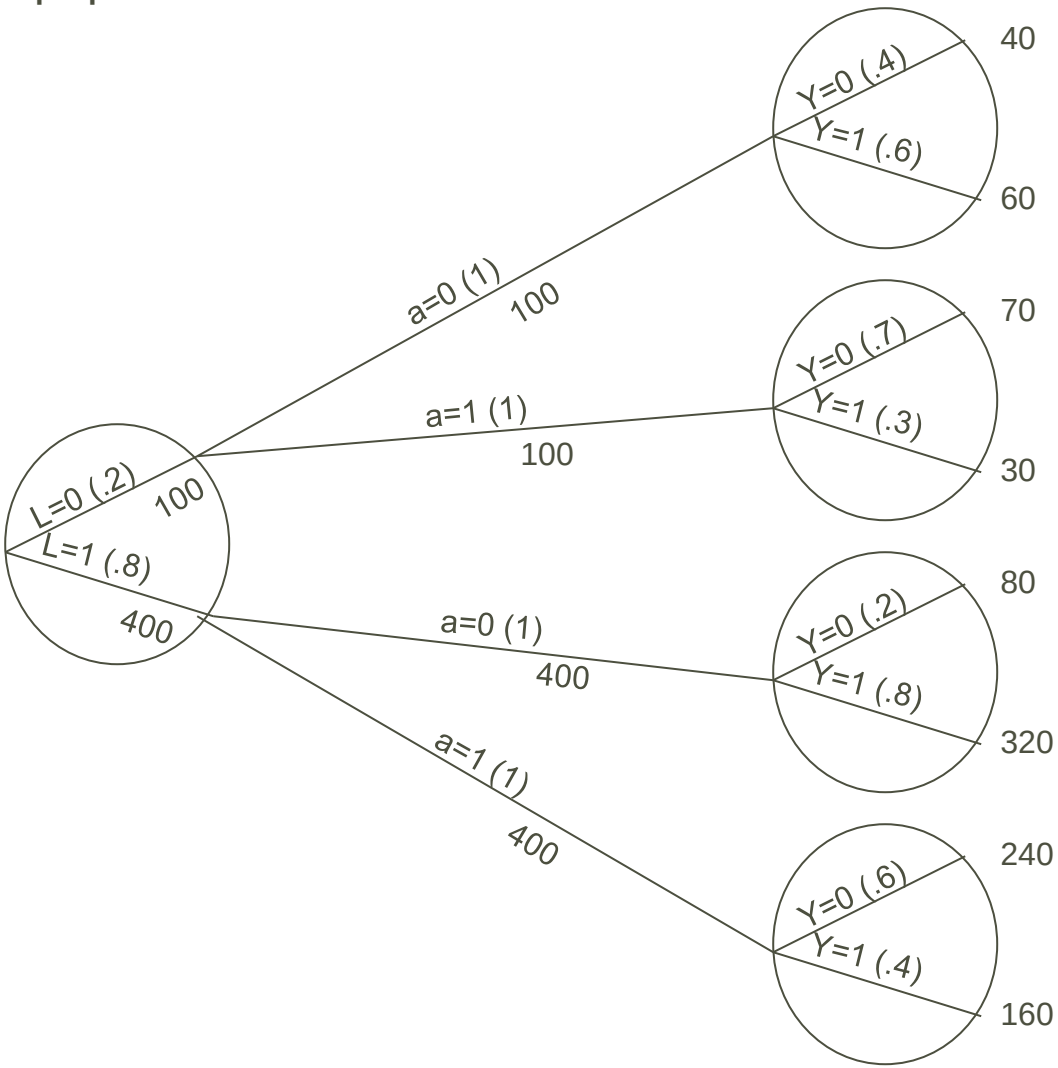
Data had everyone been treated

- *L=1:* CD4 cell count <200 cells/mm^3
- *A=1:* on HAART
- *Y=1:* AIDS



Data had everyone been treated and untreated

Pseudopopulation



Pseudopopulation data analysis

	$Y_a=1$	$Y_a=0$
a=1	190	310
a=0	380	120

- Pr[$Y_{a=1}$=1] = 190/(190+310) = 0.38
- Pr[$Y_{a=0}$=1] = 380/(380+120) = 0.76
- Causal risk ratio = 0.38/0.76 = 0.5
- YOU DID IT! Computed the causal risk ratio using IPW

Which assumption are you making?

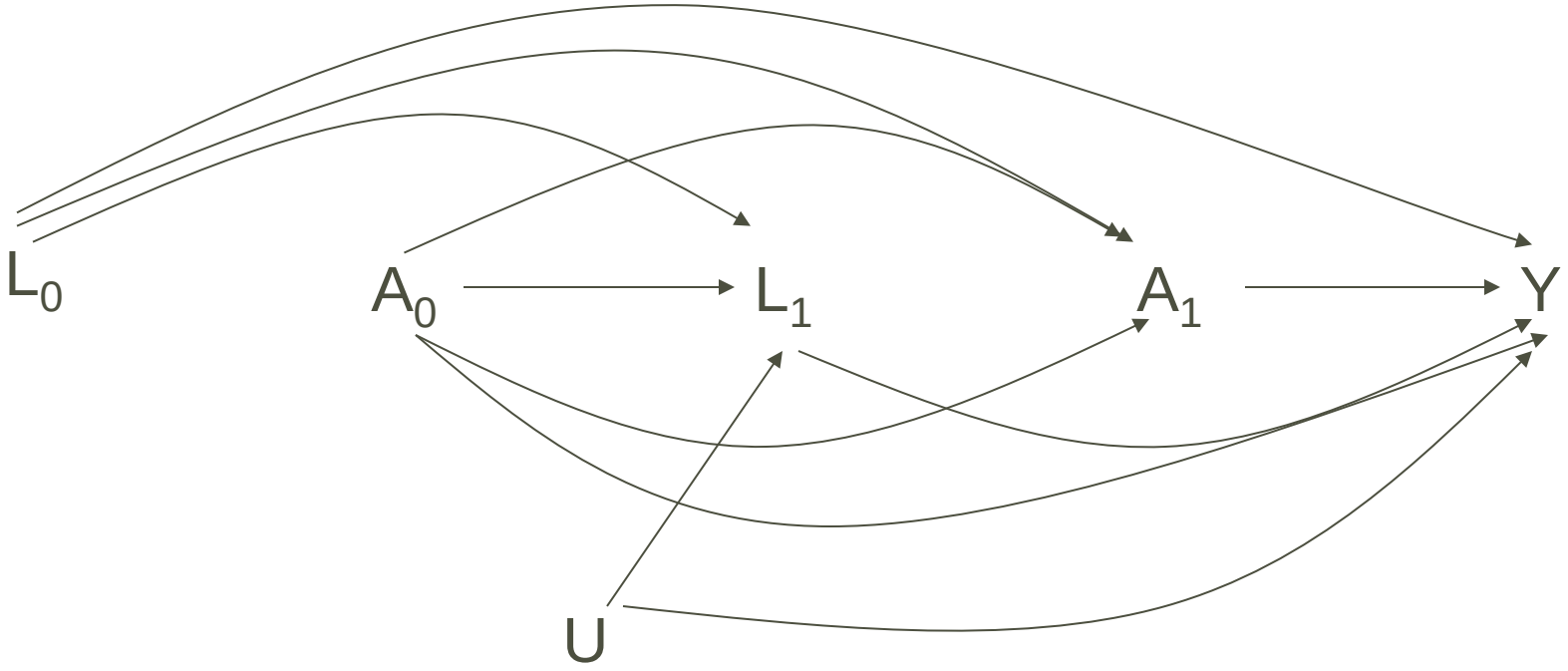
$$Y_a \amalg A \mid L=l$$

- Conditional exchangeability in the population
  - Exposure is randomized within levels of L
  - No unmeasured confounding within levels of the measured variable L
- Within levels of L, the risk among the exposed if they were unexposed is the same as the risk among the unexposed in the population
  - and vice versa

Under conditional exchangeability

- The observational study in the original population is a randomized experiment *within levels of L*
- The study in the pseudopopulation created by IPW is a randomized experiment
  - Exposed and unexposed subjects are (unconditionally) exchangeable because they are the same individuals
  - Exposure is randomized (i.e. equally probable across levels of the covariate L)
  - There is no confounding
- In the pseudopopulation, causal effects can be estimated as in a randomized experiment
  - No need for adjustment of any sort

Directed Acyclic Graph in Pseudopopulation



Use of models for IPW

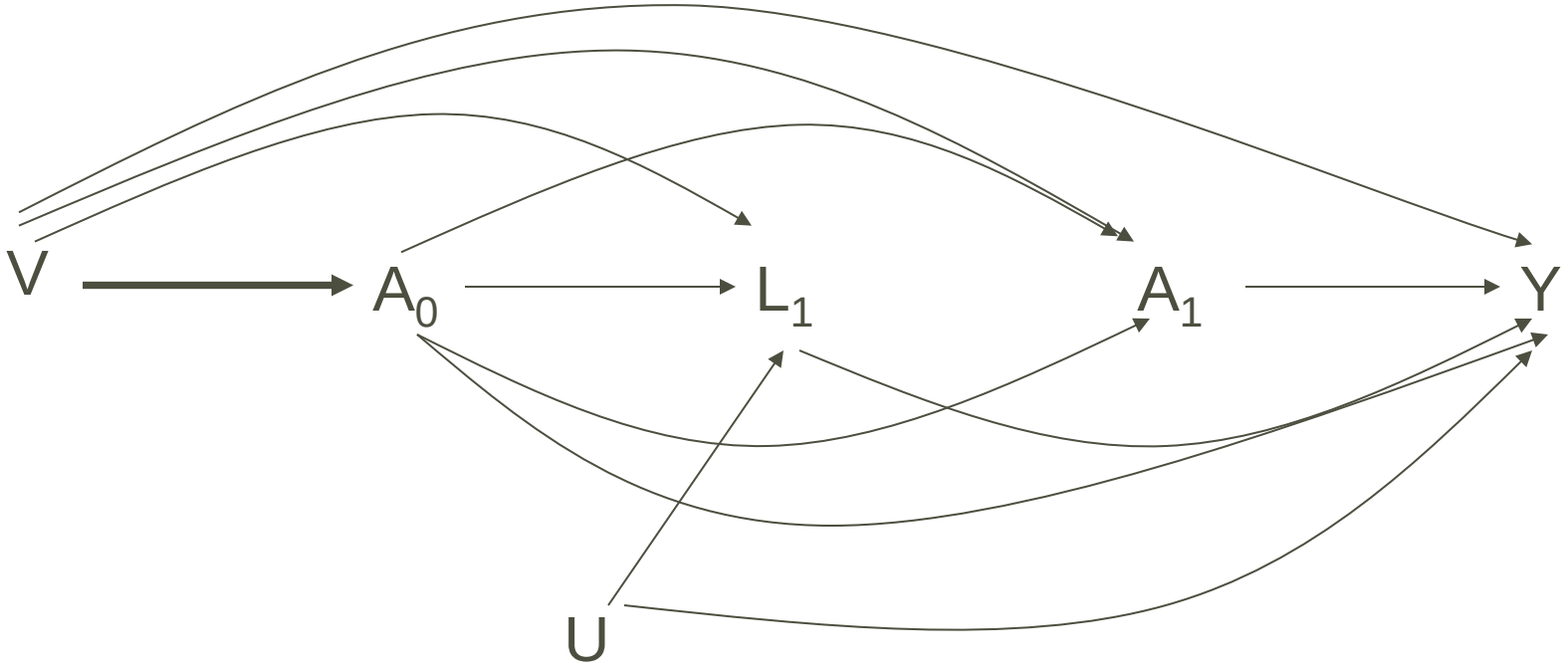
- Reality is we deal with high-dimensional data with multiple covariates (Ls), some with multiple levels
  - Cannot obtain meaningful non-parametric estimates of the weights
  - Model the probability of exposure with Ls as the covariates
- Some individuals may contribute a really high weight due to their a relatively small probability of having the exposure they had given their covariate history
  - Stabilize the weights by using the probability of treatment in the numerator
  - Apply stabilized weights (SW) to estimate the parameters of a marginal structural model
    - reduce variance in model for the outcome

Stabilized Inverse Probability of Treatment Weights

$$SW(V) = \prod_{k=0}^{K} \frac{f\{A(k)|\overline{A}(k-1), V\}}{f\{A(k)|\overline{A}(k-1), \overline{L}(k)\}}$$

- Numerator: The probability that the subject received his/her observed treatment at week k, conditional on past treatment history and baseline covariates.
- Denominator: The probability that the subject received his/her own observed treatment at week k, given past treatment history and covariate history (baseline and time-dependent).

Directed Acyclic Graph in Pseudopopulation with SW



Estimating IPW and fitting the MSM

- Estimate SW for both treatment and censoring:
  - Fit logistic regression models for treatment and censoring
  - Use predicted values from the models to calculate stabilized weights
- Estimate the IPW estimate of HAART on mortality:
  - Fit weighted pooled logistic model using the estimated stabilized weights.
  - Use “robust” variance estimators (GEE) to allow for correlated observations created by weighting – conservative 95% CI.

Case Example: Confounders

- Age
- Sex
- Race/Ethnicity
- Week of Follow-up
- Calendar Year
- CDC Clinical Category
- CD4%
- Total lymphocyte count
- White blood cell count
- Hematocrit
- Albumin

SAS Code for Estimating Numerator and Denominator for Treatment IPW

```
/*Model 1-Numerator of treatment weight - Modeling prob. of remaining off HAART*/ ;
proc logistic data=popnall ;
where week<=hrtweek or hrtweek=. ;
model onhrt= cfbcd4 cfbcd41 cfbcd42 cfbcdc btlclow bwbclow bhq1low baq1low week week1
        age0_1 age2_3 age4_6 YEAR96 YEAR97 YEAR98
            male black hispanic ;
output out=model1 (keep=patid week phrt_0) p=phrt_0 ;
run ;

/*Model 2 - Denominator of treatment weight - Modeling prob. of remaining off HAART*/ ;
proc logistic data=popnall ;
where week<=hrtweek or hrtweek=. ;
model onhrt= cfbcd4 cfbcd41 cfbcd42 cfbcdc week week1 btlclow bwbclow bhq1low baq1low
        age0_1 age2_3 age4_6 YEAR96 YEAR97 YEAR98
    male black hispanic lvcd4 lvcd41 lvcd42 lvcdc tlclow wbclow hq1low aq1low;
output out=model2 (keep=patid week phrt_w) p=phrt_w ;
run ;
```

SAS Code for Estimating Numerator and Denominator for Censoring IPW

```
/*Model 3-Numerator of censoring weight - Modeling prob. of remaining uncensored*/ ;
proc logistic data=popnall ;
model censor= onhrt cfbcd4 cfbcd41 cfbcd42 cfbcdc btlclow bwbclow bhq1low baq1low
        week week1 age0_1 age2_3 age4_6
    YEAR96 YEAR97 YEAR98 male black hispanic  ;
output out=model3 (keep=patid week punc_0) p=punc_0 ;
run ;

/*Model 4 - Denominator of censoring weight - Modeling prob. of remaining uncensored*/ ;
proc logistic data=popnall ;
model censor= onhrt cfbcd4 cfbcd41 cfbcd42 cfbcdc btlclow bwbclow bhq1low baq1low
    week week1 age0_1 age2_3 age4_6 YEAR96 YEAR97 YEAR98 male black hispanic
    lvcd4 lvcd41 lvcd42 lvcdc tlclow wbclow hq1low aq1low;
output out=model4 (keep=patid week punc_w) p=punc_w ;
run ;
```

SAS Code for Calculating IPW and stabilized IPW (1)

```
data main_w ;
merge model1 model2 model3 model4 popnall ;
by patid week ;
/*variable ending with _0 refer to the numerator of the weights
  variable ending with _w refer to the denominator of the weights*/ ;

/*reset the variables for a new patient*/ ;
if first.patid then do ;
k1_0 = 1 ; k2_0 = 1 ; k1_w = 1 ; k2_w = 1 ; end ;
retain k1_0 k2_0 k1_w k2_w ;

/*Inverse probability of censoring weights*/
k2_0 = k2_0*punc_0 ;
k2_w = k2_w*punc_w ;

/*Inverse probability of treatment weights*/
/*patients not on HAART*/
if hrtweek>week or hrtweek = . then do ;
k1_0 = k1_0*phrt_0 ;
k1_w = k1_w*phrt_w ;
end ;

/*patients that start HAART this week*/
else if hrtweek=week then do ;
k1_0 = k1_0*(1-phrt_0) ;
k1_w = k1_w*(1-phrt_w) ;
end ;

/*patients that have already started HAART*/
else do ;
k1_0=k1_0 ;
k1_w=k1_w ;
end ;

/*Stabilized weights and non stabilized weights*/ ;
stabw = (k1_0*k2_0)/(k1_w*k2_w) ;
nstabw= 1/(k1_w*k2_w) ;

*Stabilized Treatment weight* ;
trtwght = k1_0/k1_w ;
*Stabilized Censoring weight* ;
cenwght = k2_0/k2_w ;
run ;
```

Example Data

Patid	Week	HAART	Censored	k1_0 IPTWnum	phrt_0 TrtPredictNum	k1_w IPTWden	phrt_w TrtPredictDen	k2_0 IPCWnum	punc_0 CensPredictNum	k2_w IPCWden	punc_w CensPredictDen
49360	0	0	0	0.96375	0.96375	0.9658	0.9658	0.98868	0.98868	0.97466	0.97466
49360	13	0	0	0.92911	0.96406	0.93651	0.96967	0.97643	0.98761	0.95619	0.98105
49360	26	0	0	0.89599	0.96436	0.90843	0.97002	0.96318	0.98643	0.93807	0.98105
49360	39	0	0	0.86433	0.96466	0.8815	0.97036	0.94888	0.98515	0.9203	0.98105
49360	52	0	0	0.83404	0.96496	0.85273	0.96735	0.93346	0.98375	0.89698	0.97466
49360	65	1	0	0.02898	0.96525	0.03368	0.96051	0.92481	0.99074	0.87097	0.97101
49360	78	1	0	0.02898	.	0.03368	.	0.91543	0.98986	0.84129	0.96592
49360	91	1	0	0.02898	.	0.03368	.	0.90526	0.98889	0.81261	0.96592
49360	104	1	0	0.02898	.	0.03368	.	0.89426	0.98784	0.77494	0.95364
49360	117	1	0	0.02898	.	0.03368	.	0.88235	0.98669	0.73902	0.95364
49360	130	1	0	0.02898	.	0.03368	.	0.8695	0.98543	0.71683	0.96997
49360	143	1	0	0.02898	.	0.03368	.	0.85564	0.98406	0.6836	0.95364
49360	156	1	0	0.02898	.	0.03368	.	0.84071	0.98255	0.65191	0.95364
49360	169	1	0	0.02898	.	0.03368	.	0.82466	0.98091	0.62169	0.95364
49360	182	1	0	0.02898	.	0.03368	.	0.80743	0.97912	0.59287	0.95364
49360	195	1	0	0.02898	.	0.03368	.	0.78899	0.97716	0.56539	0.95364
49360	208	1	0	0.02898	.	0.03368	.	0.76928	0.97502	0.53918	0.95364
49360	221	1	0	0.02898	.	0.03368	.	0.74827	0.97269	0.48733	0.90384
49360	234	1	0	0.02898	.	0.03368	.	0.72593	0.97015	0.45571	0.93512
49360	247	1	0	0.02898	.	0.03368	.	0.70225	0.96737	0.43398	0.95232
49360	260	1	0	0.02898	.	0.03368	.	0.67722	0.96436	0.41329	0.95232
49360	273	1	0	0.02898	.	0.03368	.	0.65085	0.96107	0.3863	0.93471
49360	286	1	0	0.02898	.	0.03368	.	0.62318	0.95749	0.35013	0.90637
49360	299	1	0	0.02898	.	0.03368	.	0.59427	0.9536	0.32502	0.92826
49360	312	1	0	0.02898	.	0.03368	.	0.56418	0.94937	0.3017	0.92826
49360	325	1	0	0.02898	.	0.03368	.	0.53303	0.94478	0.28005	0.92826
49360	338	1	1	0.02898	.	0.03368	.	0.50095	0.9398	0.26063	0.93063

Example data worksheet

Patid	Week	HAART	Censored	k1_0 IPTWnum	phrt_0 TrtPredictNum	k1_w IPTWden	phrt_w TrtPredictDen	k2_0 IPCWnum	punc_0 CensPredictNum	k2_w IPCWden	punc_w CensPredictDen
49488	0	0	0		0.96972		0.97553		0.98239		0.94649
49488	13	0	0		0.96998		0.97967		0.98074		0.96081
49488	26	1	0		0.97023		0.97609		0.989		0.93731
49488	39	1	0		.		.		0.98796		0.93153
49488	52	1	0		.		.		0.98682		0.93941
49488	65	1	0		.		.		0.98557		0.93731
49488	78	1	0		.		.		0.98421		0.93731
49488	91	1	1		.		.		0.98272		0.93771

Example data worksheet – calculate SW

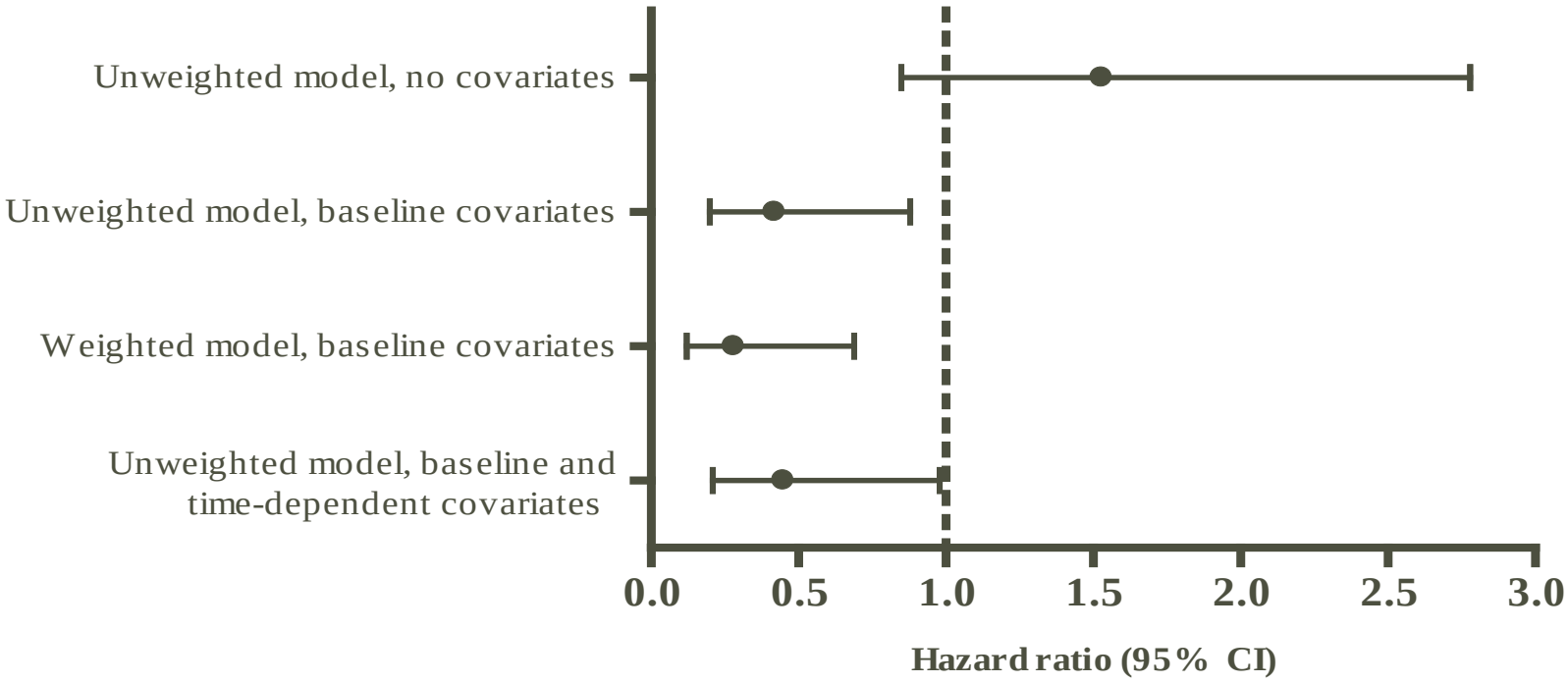
Patid	Week	k1_0 IPTWnum	k1_w IPTWden	k2_0 IPCWnum	k2_w IPCWden	Stabilized Weight
49488	0	0.96972	0.97553	0.98239	0.94649	
49488	13	0.9406	0.9557	0.96347	0.9094	
49488	26	0.028	0.02285	0.95287	0.85239	
49488	39	0.028	0.02285	0.9414	0.79402	
49488	52	0.028	0.02285	0.92899	0.74591	
49488	65	0.028	0.02285	0.91559	0.69915	
49488	78	0.028	0.02285	0.90113	0.65532	
49488	91	0.028	0.02285	0.88556	0.6145	

SAS Code for Final MSM

```
proc genmod data=main_w descending  ;
ods exclude ClassLevelInfo TypeIII Association ;
class patid ;
model status= onhrt week week1 cfbcd4 cfbcd41 cfbcd42 cfbcdc btlclow bwbclow bhq1low baq1low
            age0_1 age2_3 age4_6 YEAR96 YEAR97 YEAR98 male black hispanic

                    /link=logit dist=bin ;
scwgt stabw ;
repeated subject=patid/type=ind ;
estimate 'Beta onhrt' onhrt 1/exp ;
estimate 'HR age0_1' age0_1 1/exp ;
estimate 'HR age2_3' age2_3 1/exp ;
estimate 'HR age4_6' age4_6 1/exp ;
estimate 'HR Year96' YEAR96 1/exp ;
estimate 'HR Year97' YEAR97 1/exp ;
estimate 'HR Year98' YEAR98 1/exp ;
estimate 'HR male' male 1/exp ;
estimate 'HR black' black 1/exp ;
estimate 'HR hispanic' hispanic 1/exp ;
estimate 'Beta cfbcdc' cfbcdc 1/exp ;
estimate 'Beta btlclow' btlclow 1/exp ;
estimate 'Beta bwbclow' bwbclow 1/exp ;
estimate 'Beta bhq1low' bhq1low 1/exp ;
estimate 'Beta baq1low' baq1low 1/exp ;
run ;
```

Estimated Effect of HAART on Mortality from Unweighted (Standard) and Weighted Models



Assumptions for IPW estimation of a MSM

- Conditional exchangeability within levels of measured covariates
  - Unable to adjust for HIV-1 viral load
  - Used to guide decisions about when to initiate HAART in recent years and is associated with mortality
  - Reported HR likely to be underestimated
- Correct model specification for all models to estimate weights and final MSM

Conclusions

- Long-term HAART use (> 5 years) is associated with significantly lower mortality among children and adolescents infected with HIV-1 compared to non-HAART use.
  - Support current US pediatric guidelines

- Results comparable to adult RCT and previous pediatric observational studies
  - Support expanded delivery of care to HIV-infected children globally

Conclusions

- Continued follow-up is needed as this population ages and matures with the use of HAART
  - Need to estimate the effects of prolonged use of HAART on immune function, growth, sexual maturation, and quality of life parameters

Acknowledgements

- Children and Families of PACTG 219/219C
- PACTG 219/219C Team and Participating Institutions
- Funded by NIAID, NICHD
- Supported by the Statistical and Data Analysis Center (SDAC) of the PACTG under the NIAID cooperative agreement No. 5 U01 AI141110
- T32 HIV/AIDS Training Grant