



## Practice of Epidemiology

# An Illustration of Inverse Probability Weighting to Estimate Policy-Relevant Causal Effects

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Traditional epidemiologic approaches allow us to compare counterfactual outcomes under 2 exposure distributions, usually 100% exposed and 100% unexposed. However, to estimate the population health effect of a proposed intervention, one may wish to compare factual outcomes under the observed exposure distribution to counterfactual outcomes under the exposure distribution produced by an intervention. Here, we used inverse probability weights to compare the 5-year mortality risk under observed antiretroviral therapy treatment plans to the 5-year mortality risk that would have been observed under an intervention in which all patients initiated therapy immediately upon entry into care among patients positive for human immunodeficiency virus in the US Centers for AIDS Research Network of Integrated Clinical Systems multisite cohort study between 1998 and 2013. Therapy-naïve patients ( $n = 14,700$ ) were followed from entry into care until death, loss to follow-up, or censoring at 5 years or on December 31, 2013. The 5-year cumulative incidence of mortality was 11.65% under observed treatment plans and 10.10% under the intervention, yielding a risk difference of  $-1.57\%$  (95% confidence interval:  $-3.08, -0.06$ ). Comparing outcomes under the intervention with outcomes under observed treatment plans provides meaningful information about the potential consequences of new US guidelines to treat all patients with human immunodeficiency virus regardless of CD4 cell count under actual clinical conditions.

antiretroviral therapy; causal inference; epidemiologic methods; HIV; intervention studies; policy; treatment guidelines

Abbreviations: AIDS, acquired immune deficiency syndrome; CI, confidence interval; CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; HIV, human immunodeficiency virus.

Epidemiologists are called upon to estimate the population health effects of interventions for public health practitioners, policy makers, and economists. For example, cost-effectiveness studies require estimates of the effect of an intervention on population health as one of many inputs in decision analyses (1). Because randomized trials of such interventions are frequently infeasible or unethical, epidemiologists must often use observational data to estimate the health effects of these interventions.

Traditional epidemiologic approaches are used to estimate the effects of exposures that may be targeted by interventions to improve health outcomes in a target population. For example, to examine the effect of an intervention to prevent a harmful exposure on mortality, a traditional analysis may be used to compare the risk of mortality between those who

are exposed and those who are unexposed. However, even with no confounding, this contrast does not estimate the effect of the intervention under consideration because the intervention would produce only 1 of these counterfactual scenarios (i.e., removal of exposure); a more useful approach might be to compare the risk of mortality in the population of interest under the observed exposure distribution with the risk of mortality in the population of interest under the counterfactual exposure distribution produced by the intervention.

Methods for such approaches are well established. When the contrast of interest is between the risk of the outcome in the observed population and the risk of the outcome under complete removal of exposure, it is sometimes known as a population attributable contrast (2); the population attributable

fraction is a special case of this contrast (3). Recent work has extended methods for estimating the population attributable fraction to situations with time-varying confounding and selection bias (4–6).

An emerging set of epidemiologic questions centers on the effects of policies under consideration that would regulate harmful exposures (e.g., pollutants) or foster beneficial exposures (e.g., treatments or healthy behaviors). With these questions comes demand for methods to estimate the effects of population interventions, including simple removal of exposure and beyond (2, 7). In recent studies, investigators have used the parametric g-formula to compare the risk of an outcome in the observed data with the risk under an intervention on 1 or more exposures (2, 8–14). Although flexible, the parametric g-formula requires fitting parametric models for all time-varying covariates and outcomes, each of which is typically subject to parametric modeling assumptions. Semiparametric methods exist to estimate both the population attributable fraction and other population intervention effects (4, 5, 7, 15). However, with a few notable exceptions (16–20), these semiparametric methods have not been broadly applied to estimate population intervention effects in the epidemiologic literature.

Here, we illustrate a semiparametric approach using inverse probability weights first described by Hubbard and Van Der Laan (7) to estimate the effect of an intervention to change the distribution of an exposure in a target population. As an example of this approach, we estimate the effect of a change in human immunodeficiency virus (HIV) treatment guidelines in the United States.

### SAMPLE AVERAGE EFFECTS VERSUS POPULATION INTERVENTIONS

In many epidemiologic studies, investigators are focused on estimating the sample average causal effect of an exposure. Briefly, estimating the sample average causal effect involves comparing the potential outcomes (or the outcomes that would have been observed) had all study participants immediately become exposed with the potential outcomes that would have been observed had no study participants become exposed throughout follow-up. The sample average causal effect for  $n$  subjects can be thought of as the average of  $n$  subject-specific causal effects or the contrast between an intervention in which all participants are exposed and an intervention in which all participants are prevented from becoming exposed. Estimating the sample average causal effect requires estimating incidence of the outcome under 2 counterfactual exposure scenarios (all patients becoming exposed at study entry and all patients abstaining from exposure throughout follow-up), neither of which is observed.

The fields of epidemiology and causal inference have developed a suite of methods to use when estimating the sample average causal effect from complex longitudinal data in the presence of threats to validity from confounding (21–24), selection (25), and measurement error (26–29). However, we can rarely imagine implementing both an intervention to expose the entire population and an intervention to prevent exposure among everyone in the population.

The approach outlined here differs from traditional approaches to estimate the sample average causal effect of expo-

sure in that we compare outcomes under a counterfactual exposure distribution (all participants follow exposure plan  $\bar{a}$ ) with outcomes under the observed factual distribution of exposure (participants follow their observed exposure plans). This contrast is analogous to the contrast estimated in an active comparator trial, in which the treatment under investigation is compared with the current standard of care.

To fix ideas, assume we are interested in comparing the risks of mortality in 2 different scenarios: one in which exposure  $A$  is set to plan  $\bar{a}$  according to some intervention (the intervention exposure plan) and one in which exposure is unchanged from the value it assumes in the real world (the factual exposure plan). The risk under the factual exposure plan is sometimes known as the natural course in analyses using the g-formula. We define risk for the factual scenario as the cumulative distribution function for the time to death,  $R(t) = P(T \leq t)$  (30). We define the risk for the counterfactual intervention scenario as the cumulative distribution function for the potential time to death under exposure plan  $\bar{a}$ , or  $R^{\bar{a}}(t) = P(T^{\bar{a}} \leq t)$ . The parameters of interest then include risk differences at time  $t$  (i.e.,  $R^{\bar{a}}(t) - R(t)$ ) and risk ratios at time  $t$  (i.e.,  $R^{\bar{a}}(t)/R(t)$ ).

### ESTIMATION OF INTERVENTION EFFECTS USING INVERSE PROBABILITY WEIGHTS

In this section, we describe one technique for estimating the desired contrast between  $R^{\bar{a}}(t)$  and  $R(t)$  using inverse probability weights. Other estimation procedures are possible, including algorithms using the parametric g-formula (31) or doubly robust estimators, such as targeted minimum loss estimators (7, 18).

Suppose we observe follow-up to time  $Y_i$  in  $i = 1, \dots, n$  individuals, where  $Y_i$  is the minimum of  $T_i$ , the time from study entry until the outcome of interest, and  $C_i$  is the time from study entry until censoring due to loss to follow-up or administrative reasons. Let  $\delta_i$  represent an indicator of experiencing the outcome during the study:  $\delta_i = 1(T_i < C_i)$ . The unique event times are indexed by  $j$ . Capital letters will typically represent random variables and lower case variables will typically represent realizations of random variables or constants. We will suppress participant-specific indices where possible below.

#### Estimating risk under the factual exposure plans

The risk of mortality under the factual exposure plan,  $R(t)$ , is simply the cumulative distribution function of the time to death,  $P(T \leq t)$ . Under the assumptions of no outcome measurement error, no informative censoring, and no competing risks, we can estimate  $R(t)$  using the complement of the Kaplan-Meier estimator of the survival function. This estimator can be written as

$$\hat{R}(t) = 1 - \prod_{t_j < t} \left\{ 1 - \frac{\sum_{i=1}^N 1(Y_i = t_j) \delta_i}{\sum_{m=1}^N 1(t_j \leq Y_m)} \right\},$$

where  $t_j$  indexes the unique ordered event times,  $\sum_{i=1}^N 1(Y_i = t_j) \delta_i$  is the number of events at time  $t_j$ , and  $\sum_{m=1}^N 1(t_j \leq Y_m)$  is the number at risk at time  $t_j$ .

We can relax the assumption of no informative censoring using inverse probability weights under the assumption that

censoring is independent of the outcome, given measured covariates. When censoring is affected by measured predictors of the outcome, the complement of the weighted Kaplan-Meier estimator of the survival function is a consistent estimator of  $R(t)$  (32):

$$\hat{R}(t) = 1 - \prod_{t_j < t} \left\{ 1 - \frac{\sum_{i=1}^N 1(Y_i = t_j) \delta_i \pi_i^C(t_j)}{\sum_{m=1}^N 1(t_j \leq Y_m) \pi_m^C(t_j)} \right\},$$

where  $\sum_{i=1}^N 1(Y_i = t_j) \delta_i \pi_i^C(t_j)$  is the weighted number of events and  $\sum_{m=1}^N 1(t_j \leq Y_m) \pi_m^C(t_j)$  is the weighted number at risk at time  $t_j$  (33, 34). Weights are the inverse probability of remaining uncensored through time  $t$  and are estimated as

$$\hat{\pi}^c(t) = \prod_{k=0}^{\lfloor t \rfloor} \frac{P\{C(k) = 0 | \bar{C}(k-1) = 0\}}{P\{C(k) = 0 | \bar{C}(k-1) = 0, \mathbf{L}, \bar{\mathbf{Z}}(\mathbf{k})\}},$$

where  $k$  indexes months after study entry,  $C(t) = I(C_i \leq t)$ ,  $\mathbf{L}$  is a vector of covariate history (possibly including the variable to be intervened upon) through time  $k$  (32). Further-refined approaches exist to estimate risk of an outcome in the presence of competing risks (35) and outcome measurement error (36).

### Estimating counterfactual risks under interventions

Next, we estimate the risk of the outcome under the intervention exposure plan  $\bar{a}$ ,  $R^{\bar{a}}(t)$ . If exposure history were randomized in our data, we could estimate  $R^{\bar{a}}(t) = P(T^{\bar{a}} \leq t)$  as  $P(T \leq t | \bar{A} = \bar{a})$  under the assumption of unconditional exchangeability (i.e., the assumption that the observed outcomes among exposed patients can accurately reflect the outcomes that would have been observed for unexposed patients had they been treated). Under the assumption of unconditional exchangeability between exposed and unexposed participants,  $R^{\bar{a}}(t)$  is the complement of the survival function estimated among participants with  $A(t) = a$ .

However, when exposure is not randomly assigned, it is rare that participants who did not follow exposure plan  $\bar{a}$  would have the same potential outcome under the intervention to impose exposure plan  $\bar{a}$  as participants who naturally followed exposure plan  $\bar{a}$ . Using the inverse probability of exposure weights allows us to make the weakened assumption of conditional exchangeability. That is, we assume exposure assignment was independent of potential outcomes, given a set of measured covariates; conditional exchangeability requires positivity, or a probability of receiving exposure  $a$  between 0 and 1 for every strata of this set of covariates. As in standard inverse probability-weighted marginal structural models (22), the exposure weights are given by

$$\pi^E(t) = \prod_{k=0}^{\lfloor t \rfloor} \frac{f\{A(k) | \bar{A}(k-1)\}}{f\{A(k) | \bar{A}(k-1), \mathbf{L}, \bar{\mathbf{Z}}(\mathbf{k})\}},$$

where  $f\{\cdot | \cdot\}$  is the conditional density function evaluated at the observed covariate values. The counterfactual risk function under intervention  $a$  can be estimated as

$$\hat{R}^{\bar{a}}(t) = 1 - \prod_{t_j < t} \left\{ 1 - \frac{\sum_{i=1}^N 1(Y_i = t_j, A(t_j) = a) \delta_i \pi_i(t_j)}{\sum_{m=1}^N 1(t_j \leq Y_m, A(t_j) = a) \pi_m(t_j)} \right\},$$

where the weights  $\hat{\pi}(t)$  are the product of these exposure weights and the censoring weights,  $\hat{\pi}(t) = \hat{\pi}^E(t) \times \hat{\pi}^C(t)$ ,  $\sum_{i=1}^N 1(Y_i = t_j, A(t_j) = a) \delta_i$  is the number of events with exposure  $a$  at time  $t_j$ , and  $\sum_{m=1}^N 1(t_j \leq Y_m, A(t_j) = a)$  is the number at risk with exposure  $a$  at time  $t_j$ . The numerators and denominators of the censoring and exposure weights can be estimated using pooled logistic regression (37, 38) or ensemble learning approaches (39, 40).

### EXAMPLE

To illustrate the use of inverse probability weights to estimate the effects of population interventions, we use an example from HIV epidemiology. The parameter of interest is the difference between the estimated 5-year cumulative incidence of mortality under immediate initiation of antiretroviral therapy upon entry into HIV care for all patients (the “intervention”) and the 5-year cumulative incidence of mortality under the observed treatment patterns (the “factual exposure plan”).

Antiretroviral therapy is known to be effective in extending life expectancy for people living with HIV (23, 41–43), and previous guidelines recommended therapy initiation for patients with CD4 cell counts below some threshold and for patients with acquired immune deficiency syndrome (AIDS)-defining illnesses. With increasing evidence that early therapy initiation reduces morbidity and prevents the transmission of HIV (44), recent guidelines have recommended that patients with HIV receive therapy immediately upon entry into HIV-related medical care. We compare estimated mortality under these recent guidelines to mortality under the observed treatment plans in place between 1998 and 2013 in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort.

Using the method described here, rather than a traditional marginal structural model in which we compare potential outcomes between universal treatment and no treatment, is appealing in this example. An intervention to treat all patients immediately upon study entry is reasonable, but there has been no point since 1998 when we would consider an intervention that would deny life-saving treatment to the entire study population throughout follow-up.

### Study sample

The CNICS cohort (45) includes HIV-positive adults engaged in clinical care from January 1, 1995, to the present at 8 Centers for AIDS Research sites (Case Western Reserve University, Cleveland, Ohio; Fenway Community Health Center of Harvard University, Cambridge, Massachusetts; Johns Hopkins University, Baltimore, Maryland; University of Alabama at Birmingham, Birmingham, Alabama; University of California, San Diego, La Jolla, California; University of California, San Francisco, San Francisco, California; University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and University of Washington, Seattle, Washington). Patients who attended 2 primary HIV medical care visits at 1 of the 8 study sites were enrolled in CNICS. Data on clinical events, laboratory measurements, and antiretroviral medications were collected as part of routine clinical care. Institutional review boards at each site approved study protocols.

**Table 1.** Demographic and Clinical Characteristics of 14,700 Patients at Study Entry<sup>a</sup>, Centers for AIDS Research Network of Integrated Clinical Systems Cohort, 1998–2013

Characteristic	Patients at Study Entry (n = 14,700)		Person-Years of Follow-Up (n = 47,832), %
	No.	%	
Male sex	11,951	81	81
Black race	5,831	40	39
Hispanic ethnicity	1,604	11	11
Injection drug user	2,413	16	16
MSM	8,801	60	60
AIDS	3,103	21	27
Year at study entry			
1998–2002	4,854	33	35
2003–2007	5,003	34	38
2008–2013	4,843	33	27
CD4 cell count, copies/mL			
<200	5,148	35	19
200–350	3,165	22	22
351–500	2,872	20	24
501–750	2,472	17	16
>750	1,043	7	7
Suppressed viral load <sup>b</sup>	0	0	45
On therapy	0	0	66

Abbreviations: AIDS, acquired immune deficiency syndrome; MSM, man who has sex with men.

<sup>a</sup> Patients were linked to care at a Centers for AIDS Research Network of Integrated Clinical Systems site between January 1, 1998, and December 31, 2013, at 8 US clinical sites and followed for death for up to 5 years.

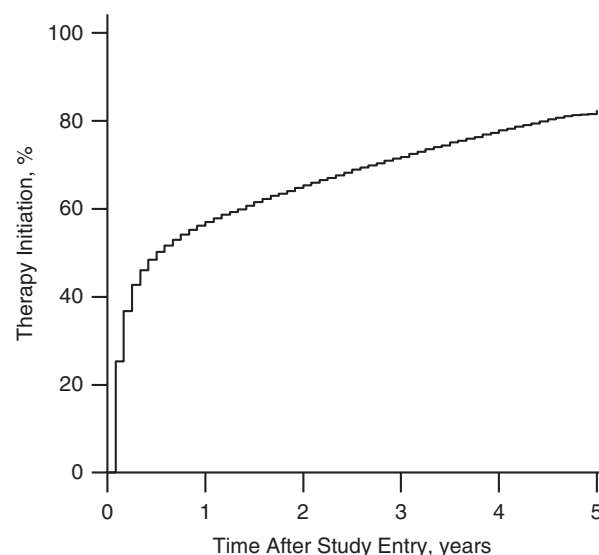
<sup>b</sup> Fewer than 500 copies/mL; only patients with unsuppressed viral load at cohort entry were included in the study.

The study sample for the present analysis included 14,700 patients who enrolled in CNICS before initiation of antiretroviral therapy and had an unsuppressed viral load (>500 copies/mL) at cohort entry between January 1, 1998, and December 30, 2013. Therapy initiation was defined as the date on which a patient was first prescribed 3 or more antiretroviral agents (for at least 30 days), and patients were considered to be unexposed to therapy until the date of therapy initiation. Unexposed patients may have received monotherapy or dual therapy.

The outcome of interest was all-cause mortality. Deaths were obtained through clinic sources, death certificates, and the Social Security Death index, which is regularly queried by investigators at the CNICS sites.

## Statistical methods

Patients were followed from entry into care at a CNICS site until death, loss to follow-up, or administrative censoring 5 years after study entry or on December 31, 2012. Because of missing information on treatment and time-varying covariates,

**Figure 1.** Cumulative incidence of antiretroviral therapy initiation under observed treatment plans (also known as the “natural course”) among 14,700 patients at 8 sites in the United States, Centers for AIDS Research Network of Integrated Clinical Systems cohort, 1998–2013.

patients were considered to be lost to follow-up after the first 12 months without a documented clinic visit to a CNICS site.

We compared the 5-year risk that would have occurred had all patients initiated treatment immediately upon entry into care with the 5-year cumulative incidence of mortality under the factual treatment plans (i.e., no intervention on treatment). As described above, we estimated the risk of mortality under the factual treatment plans,  $R(t) = P(T \leq t)$ , as the complement of the inverse probability of censoring–weighted Kaplan-Meier estimator of the survival function, in which the denominator of the censoring weights included time-fixed covariates (race, sex, and HIV transmission factor, as well as age, year, and CD4 cell count at study entry) and time-varying covariates (treatment history, AIDS diagnosis, monotherapy or dual therapy use, CD4 cell count, and an indicator of detectable viral load (>500 copies/mL)). The numerator and denominator of the censoring weights were estimated using pooled logistic regression, and all continuous variables were modeled flexibly using restricted quadratic splines (46).

We estimated the risk of mortality under the intervention to treat all patients immediately,  $R^{\bar{a}=1}(t) = P(T^{\bar{a}=1} \leq t)$  as the complement of the Kaplan-Meier estimator of the survival function, estimated among treated patients and weighted to represent the total study sample. Weights  $\hat{\pi}(t)$  were the product of the exposure and censoring weights,  $\hat{\pi}(t) = \hat{\pi}^E(t) \times \hat{\pi}^C(t)$ . The denominator of the exposure weights included the same sets of time-fixed and time-varying covariates that were included in the censoring weights. Again, all continuous variables were modeled flexibly using restricted quadratic splines (46). To summarize treatment history, we follow convention and let  $\bar{A}(k-1) = 1$  if the patient had initiated treatment through time  $k-1$  and  $\bar{A}(k-1) = 0$  otherwise. By definition,



**Table 2.** Weighted Number of Deaths, Number of Person-Years, and 5-Year Cumulative Incidence of Mortality Under the Observed Treatment Plans and 2 Interventions<sup>a</sup> Among 14,700 Patients<sup>b</sup>, Centers for AIDS Research Network of Integrated Clinical Systems Cohort, 1998–2013

Intervention <sup>c</sup>	No. of Deaths	No. of Person-Years	5-Year Mortality	RR	95% CI	RD	95% CI
No intervention	1,185	47,852	11.65	1.00	Referent	0.00	Referent
Initiate treatment at entry into care	530	28,026	10.10	0.87	0.75, 1.00	-1.57	-3.08, -0.06
Never treat	1,162	16,494	30.20	1.00	Referent	0.00	Referent
Initiate treatment at entry into care	530	28,026	10.10	0.33	0.22, 0.50	-20.12	-31.44, -8.80

Abbreviations: CI, confidence interval; RD, risk difference; RR, risk ratio.

<sup>a</sup> An intervention to initiate treatment immediately upon entry into care and an intervention to prohibit treatment throughout follow-up.

<sup>b</sup> Patients received care at a Centers for AIDS Research Network of Integrated Clinical Systems site between January 1, 1998, and December 31, 2013, at 8 US clinical sites and were followed for death for up to 5 years.

<sup>c</sup> In the “no intervention” arm, deaths, person years and cumulative incidence estimates were weighted to account for informative censoring. In the “immediate treatment” and “never treatment” arms, quantities were weighted to account for informative censoring and confounding. The means of the censoring weights and exposure weights were 1.00.

$P\{A(k) = 1 | \bar{A}(k-1) = 1\} = 1$  under an observational analog of the intent to treat assumption (47).

To calculate the numerator and denominator of the intervention weights, we fit pooled logistic regression models to estimate the probability of initiating treatment at each time point. The logistic regression model for the denominator, fit only for records in which  $\bar{A}(k-1) = 0$  had the form

$$P(A(k) = 1 | \bar{A}(k-1), \mathbf{L}, \bar{\mathbf{Z}}(\mathbf{k})) = \text{expit}\{\beta_0 + \beta_1 g(t) + \beta_2 \mathbf{L} + \beta_3 \mathbf{Z}(\mathbf{k})\},$$

where  $\text{expit}(\cdot) = \exp(\cdot) / \{1 + \exp(\cdot)\}$ .

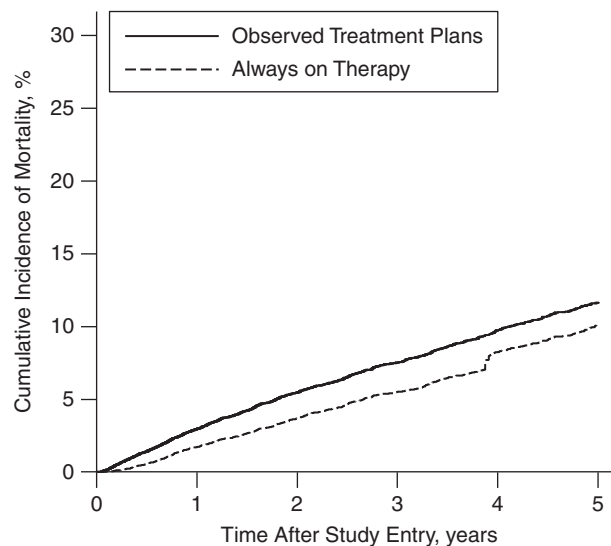
We compared the cumulative incidence of mortality under the intervention to immediately treat all patients with the cumulative incidence of mortality under no intervention on treatment plan using risk ratios and risk differences at 5 years. The 5-year risk differences were estimated as  $R^{\bar{a}=1}(5) - R(5)$ , and 5-year risk ratios were estimated as  $R^{\bar{a}=1}(5) / R(5)$ . Ninety-five percent confidence intervals for risk differences and risk ratios were calculated using standard errors estimated by the standard deviation of the effect measures in 200 nonparametric bootstrap samples with replacement from the original study sample size with equal probability (11). Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). We could alternatively compare the time to death between the intervention scenario and the natural course using hazard ratios. Details on implementation of this approach in a Cox proportional hazards model are provided in the Appendix. We compared results from this analysis to results from a traditional marginal structural model in which we compared interventions to treat all patients immediately and to withhold treatment from all patients throughout follow-up (22, 37, 38).

### Example results

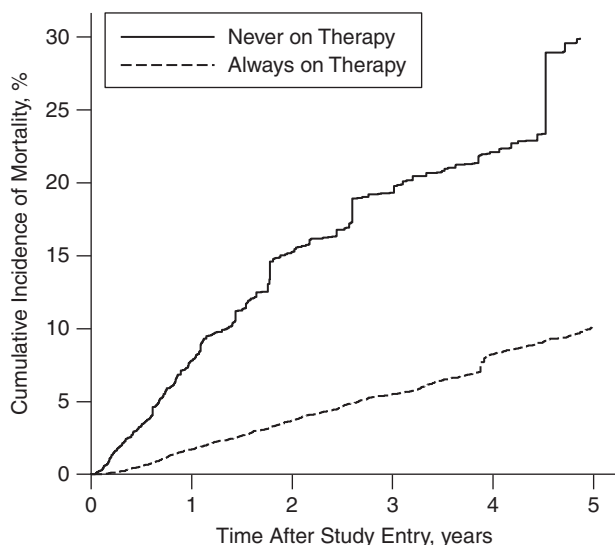
Between 1998 and 2013, a total of 14,700 antiretroviral therapy-naïve patients with a detectable viral load enrolled

in HIV care at a CNICS site. Table 1 describes the characteristics of the study sample at study entry and over 47,852 person-years of follow-up. Of the 14,700 patients included in the study, 81% were male, 40% were black, and 60% were men who have sex with men. The median CD4 cell count at study entry was 343 cells/mm<sup>3</sup> (interquartile range, 154–552). A very small proportion of patients entered care with a CD4 cell count higher than 750 cells/mm<sup>3</sup> (7%).

Over the 5-year study period, 10,035 patients initiated therapy, and the cumulative incidence of therapy initiation



**Figure 2.** Weighted cumulative incidence of mortality under observed treatment plans and under an intervention to initiate treatment for all patients at entry into care among 14,700 patients at 8 sites in the United States, Centers for AIDS Research Network of Integrated Clinical Systems cohort, 1998–2013.



**Figure 3.** Weighted cumulative incidence of mortality under an intervention to prevent treatment throughout follow-up and under an intervention to initiate treatment for all patients at entry into care among 14,700 patients at 8 sites in the United States, Centers for AIDS Research Network of Integrated Clinical Systems cohort, 1998–2013.

was 82% (Figure 1). One-fourth of all patients initiated therapy immediately upon entry into care, and half of the patients initiated therapy within 6 months of entry into care. Web Figure 1 (available at <http://aje.oxfordjournals.org/>) depicts the cumulative incidence of therapy initiation by baseline CD4 cell count. Under the observed treatment plans, 1,185 deaths occurred over the 5-year study period, and the 5-year cumulative risk of mortality was 11.65%. Web Figure 2 shows the risk of death over time by baseline CD4 cell count.

Table 2 shows a comparison mortality under the observed treatment plans with mortality under the intervention plans. Under the intervention of immediate therapy initiation, the estimated 5-year cumulative incidence of mortality was 10.10%, yielding a risk difference of  $-1.57\%$  (95% confidence interval (CI):  $-3.08, -0.06$ ) and a risk ratio of 0.87 (95% CI: 0.75, 1.00). The estimates of 5-year mortality under the natural course and the intervention scenario are presented in Figure 2.

Table 2 also shows a comparison of the mortality under the intervention in which therapy is initiated immediately upon entry into care with an unrealistic intervention in which treatment is prohibited for all patients throughout follow-up. Under this second intervention, the estimated 5-year cumulative incidence of mortality was 30.20%. This comparison yielded a risk difference of  $-20.12\%$  (95% CI:  $-31.44, -8.80$ ) and a risk ratio of 0.33 (95% CI: 0.22, 0.50). Figure 3 presents the estimated cumulative incidence of mortality under each of these interventions.

## DISCUSSION

Recent US guidelines recommend treating all patients enrolled in HIV clinical care with antiretroviral therapy. In the

example, we estimated that 5-year mortality among patients in care for HIV between 1998 and 2013 would have been 10.1% under such an intervention, compared with 11.7% under the observed treatment plans during this time period.

Although treatment with antiretroviral therapy is known to be effective in reducing the mortality risk among people with HIV (41, 42, 47, 48), the effect of changing a treatment guideline or policy is often unknown. In recent years, large observational cohort studies have been used to study the optimal CD4 cell count at which to begin therapy (49–52) by comparing mortality risks under various hypothetical thresholds for CD4 cell counts. Here, we estimated mortality risk under the most recent treatment guideline (i.e., treat at entry into care) and compared this estimated mortality with the observed mortality under the guidelines in place between 1998 and 2013.

To identify the risk under the factual treatment plans, we assumed no error in outcome ascertainment, conditional exchangeability between patients lost to follow-up and patients who remained in the study (25), and correct specification of the models used to create the censoring weights. To identify risk under the intervention, we additionally assumed no interference (53), treatment version irrelevance (54), no measurement error in exposure or covariates (28), conditional exchangeability between treated and nontreated patients, positivity (55), and correct specification of the logistic models used to build the exposure weights. These assumptions have been described in more depth previously (30).

The example used to illustrate this approach to estimating policy effects had several limitations that should be noted. First, treatment policies and regimens changed dramatically over the study period, leading to ambiguity regarding the intervention. For example, patients were considered to have followed the intervention if they were on any type of combined antiretroviral therapy regimen, without regard to whether that regimen would be prescribed in the future. In addition, this example did not account for changes in HIV testing, care-seeking behavior, and retention in care that may be seen under the guideline recommending immediate treatment for all people living with HIV.

To estimate the effect of the new treatment guidelines, we were required to censor patients at loss to follow-up because of missing treatment data after loss to follow-up. In doing so (and applying the inverse probability of censoring weights), we estimated the risks under the intervention and the natural course that would have been seen had all patients remained in care at a CNICS site, which of course was not the case. From a public health perspective, we may actually be interested in the total effect of having all patients initiate antiretroviral treatment immediately upon entry into care, which might include improvements in life expectancy due to the indirect effects of therapy, such as improved retention in care. Unfortunately, this total effect is not directly estimable using these data. In the CNICS cohort, however, mortality was similar (5-year risk ratio = 1.2, 95% CI: 0.9, 1.5) before and after loss to follow-up at a CNICS site (56), suggesting that the total effect of a proposed intervention to provide immediate treatment was likely similar to the effect we estimated that was conditional on retention in care at a CNICS site.

Although the cumulative incidence of loss to follow-up was high (46% at 5 years), prior work showing similar mortality

risks before and after loss to follow-up (56) after accounting for the variables used in the censoring weights suggests that any selection bias induced by the high incidence of drop out is likely to be modest. Results were similar with and without application of the censoring weights. Web Figure 3 depicts the cumulative incidence of loss to follow-up by CD4 cell count at baseline, which was a variable included in the denominator of the censoring weights.

Because the indicators for treatment with antiretroviral therapy have been well described, we have likely captured many of the important covariates for the intervention weights. However, if an unmeasured predictor of mortality, such as income or an unrecorded comorbid condition, were associated with therapy initiation, our results could include bias due to unmeasured confounding.

In the example, we assumed that a policy that recommended immediate treatment for patients presenting to care with HIV would result in treatment initiation by the patient's second clinic visit. This assumption could be relaxed by allowing a grace period for patients to be initiated on therapy under the intervention. Use of a grace period in inverse probability-weighted marginal structural models has been illustrated by Cain et al. (57).

Because patients who come to CNICS before initiating therapy routinely present to care with CD4 cell counts below 500 copies/mL, many patients were treated soon after enrollment in the cohort under their observed treatment plans. For this reason, the intervention to treat all patients immediately upon entry into care did not produce a drastic change in the distribution of treatment. Therefore, although therapy is known to reduce mortality, the incremental effect of transitioning from the existing treatment policies from 1998 to 2013 to a policy to treat all patients in CNICS at entry into care is modest. However, in a hypothetical cohort in which patients were enrolled at HIV seroconversion, we would expect the effect of a policy to provide universal immediate treatment to be much larger.

As outlined above, an inverse probability-weighted estimator can be used to estimate the risk of an outcome under counterfactual distributions of exposure(s) produced by public health or treatment interventions under a set of identification assumptions (30, 38). We could have alternatively used the parametric g-formula to estimate the risk under various interventions on exposure (23, 58). Both inverse probability weighting and parametric g-formula approaches are susceptible to model misspecification, though the models one is required to specify correctly differ between the approaches. A doubly robust estimator for population intervention effects that offers some protection against model misspecification (i.e., the estimator is consistent if models for treatment assignment or outcome are correct) has been described (7), and theory suggests it would improve efficiency over the estimator in which inverse probability weighting is used alone, although the present approach provides a consistent estimator when the identification assumptions hold.

Here, rather than compare potential outcomes under 2 counterfactual exposure distributions, we compared the potential outcomes under the intervention to the potential outcomes under the observed exposure distribution—a factual, rather than counterfactual, exposure distribution. The factual exposure distribution is an appealing and informative referent

because it is a clear and realistic alternative to the intervention; it is simply the descriptive epidemiology for the outcome of interest. By comparing outcomes of feasible (or proposed) interventions with outcomes under the status quo, we can produce results from epidemiologic studies that are more directly relevant to public health practice.

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## APPENDIX

### Estimation of Hazard Ratios

To estimate hazard ratios comparing mortality under an intervention to treat all patients immediately upon entry into care with the observed mortality, weights were created as described above. Briefly, the reference group simply comprises the observed data. All records in the reference group receive a weight of 1. A second copy of the data is weighted as described in the body of the paper to represent the experience of the study population under the intervention. These 2 data sets are concatenated, and an indicator is assigned denoting whether each record is from the reference group (here, INT = 0) or the intervention group (INT = 1).

Next, a Cox proportional hazards model is used to maximize the weighted partial likelihood

$$L(\theta) = \prod_{i=1}^N \left\{ \frac{\exp\{\theta \times \text{INT}\}}{\sum_{j=1}^N I(y_j \geq y_i) \times \exp\{\theta \times \text{INT}\} \times w_j(y_i)} \right\}^{\delta_i \times w_i(y_i)},$$

where  $w$  is the weight as described above,  $Y_i$  is the time from study entry to death or censoring,  $\delta_i$  is an event indicator, and  $I(y_j \geq y_i)$  is an indicator of whether individual  $j$  is in the risk set at time  $y_i$ . The hazard ratio may be estimated as  $\exp(\theta)$ .