

Estimating the Effects of Multiple Time-varying Exposures Using Joint Marginal Structural Models

Alcohol Consumption, Injection Drug Use, and HIV Acquisition

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Abstract: The joint effects of multiple exposures on an outcome are frequently of interest in epidemiologic research. In 2001, Hernán et al (*J Am Stat Assoc.* 2001;96:440–448) presented methods for estimating the joint effects of multiple time-varying exposures subject to time-varying confounding affected by prior exposure using joint marginal structural models. Nonetheless, the use of these joint models is rare in the applied literature. Minimal uptake of these joint models, in contrast to the now widely used standard marginal structural model, is due in part to a lack of examples demonstrating the method. In this paper, we review the assumptions necessary for unbiased estimation of joint effects as well as the distinction between interaction and effect measure modification. We demonstrate the use of marginal structural models for estimating the joint effects of alcohol consumption and injection drug use on HIV acquisition, using data from 1525 injection drug users in the AIDS Link to Intravenous Experience cohort study. In the joint model, the hazard ratio (HR) for heavy drinking in the absence of any drug injections was 1.58 (95% confidence interval = 0.67–3.73). The HR for any drug injections in the absence of heavy drinking was 1.78 (1.10–2.89). The HR for heavy drinking and any drug injections was 2.45 (1.45–4.12). The *P* values for multiplicative and additive interaction were 0.7620 and 0.9200, respectively, indicating a lack of departure

from effects that multiply or add. We could not rule out interaction on either scale due to imprecision.

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The joint effects of multiple exposures on an outcome are frequently of interest in epidemiologic research.¹ Joint effects concern the combined effect of 2 or more exposures on an outcome and whether this combined effect is more or less than expected on a given scale (ie, additive or multiplicative). Departures from expected combined effects are referred to as interaction. In contrast, effect measure modification focuses on whether the effect of a single exposure on an outcome varies with the level of second variable.² For example, in the area of cardiovascular disease epidemiology, if the study objective was to estimate the combined effect of oral contraceptive use and smoking on the risk of myocardial infarction, then the research would attempt to estimate the joint effects of (and interaction between) oral contraceptive use and smoking on the risk of myocardial infarction. However, if the objective was whether the effect of oral contraceptive use on myocardial infarction varied by smoking status, then the aim would be to estimate effect measure modification.

In 2001, Hernán et al³ presented methods for estimating the joint effects of multiple time-varying exposures subject to time-varying confounding using joint marginal structural models. We refer to these marginal structural models as “joint” models, given that they examine the potential outcome across the joint distribution of the 2 or more exposures (not to be confused with models for the joint distribution of survival and a repeated measure).⁴ Standard marginal structural models^{5,6} avoid removal of indirect effects, and they also avoid the selection bias that can occur with standard adjustment techniques when estimating the effect of a time-varying exposure subject to time-varying confounding affected by prior exposure. Joint marginal structural models have the same methodological advantage when estimating the effect of multiple time-varying exposures, each affected by time-varying confounders affected by prior exposure. Both standard and joint marginal struc-

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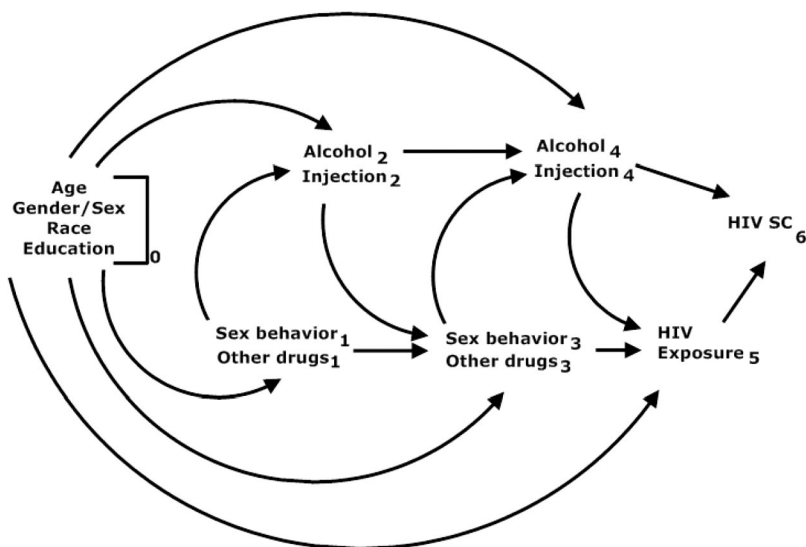


FIGURE 1. Causal diagram for the effect of alcohol consumption and injection drug use on HIV acquisition.

tural models can also be used to account for selection bias due to censoring.

Although estimating joint effects of time-varying exposures is of interest in both chronic and infectious disease epidemiology,^{7–10} a decade after the paper by Hernán et al³ was published, we found only 3 publications^{11–13} that used a joint marginal structural model in the applied biomedical and epidemiologic literature among articles citing that paper. This low uptake of joint marginal structural models, in contrast to the widely used standard marginal structural model,^{6,14–19} may be due to a lack of examples showing the implementation of the model.

The objective of this paper is to describe and demonstrate joint marginal structural Cox proportional hazards models based on an example from the HIV literature. (Although joint marginal structural models can be fit for other types of regression models,^{2,3} these other models are not the focus of this paper.) Previous work^{7,8,19} has indicated alcohol consumption as well as injection drug use as risk factors for HIV acquisition. To identify groups at particularly high risk for HIV infection, the interaction between risk factors for HIV acquisition has been of interest.^{7,8} As depicted in Figure 1, both time-varying alcohol consumption and injection drug use are likely subject to time-varying confounding affected by prior exposure. In particular, sexual risk behaviors and other patterns of drug use are likely common causes of alcohol consumption, injection drug use, and HIV acquisition and may be affected by prior alcohol consumption or injection drug use. Therefore, unbiased estimation of the joint effects of these 2 risk factors on HIV acquisition likely requires use of joint marginal structural models.

We used data from the AIDS Link to Intravenous Experience (ALIVE) cohort study²⁰ to demonstrate estima-

tion of the joint effects of alcohol consumption and injection drug use on HIV acquisition. The SAS (SAS Institute, Inc., Cary, NC) code used to estimate these joint effects is provided in the eAppendix (<http://links.lww.com/EDE/A567>). Assumptions necessary for unbiased estimation of joint effects will be described generally, as well in the context of the ALIVE example. Finally, we will make additional clarifications regarding the distinction between interaction and effect measure modification.

METHODS

Study Population

Details regarding recruitment, inclusion criteria, and data collection for this example are provided elsewhere.^{19,20} Briefly, the ALIVE cohort enrolled 3627 HIV seronegative adults with a history of injection drug use in Baltimore, MD, between 1988 and 2008. Through extensive community outreach, participants were recruited from venues where injection drug users in Baltimore were known to be frequent, as well as from other local settings, such as sexually transmitted disease clinics, drug abuse treatment programs, homeless shelters, and emergency rooms.

Of 3627 enrollees, 1525 were African American, with complete demographic information who were seronegative at entry and who had at least one seronegative follow-up visit subsequent to baseline, thereby making them eligible for the analysis. Blood samples, as well as information on demographic characteristics, drug and alcohol use history and practices, and sexual behaviors, were collected at study entry and every 6 months thereafter. Blood specimens were tested for HIV antibodies by enzyme-linked immunoassay, and reactive specimens were confirmed by Western blot. The 1525 participants were followed for up to 20 years, yielding

8181 person-years of follow-up, during which time 155 acquired HIV.

Notation

Let uppercase letters denote random variables, and lowercase letters represent possible realizations of random variables. In the ALIVE cohort of $i = 1, 2, \dots, N = 1525$ participants with $k_{i(1)} < k_{i(2)} < \dots k_{i(M)}$ ordered measurement times since study entry, T_i is the time in years from study entry to HIV infection and C_i is the time in years from study entry to censoring due to dropout, death, or reaching the end of the study. Therefore, $Y_i = \min(T_i, C_i)$ and δ_i is an indicator of whether HIV infection was observed, where $\delta_i = 1$ if $y_i = t_i$ and $\delta_i = 0$ if $y_i = c_i$. Below, the subscript i will be suppressed where possible. Let $X_{1i}(k_{(m)})$ and $X_{2i}(k_{(m)})$ be the level of alcohol consumption and injection drug use status at time $k_{(m)}$, respectively.

Let $L_{1i}(k_{(m)})$ be a vector denoting the levels of potential confounders of the relationship between X_1 and T at time $k_{(m)}$, while Z_{1i} is a vector subset of $L_{1i}(k_{(m)})$ corresponding to time-fixed confounders measured at study entry. Let $L_{2i}(k_{(m)})$ be a vector denoting the levels of potential confounders of the relationship between X_2 and T at time $k_{(m)}$, while Z_{2i} is a vector subset of $L_{2i}(k_{(m)})$ corresponding to time-fixed confounders measured at study entry. Let $L_{3i}(k_{(m)})$ be a vector denoting the levels of common predictors of the relationship between T and C at time $k_{(m)}$, whereas Z_{3i} is a vector subset of $L_{3i}(k_{(m)})$ corresponding to time-fixed common predictors measured at study entry. Covariates L_1 , L_2 , and L_3 were assumed to be the same and included those that were time-fixed (ie, age at entry, sex, and years of education) as well as time-updated pertaining to the prior 6 months (ie, cocaine use; shooting gallery attendance; number of sexual partners; male sex with men; sexually transmitted infections, including genital herpes simplex virus, genital warts, gonorrhea, and syphilis). Selected covariates were variables shown to independently increase the risk of HIV infection among study participants.^{7,8}

Allow overbars to represent the history of a given random variable from study entry to $k_{(m)}$ (eg, $\bar{X}_{1i}(k_{(m)}) = \{X_{1i}(k_{(1)}), X_{1i}(k_{(2)}), \dots, X_{1i}(k_{(m)})\}$). Therefore, let $T_i^{\bar{X}_{1i}(k_{(m)}), \bar{X}_{2i}(k_{(m)})}$ represent the potential time to HIV infection for participant i had he or she been assigned alcohol consumption and injection drug use history $\bar{x}_{1i}(k_{(m)})$ and $\bar{x}_{2i}(k_{(m)})$ rather than the observed alcohol consumption and injection drug use history of $\bar{X}_{1i}(k_{(m)})$ and $\bar{X}_{2i}(k_{(m)})$. Similarly, $T_i^{\bar{X}_{1i}(k_{(m)}), \bar{X}_{2i}(k_{(m)})}$ represents the observed time to HIV infection for participant i for observed alcohol consumption and injection drug use history $\bar{X}_{1i}(k_{(m)})$ and $\bar{X}_{2i}(k_{(m)})$. Finally, let $D_{1i}(k_{(m)})$ be an indicator that participant i is censored due to dropout at time $k_{(m)}$, $D_{2i}(k_{(m)})$ be an indicator that participant i is censored due to death at time $k_{(m)}$, $X_i = [X_{1i}, X_{2i}]$, $L_i = [L_{1i}, L_{2i}, L_{3i}]$, $Z_i = [Z_{1i}, Z_{2i}, Z_{3i}]$, and $D_i = [D_{1i}, D_{2i}]$.

Joint Marginal Structural Cox Proportional Hazards Model

Equation (1) shows the marginal structural Cox proportional hazards model for the joint effects of $X_1(k_{(m)})$ and $X_2(k_{(m)})$ on $T^{\bar{x}}$,

$$\lambda_{T^{\bar{x}}}(k_{(m)}|Z) = \lambda_0(k_{(m)}) \times \exp(\alpha_1 x_1(k_{(m)}) + \alpha_2 x_2(k_{(m)}) + \alpha_3 x_1(k_{(m)})x_2(k_{(m)}) + \alpha'_4 Z_1 + \alpha'_5 Z_2 + \alpha'_6 Z_3), \quad (1)$$

where $T^{\bar{x}} = T^{\bar{x}_1, \bar{x}_2}$. Also, $\lambda_0(k_{(m)})$ is the baseline hazard function at time $k_{(m)}$ and $\lambda_{T^{\bar{x}}}(k_{(m)}|Z)$ is the hazard function for $T^{\bar{x}}$ at time $k_{(m)}$ conditional on Z . The parameter α_1 is the log hazard ratio for the effect of $X_1(k_{(m)})$ on $T^{\bar{x}}$ when $X_2(k_{(m)}) = 0$, α_2 is the log hazard ratio for the effect of $X_2(k_{(m)})$ on $T^{\bar{x}}$ when $X_1(k_{(m)}) = 0$, and α_3 is the log of the ratio of hazard ratios for the effect of $X_1(k_{(m)})$ and $X_2(k_{(m)})$ on $T^{\bar{x}}$. In addition, α_4 , α_5 , and α_6 are the vectors of log hazard ratios for the time-fixed covariates comprising Z_1 , Z_2 , and Z_3 , respectively while $\alpha = [\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6]$.

The joint marginal structural model in equation (1) is fit in a two-part process using inverse probability weights (ie, W_i) described later. Conditional on the estimated weights, the weighted maximum partial likelihood estimates for $\hat{\alpha}$ in equation (1) are obtained by maximizing,

$$WL(\alpha) = \prod_{i=1}^N \left\{ \frac{\exp\left(\alpha_1 x_1(k_{(m)}) + \alpha_2 x_2(k_{(m)}) + \alpha_3 x_1(k_{(m)})x_2(k_{(m)}) + \alpha'_4 Z_1 + \alpha'_5 Z_2 + \alpha'_6 Z_3\right)}{\sum_{r=1}^N I[y_r \geq y_i] \times \exp\left(\alpha_1 x_1(k_{(m)}) + \alpha_2 x_2(k_{(m)}) + \alpha_3 x_1(k_{(m)})x_2(k_{(m)}) + \alpha'_4 Z_1 + \alpha'_5 Z_2 + \alpha'_6 Z_3\right)} \times \hat{w}_r(y_i) \right\}^{\delta_i \times \hat{w}_i(y_i)}$$

where $I[y_r \geq y_i]$ is an indicator of participant r being in the risk set at follow-up time y_i . Given necessary assumptions outlined below, $\hat{\alpha}_1$, $\hat{\alpha}_2$, and $\hat{\alpha}_3$ are consistent asymptotically normal estimates of the joint effects of X_1 and X_2 on $T^{X_1 \times X_2}$ while correcting for potential time-varying confounding by L_1 and L_2 as well as selection bias due to censoring informed by L_3 . Therefore, $\hat{\alpha}_3$ can be used to consistently assess the presence or absence of multiplicative interaction.

Inverse Probability Weights

The following stabilized weights can be used to fit the joint marginal structural model in equation (1):

$$W(t) = W^{X_1}(t)W^{X_2}(t)W^{D_1}(t)W^{D_2}(t), \quad (2)$$

where

$$W^{X_1}(t) = \prod_{k(m) \leq t} \frac{f \left[\begin{array}{c} X_1(k(m)) | \bar{X}_1(k(m-1)), \bar{X}_2(k(m-1)), Z_1, \\ \bar{D}(k(m)) = 0, T \geq k(m) \end{array} \right]}{f \left[\begin{array}{c} X_1(k(m)) | \bar{X}_1(k(m-1)), \bar{X}_2(k(m-1)), \bar{L}_1(k(m-1)), \\ \bar{D}(k(m)) = 0, T \geq k(m) \end{array} \right]}, \quad (3)$$

$$W^{X_2}(t) = \prod_{k(m) \leq t} \frac{f \left[\begin{array}{c} X_2(k(m)) | \bar{X}_1(k(m)), \bar{X}_2(k(m-1)), Z_2, \\ \bar{D}(k(m)) = 0, T \geq k(m) \end{array} \right]}{f \left[\begin{array}{c} X_2(k(m)) | \bar{X}_1(k(m)), \bar{X}_2(k(m-1)), \bar{L}_2(k(m-1)), \\ \bar{D}(k(m)) = 0, T \geq k(m) \end{array} \right]}, \quad (4)$$

$$W^{D_1}(t) = \prod_{k(m) \leq t} \frac{P \left[\begin{array}{c} D_1(k(m)) = 0 | \bar{X}(k(m)), Z_3, \\ \bar{D}(k(m-1)) = 0, T \geq k(m) \end{array} \right]}{P \left[\begin{array}{c} D_1(k(m)) = 0 | \bar{X}(k(m)), \bar{L}_3(k(m-1)), \\ \bar{D}(k(m-1)) = 0, T \geq k(m) \end{array} \right]} \quad (5)$$

$$W^{D_2}(t) = \prod_{k(m) \leq t} \frac{P \left[\begin{array}{c} D_2(k(m)) = 0 | \bar{X}(k(m)), Z_3, \\ \bar{D}(k(m-1)) = 0, T \geq k(m) \end{array} \right]}{P \left[\begin{array}{c} D_2(k(m)) = 0 | \bar{X}(k(m)), \bar{L}_3(k(m-1)), \\ \bar{D}(k(m-1)) = 0, T \geq k(m) \end{array} \right]} \quad (6)$$

The exposure weight $W^{X_1}(t)$ corrects for potential time-varying confounding by L_1 . The exposure weight $W^{X_2}(t)$ corrects for potential time-varying confounding by L_2 . The censoring weight $W^{D_1}(t)$ corrects for potential selection bias due to censoring at dropout informed by L_3 . The censoring weight $W^{D_2}(t)$ corrects for potential selection bias due to censoring at death informed by L_3 .

For $j = 1, 2$ and $\text{logit } p = \ln(p/(1 - p))$, the numerator for the weights in equations (3) and (4) can be estimated from the following pooled logistic regression model:

$$\text{logit } P[X_j(k(m)) = x_j | Q_j, \bar{D}(k(m)) = 0] = \beta_{j0}(k(m)) + \beta'_{j1} Q_j(k(m)). \quad (7)$$

Note that $\beta_{j0}(k(m))$ are the time-specific intercepts with time-fixed confounders included in the pooled model. In addition, $Q_1(k(m)) = \{\bar{X}_1(k(m-1)), \bar{X}_2(k(m-1)), Z_1\}$, $Q_2(k(m)) = \{\bar{X}_1(k(m)), \bar{X}_2(k(m-1)), Z_2\}$, and β_{j1} is a vector of log hazard ratios for the effect of $\bar{X}$ and Z_j on $X_j(k(m))$. The denominator for the weights in equations (3) and (4) can be estimated from the following pooled logistic regression model:

$$\text{logit } P[X_j(k(m)) = x_j | U_j, \bar{D}(k(m)) = 0] = \gamma_{j0}(k(m)) + \gamma'_{j1} U_j(k(m)) \quad (8)$$

Note that $\gamma_{j0}(k(m))$ are the time-specific intercepts with time-fixed and time-varying confounders included in the pooled model. In addition, $U_1(k(m)) = \{\bar{X}_1(k(m-1)), \bar{X}_2(k(m-1)),$

$\bar{L}_1(k(m-1))\}$, $U_2(k(m)) = \{\bar{X}_1(k(m)), \bar{X}_2(k(m-1)), \bar{L}_2(k(m-1))\}$, and γ_{j1} is a vector of log hazard ratios for the effect of $\bar{X}$ and $\bar{L}_j(k(m-1))$ on $X_j(k(m))$.

Similarly, the numerator and denominator for the weights in equations (5) and (6) can be estimated from the following 2 pooled logistic regression models:

$$\begin{aligned} \text{logit } P[D_j(k(m)) = 0 | \bar{X}, Z_3, \bar{D}(k(m-1)) = 0] \\ = \theta_{j0}(k(m)) + \theta'_{j1} \bar{X}(k(m)) + \theta'_{j2} Z_3 \end{aligned} \quad (9)$$

$$\begin{aligned} \text{logit } P[D_j(k(m)) = 0 | \bar{X}, \bar{L}_3, \bar{D}(k(m-1)) = 0] \\ = \nu_{j0}(k(m)) + \nu'_{j1} \bar{X}(k(m)) + \nu'_{j2} \bar{L}_3(k(m)), \end{aligned} \quad (10)$$

where $\theta_{j0}(k(m))$ and $\nu_{j0}(k(m))$ are time-specific intercepts with solely time-fixed and all common predictors, respectively, included in the pooled model. In addition, θ_{j1} and ν_{j1} are vectors of log hazard ratios for the effect of $\bar{X}(k(m))$ on $D_j(k(m))$ adjusting for solely time-fixed and all common predictors of T and C , respectively. Finally, θ_{j2} and ν_{j2} are vectors of log hazard ratios for the effect of Z_3 and $\bar{L}_3(k(m))$ on $D_j(k(m))$, respectively, adjusting for $\bar{X}(k(m))$.

Data Analysis

In the pooled logistic regression models as well as the joint marginal structural Cox model, X_1 was alcohol consumption as drinks per week in the prior 6 months and X_2 was drug injections per week in the prior 6 months. Drinks per week were categorized as 0–20 and 21–140, with the latter category termed “heavy” alcohol consumption. Drug injections per week were categorized as 0 and 1–39, with the latter category termed “any” drug injections. These categories were selected based on prior research¹⁹ and to ensure an ample number of HIV cases across the levels of the joint distribution of X_1 and X_2 while minimizing extreme weights and preserving meaningful comparisons.

In all models, predictors were included as either indicator variables for categories or a restricted quadratic spline with knots at the 5th, 35th, 65th, and 95th percentiles.²¹ In the pooled logistic regression models, the time-varying cofounders included in L_1 and L_2 were from the prior measurement time, while the time-varying common predictors included in L_3 were from the most recent measurement time. Weights estimated from the pooled logistic models had a mean of 1.03 (standard deviation = 0.56), with a range of 0.11 to 17.99. These weights are shown over follow-up in Figure 2.

To examine additive interaction, results from the joint marginal structural model with a product term between alcohol consumption and injection drug use were used to estimate the relative excess risk due to interaction (RERI) as well as the corresponding confidence limits and P value based on the multivariate delta method. The RERI ($= \exp(\hat{\alpha}_1 + \hat{\alpha}_2 + \hat{\alpha}_3) - \exp(\hat{\alpha}_1) - \exp(\hat{\alpha}_2) + 1$) represents the increased hazard due to

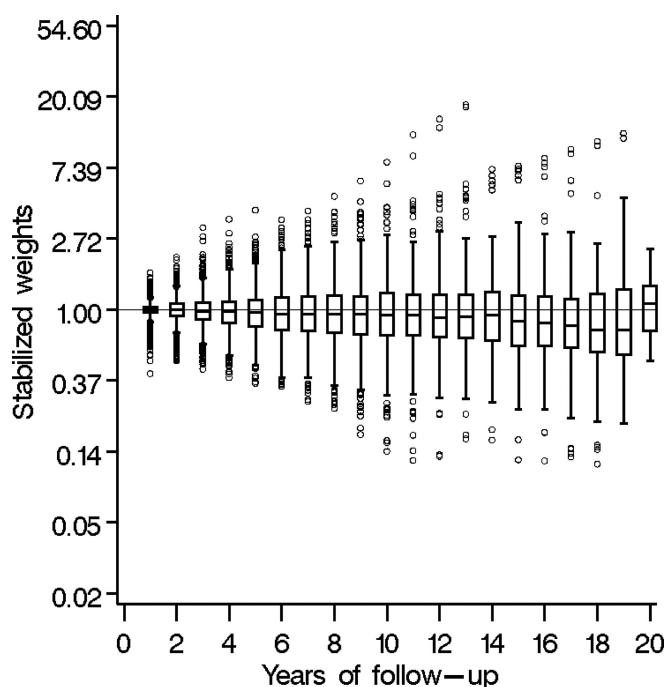


FIGURE 2. Box plots of stabilized weights estimated from pooled logistic models using data on 1525 African American injection drug users with 8181 person-years of follow-up, ALIVE cohort, 1988–2008.

additive interaction where an $RERI = 0$ corresponds to the null hypothesis of no additive interaction.²²

Unadjusted and standard adjusted Cox models were provided for comparison. The standard adjusted model accounted for the same confounders as the weighted model, as well as concurrent values of time-varying confounders, to reflect practices in the literature.^{7,8,23} The product term between alcohol consumption and injection drug use would represent interaction in these models only in the absence of bias due to confounding, measurement, or selection with respect to both exposures. Conversely, the product term would represent effect measure modification if bias due to confounding, measurement, or selection was present for only 1 of the 2 exposures.² Given that the product term between alcohol consumption and injection drug use in the joint marginal structural model was not statistically significant on the multiplicative scale, a joint marginal structural model as well as unadjusted and standard adjusted Cox models without the corresponding product terms were examined.

We assessed proportional hazards in the weighted Cox model by a joint robust Wald test on the product terms between the indicator for heavy drinks per week and time and between the indicator for any drug injections per week and time in the model without a product term between alcohol consumption and injection drug use. A similar joint Wald test was performed for log time. For the joint Wald test for the

product terms with time, $P = 0.0817$; for the joint Wald test for the product terms with log time, $P = 0.0315$. The coefficients corresponding to the P value for the joint Wald test in the time model were also closer to the null than the coefficients in the log time model. This suggests nonproportionality in the weighted Cox model with respect to log time and, to a lesser degree, time.

To explore this nonproportionality, the effects of alcohol consumption and injection drug use were examined for follow-up times within the first 3 years of study enrollment and after 3 years, while including a product term between alcohol consumption and injection drug use in the joint weighted model. The duration of 3 years was selected because it was approximately the median time to infection among the HIV cases. To circumvent any occurrences of nonproportionality potentially due to selection bias innate to the hazard ratio,²⁴ the cumulative incidence curves (ie, complement of survival functions) were compared by strata of alcohol consumption and injection drug use. All analyses were performed in SAS version 9.2.

RESULTS

Table 1 describes the characteristics in the prior 6 months of participants at study entry and during follow-up. Among the 1525 participants, 28% were female. At study entry, the median age was 37 (quartiles = 32; 42) years and the median number of years of formal education was 10 (quartiles = 10; 12). During follow-up, 63% of the person-years occurred while participants were consuming any alcohol and 58% occurred while injecting drugs in the prior 6 months. Figure 3 shows alcohol consumption and injection drug use in the prior 6 months by years of follow-up. Alcohol consumption and any drug injecting in the prior 6 months seemed to decrease during follow-up.

Table 2 shows crude, adjusted, and weighted hazard ratios with 95% confidence intervals (CIs) for the joint effects of alcohol consumption and injection drug use in the prior 6 months on HIV acquisition averaged over the 8181 person-years of follow-up. These models each included a product term between alcohol consumption and injection drug use. In the weighted model, the effect of heavy drinking per week in the absence of any drug injections was a hazard ratio of 1.58 (95% CI = 0.67 to 3.73). The effect of any drug injections per week in the absence of heavy drinking was a hazard ratio of 1.78 (1.10 to 2.89). The effect of heavy drinking and any drug injections was a hazard ratio of 2.45 (1.45 to 4.12). The robust P value for the Wald test for the product term was 0.7620. The corresponding $RERI$ was 0.08 (95% CI = -1.43 to 1.59), which corresponded to a P value of 0.9200. Analogous unadjusted hazard ratio estimates were 1.67 (0.72 to 3.84), 2.07 (1.31 to 3.28), and 3.36 (2.07 to 5.44), respectively, with a P value of 0.9474 for the Wald test for the product term. The corresponding standard adjusted hazard

TABLE 1. Characteristics in the Prior 6 Months of 1525 African American Injection Drug Users at Study Entry and Over 8181 Person-years of Follow-up, ALIVE Cohort, 1988–2008

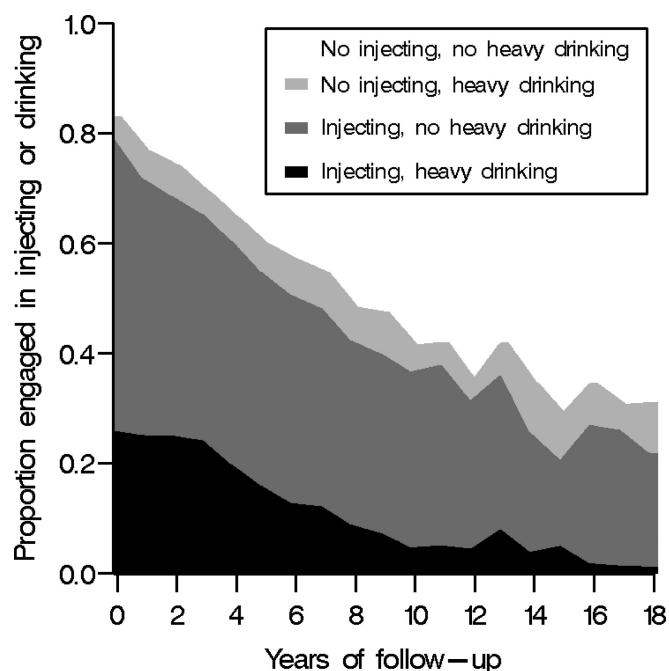
Characteristic	Entry	Follow-up
	(n = 1525 Participants)	(n = 8181 Person-years)
Age (years) ^a	37 (32; 42)	42 (36; 48)
Older than age 37 (years); % (no.)	48 (736)	72 (5890)
Female sex; % (no.)	28 (428)	28 (2291)
Education (years) ^a	10 (10; 12)	10 (10; 12)
More than 10 years of education; % (no.)	43 (662)	44 (3600)
Cocaine use ^b ; % (no.)	78 (1184)	58 (4745)
No. sexual partners; % (no.)		
>1	40 (604)	29 (2373)
1	43 (661)	47 (3845)
0	17 (260)	24 (1963)
Man having sex with a man; % (no.)	1 (16)	0.6 (49)
Any sexually transmitted infections ^c ; % (no.)	3 (52)	2 (164)
No. drug injections/week ^a	6 (1; 14)	1 (0; 7)
No. drug injections/week; % (no.)		
1–39	80 (1222)	58 (4745)
0	20 (303)	42 (3436)
Inject heroin only; % (no.)	61 (929)	42 (3436)
Inject cocaine only; % (no.)	57 (867)	36 (2945)
Inject both heroin and cocaine; % (no.)	57 (865)	39 (3191)
Attended shooting gallery; % (no.)	13 (199)	6 (491)
No. drinks/week ^a	8 (1; 28)	4 (0; 18)
No. drinks/week; % (no.)		
21–140	32 (491)	23 (1882)
1–20	44 (668)	40 (3272)
0	24 (366)	37 (3027)

^aMedian (quartiles).^bCrack, snort cocaine, inject cocaine only, and inject both heroin and cocaine.^cGenital herpes simplex virus, genital warts, gonorrhea, or syphilis.

ratio estimates were 1.34 (0.57 to 3.13), 1.56 (0.87 to 2.77), and 2.13 (1.15 to 3.95), respectively, with a *P* value of 0.9597 for the Wald test for the product term.

Figure 4 shows the proportion who became HIV-positive by alcohol consumption and injection drug use for the prior 6 months based on the weighted Cox model. Proportions were estimated among men at the median age and years of education of the entire cohort at study entry. Participants who reported both injecting and heavy drinking had the highest proportion of HIV infections during follow-up. Those who reported either injecting or heavy drinking, but not both, had the second highest proportion of HIV infections. Those who did not report injecting or heavy drinking had the lowest proportion of HIV infections.

In the weighted Cox model without a product term between alcohol consumption and injection drug use, the effect of heavy drinking per week was a hazard ratio of 1.41

**FIGURE 3.** Alcohol consumption and injection drug use in the prior 6 months by years of follow-up among 1525 African American injection drug users with 8181 person-years of follow-up, ALIVE cohort, 1988–2008.

(0.98 to 2.01). The effect of any drug injections per week was a hazard ratio of 1.72 (1.12 to 2.64). Analogous unadjusted hazard ratio estimates were 1.63 (1.17 to 2.27) and 2.06 (1.38 to 3.07), respectively. The corresponding standard adjusted hazard ratio estimates were 1.36 (0.97 to 1.92) and 1.57 (0.94 to 2.62), respectively.

Table 3 shows the weighted hazard ratio with 95% CI for the joint effects of heavy drinking and any drug injections in the prior 6 months within the first 3 years of follow-up and after. This model included a product term between alcohol consumption and injection drug use. The joint effects were larger in the first 3 years of follow-up compared with between 3 and 20 years. However, the CI for follow-up times within the first 3 years was particularly imprecise.

DISCUSSION

Among 1525 African American injection drug users in the ALIVE cohort followed for 8181 person-years, the effects of heavy drinking and any drug injections on HIV acquisition seemed not to depart from multiplicative or additive effects. We could not rule out interaction on either scale due to imprecision. If the results of the weighted analysis are corroborated by independent data sources, these results would suggest that alcohol-specific HIV risk reduction interventions should be targeted to both injectors and noninjectors and, similarly, injection-specific interventions should be targeted to both heavy and nonheavy drinkers.

TABLE 2. Crude, Adjusted, and Weighted Estimates for Joint Effects of Alcohol Consumption and Injection Drug Use in the Prior 6 Months on HIV Acquisition Among 1525 African American Injection Drug Users Followed for 8181 Person-years, ALIVE Cohort, 1988–2008

No. Injections/Week	No. Drinks/ Week	No. HIV Infections/ No. Person-years	Hazard Ratio (95% CI)		
			Crude	Adjusted ^a	Weighted ^a
1–39	21–140	53/1475	3.36 (2.07–5.44)	2.13 (1.15–3.95)	2.45 (1.45–4.12)
	0–20	68/3283	2.07 (1.31–3.28)	1.56 (0.87–2.77)	1.78 (1.10–2.89)
	Overall	121/4758			
0	21–140	7/436	1.67 (0.72–3.84)	1.34 (0.57–3.13)	1.58 (0.67–3.73)
	0–20 ^b	27/2987	1.00	1.00	1.00
	Overall	34/3423			
<i>P</i> value for product term ^c			<i>P</i> = 0.9474	<i>P</i> = 0.9597	<i>P</i> = 0.7620
Overall		155/8181			

^aAccounted for age at entry, sex, years of education, cocaine use, shooting gallery attendance, number of sexual partners, male sex with men, as well as sexually transmitted infections, including genital herpes simplex virus, genital warts, gonorrhea, and syphilis.

^bReference category.

^cThe product term would represent interaction only in the absence of bias due to confounding, measurement, or selection with respect to both exposures. Conversely, the product term would represent effect measure modification if bias due to confounding, measurement, or selection was present for only 1 of the 2 exposures. Unbiased estimation of joint effects and in turn interaction also requires consistency, positivity, and correct model specification.

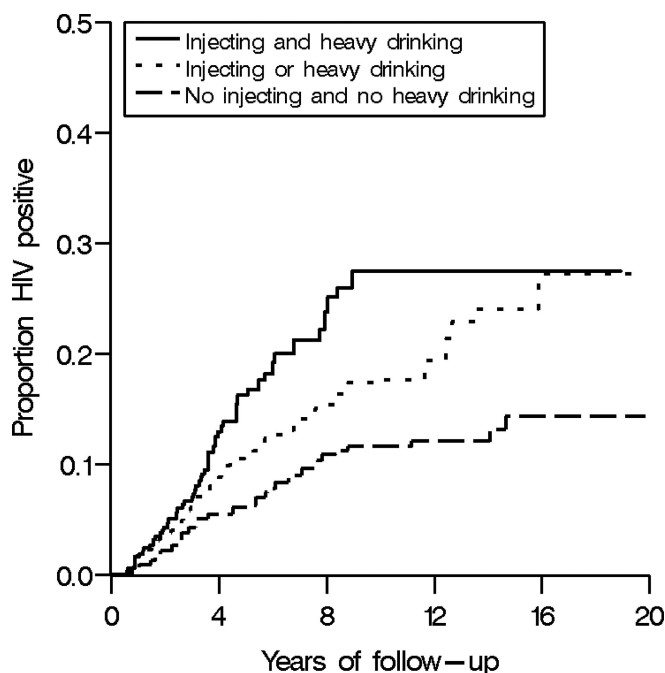


FIGURE 4. Proportion who became HIV-positive by alcohol consumption and injection drug use in the prior 6 months among 1525 African American injection drug users with 8181 person-years of follow-up, ALIVE cohort, 1988–2008. Proportions were estimated among men at the median age and years of education of the entire cohort at study entry.

However, based on the weighted model, the hazard ratio for the effect of heavy drinking and any drug injections seemed to be larger within the first 3 years of follow-up. This larger hazard ratio may be due to a waning effect of heavy drinking and injecting on HIV acquisition over time. Evidence against a

waning effect was provided in Figure 4, which shows that participants who reported both injecting and heavy drinking consistently had the highest proportion of HIV infections. Alternatively, chance or selection bias due to a greater initial depletion of those susceptible to HIV infection among heavy drinkers and injectors may be the source of the observed attenuation with time.²⁴ Selection bias due to a greater initial depletion of susceptible heavy drinkers and injectors would not be accounted for in the censoring weights, given that a measure of innate susceptibility to HIV infection was not available as a covariate when estimating the censoring weights.

The standard adjusted analysis provided hazard ratio estimates that were somewhat attenuated compared with the results from the weighted analysis, both analyses included product terms between alcohol consumption and injection drug use. Specifically, the excess hazard for the effect of heavy drinking and any drug injections from the weighted analysis was 22% (1–1.13/1.45) stronger than results from the standard adjusted analysis. These attenuated hazard ratio estimates may be due to the fact that standard adjustment can remove indirect effects mediated through time-varying confounders and induce selection bias.^{3,25–27}

For unbiased estimation of effects in the context of standard regression and marginal structural models, the assumptions of exchangeability, consistency, positivity, and correct model specification must be met.²⁸ As noted by Hernán et al,³ as well as by VanderWeele,² the aforementioned assumptions must also hold for unbiased estimation of joint effects. In the context of the joint marginal structural model, the exchangeability assumption states that there are no unmeasured confounders of the relationship between X_1 and T as well as the relationship between X_2 and T . In addition, informative censoring by unmeasured factors

TABLE 3. Weighted Estimates for Joint Effects of Alcohol Consumption and Injection Drug Use in the Prior 6 Months on HIV Acquisition Before and After 3 Years of Follow-up Among 1525 African American Injection Drug Users Followed for 8181 Person-years, ALIVE Cohort, 1988–2008

Injections/Week	No. Drinks/ Week	No. HIV Infections Person-years	Weighted ^a Hazard Ratio (95% CI)	
			Within the First 3 Years of Follow-up	After the First 3 Years of Follow-up
1–39	21–140	53/1475	3.40 (1.13–10.23)	2.35 (1.33–4.16)
	0–20	68/3283	2.91 (0.97–8.75)	1.49 (0.88–2.55)
	Overall	121/4758		
0	21–140	7/436	3.17 (0.78–12.83)	1.11 (0.33–3.74)
	0–20 ^b	27/2987	1.00	1.00
	Overall	34/3423		
Overall		155/8181		

^aAccounted for age at entry, sex, years of education, cocaine use, shooting gallery attendance, number of sexual partners, male sex with men, as well as sexually transmitted infections, including genital herpes simplex virus, genital warts, gonorrhea, and syphilis.

^bReference category.

must be absent. Formally, $f[X(k_m)|\bar{X}(k_{m-1}), \bar{L}(k_{m-1})] = f[X(k_m)|\bar{X}(k_{m-1}), \bar{L}(k_{m-1}), T^x]$ and $f[T|L] = f[T|L, C]$. For the ALIVE example, unmeasured factors may exist, given that the indicators used for high-risk behaviors may not fully capture the association between such behaviors and HIV acquisition or censoring among participants.¹⁹ Measurement error regarding covariates of interest poses an additional threat to exchangeability as does the observed limited number of HIV infections across strata of the joint distribution of alcohol consumption and injection drug use.

Consistency states that $T^{\bar{X}} = T^{x,p}$ if $\bar{X} = \bar{x}$ for all p , where p is the mechanism by which the level of X is determined. As such, the observed failure time is the same as the failure time that would have occurred if X were assigned. It also implies that the mechanism by which the level of X is determined does not influence the effect of $\bar{X}$ on $T^{\bar{X}}$. In other words, among ALIVE participants, the time to HIV acquisition for the observed level of alcohol consumption and number of drug injections is the time to HIV acquisition that would have occurred if the level of alcohol consumption and drug injections were assigned. In addition, the effect of heavy drinking or injection drug use does not depend on drinking or injection pattern (eg, binge drinking or frequent injecting).

Positivity requires that $f[X(k_m)|\bar{X}(k_{m-1}), \bar{L}(k_{m-1}), \bar{D}(k_m) = 0, T \geq k_m] > 0$ for all $x \in X$ and $P(D(k_m) = 0|\bar{X}(k_m), \bar{L}(k_m), \bar{D}(k_{m-1}) = 0, T \geq k_m) > 0$ for all $k_m \leq \max(y_i)$. Therefore, every level of alcohol consumption as well as injection drug use must be possible in each subset of the ALIVE cohort defined by the observed histories of alcohol consumption, injection drug use, and measured confounders. Similarly, there must be participants who are not censored at each observed follow-up time within each subset of the cohort defined by the observed histories of alcohol consumption, injection drug use, and measured common predictors of censoring and HIV acquisition time. In the present

setting, we did not expect deterministic departures from positivity, and we observed no evidence of random departures from positivity. The latter is based on a lack of extreme weights.^{28,29}

Correct model specification implies that appropriate functional forms are used in the pooled logistic and final weighted models such that $f[X(k_m)|\bar{X}(k_{m-1}), \bar{L}(k_{m-1})] = f[X(k_m)|g_0(\bar{X}(k_{m-1})), g_1(\bar{L}(k_{m-1}))]$ and $P(D(k_m) = 0|\bar{X}(k_m), \bar{L}(k_m), \bar{D}(k_{m-1}) = 0, T \geq k_m) = P(D(k_m) = 0|g_2(\bar{X}(k_m)), g_3(\bar{L}(k_m)), \bar{D}(k_{m-1}) = 0, T \geq k_m)$, where $g_0(\bar{X}(k_{m-1})), g_1(\bar{L}(k_{m-1})), g_2(\bar{X}(k_m))$, and $g_3(\bar{L}(k_m))$ are coarsening functions of $\bar{X}(k_{m-1}), \bar{L}(k_{m-1}), \bar{X}(k_m)$, and $\bar{L}(k_m)$, respectively. The lack of extreme weights in the ALIVE cohort also provides some evidence against model misspecification.^{28,29} In addition, positivity and correct model specification were facilitated by careful consideration of all categorizations, particularly for alcohol consumption and injection drug use. Furthermore, indicators for categories and splines in the case of continuous predictors were used in the modeling process.

The aforementioned definitions and assumptions imply that unbiased assessment of interaction requires no unmeasured confounders of the relationship between both exposures and the outcome. In contrast, assessment of effect measure modification requires only no unmeasured confounders of the relationship between the primary exposure and outcome.

The methods presented in this paper pertain to the assessment of interaction using marginal structural models. Such methods are necessary when both exposures are potentially subject to time-varying confounding affected by prior exposure, which can occur in both chronic and infectious disease epidemiology.^{7–10} If effect measure modification of a time-varying exposure by a time-fixed secondary covariate is of interest and that exposure is subject to time-varying confounding affected by prior exposure, then a marginal struc-

tural model is needed. This model can be a standard marginal structural model with a single set of exposure weights, and a product term between the exposure and the potential time-fixed effect measure modifier can be employed. However, if effect measure modification of a time-varying exposure by a time-varying covariate is of interest and that exposure is subject to time-varying confounding affected by prior exposure, then methods such as G-estimation of structural nested models,³⁰ history-adjusted marginal structural models,³¹ or dynamic marginal structural models³² are needed.

Important to note is that a standard marginal structural model can also be considered a joint marginal structural model, with censoring playing the role of the second exposure. However, typically, we are interested only in the effect of the exposure while precluding the censoring. Therefore, rather than estimate the entire joint distribution for the exposure and censoring, we estimate the effect of the exposure with censoring set to never.

In conclusion, estimation of joint effects is frequently of interest in epidemiologic research. This paper describes and demonstrates joint marginal structural Cox proportional hazards models in the context of time-varying exposures potentially subject to time-varying confounding affected by prior exposure, with the aim to encourage the use of these valuable techniques.

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eAppendix:

DESCRIPTION OF SAS CODE USED TO FIT JOINT MARGINAL STRUCTURAL COX PROPORTIONAL HAZARDS MODEL USING DATA FROM THE AIDS LINK TO INTRAVENOUS EXPERIENCE COHORT STUDY

Here we provide SAS code to fit the joint marginal structural Cox proportional hazards model described in the main text using data from the AIDS Link to Intravenous Experience (ALIVE) cohort study.¹ The ALIVE data file, ALIVEDATA, contains multiple records per participant where each participant is uniquely identified by the variable, ID. Each record corresponds to a calendar date, VISITY, when a study measurement was taken. The ENTER variable denotes the time since study entry for the VISITY of the current record, while the variable EXIT represents the time since study entry corresponding to the VISITY of the subsequent record. However, for the final record, EXIT represents the time since study entry at exit from follow up due to HIV infection or censoring. A description of the 2-part process used to fit the joint marginal structural Cox model using ALIVEDATA follows. In general, the stabilized weight, $W(t) = W^{X_1}(t)W^{X_2}(t)W^{D_1}(t)W^{D_2}(t)$, described in the main text was estimated in parts 1a through 1e. The stabilized weight estimated in part 1 was used to fit the joint Cox model in part 2. Note in the provided SAS code, $W(t)$ is represented as, w, while $W^{X_1}(t)$, $W^{X_2}(t)$, $W^{D_1}(t)$, and $W^{D_2}(t)$ are shown as wx1, wx2, wd1, and wd2.

In part 1a, two pooled logistic models were fit to ALIVEDATA and used to estimate the conditional probabilities for the numerator and denominator of the weight, wx1. The outcome in both models was PDBIN which was an indicator of whether a participant reported heavy drinking in the prior six months at the current measurement time (PDBIN=1 for yes; PDBIN=0

for no). The *proc logistic* statement here and elsewhere without the *desc* option models the log odds that the outcome is 0, in this case that PDBIN=0.

In the pooled logistic model used to estimate the conditional probabilities for the numerator of wx1, predictors included the time-updated time-specific intercepts (ENTER ENTER1 ENTER2 ENTER3), time-updated indicators of heavy drinking (PDBIN1B) and injection drug use (INJBIN1B) in the preceding six months and collected at the prior measurement time, as well as the time-fixed confounders measured at study entry, Z_1 . These time-fixed confounders included age (AGE, AGE1, AGE2, AGE3), an indicator for sex (FEMALE), and years of education (EDY EDY1 EDY2 EDY3). Product terms between the time-fixed confounders (AGEEDY=AGE*EDY, FEMAGE=FEMALE*AGE, and FEMEDY=FEMALE*EDY) were also included as predictors. Note here and elsewhere restricted quadratic splines² were used to model the continuous predictors, ENTER, AGE, and EDY where the additional variables beyond the main effect included in the regression (e.g., AGE1, AGE2, and AGE3) correspond to the restricted quadratic spline basis functions. The pooled logistic model outputs the conditional probability that PDBIN=0 (num1) at each record. These outputted probabilities are saved in the dataset, n1. So that the numerator of the weight, wx1, is derived from the conditional probability of reporting the level of alcohol consumption that a participant reported at a given measurement time, for records where PDBIN=1, the data step subsequent to the pooled logistic regression was used to reassign num1 to correspond to the probability that PDBIN=1 in the n1 dataset.

In the pooled logistic model used to estimate the conditional probabilities for the denominator of wx1, predictors included the time-updated time-specific intercepts, the time-updated indicators of heavy drinking and injection drug use collected at the prior measurement

time, the time-fixed confounders included in the pooled logistic model used to estimate the numerator for wx_1 , as well as the time-updated confounders included in L_1 . The time-updated confounders pertained to the preceding six months and were collected at the prior measurement time. These time-updated confounders included indicators for the report of a sexually transmitted infection (STI1B), the number of sexual partners (SEX3CAT1B), male sex with a male (MSM1B), cocaine use (COKE1B), and shooting gallery attendance (GALL1B). The pooled logistic model outputs the conditional probability that $PDBIN=0$ (den1) at each record. These outputted probabilities are saved in the dataset d1. So that the denominator of the weight, wx_1 , is derived from the conditional probability of reporting the level of alcohol consumption that a participant reported at a given measurement time, for records where $PDBIN=1$, the data step subsequent to the pooled logistic regression was used to reassign den1 to correspond to the probability that $PDBIN=1$ in the d1 dataset.

In part 1b, two pooled logistic models were fit to ALIVEDATA and used to estimate the conditional probabilities for the numerator and denominator of the weight, wx_2 . The outcome in both models was INJBIN which was an indicator of whether a participant reported any injection drug use in the prior six months at the current measurement time ($INJBIN=1$ for yes; $INJBIN=0$ for no). The *proc logistic* statement models the log odds that $INJBIN=0$.

In the pooled logistic model used to estimate the conditional probability for the numerator of wx_2 , predictors included the time-updated time-specific intercepts, time-updated indicators of heavy drinking (PDBIN) and injection drug use (INJBIN1B) pertaining to the preceding six months, but collected at the concurrent and prior measurement times, respectively, as well as the time-fixed confounders measured at study entry, Z_2 . These time-fixed confounders

were the same as those included in Z_1 . The pooled logistic model outputs the conditional probability that INJBIN=0 (num2) at each record. These outputted probabilities are saved in the dataset, n2. So that the numerator of the weight, wx2, is derived from the conditional probability of reporting the level of injection drug use that a participant reported at a given measurement time, for records where INJBIN=1, the data step subsequent to the pooled logistic regression was used to reassign num2 to correspond to the probability that INJBIN=1 in the n2 dataset.

In the pooled logistic model used to estimate the conditional probability for the denominator of wx2, predictors included the time-updated time-specific intercepts, time-updated indicators of heavy drinking and injection drug use pertaining to the preceding six months, but collected at the concurrent and prior measurement times, time-fixed confounders included in the pooled logistic model used to estimate the numerator of wx2, as well as the time-updated confounders included in L_2 . These time-updated confounders were the same as those included in L_1 . The pooled logistic model outputs the conditional probability that INJBIN=0 (den2) at each record. These outputted probabilities are saved in the dataset d2. So that the denominator of the weight, wx2, is derived from the conditional probability of reporting the level of injection drug use that a participant reported at a given measurement time, for records where INJBIN=1, the data step subsequent to the pooled logistic regression was used to reassign den2 to correspond to the probability that INJBIN=1 in the d2 dataset.

In part 1c, two pooled logistic models were fit to ALIVEDATA and used to estimate the conditional probabilities for the numerator and denominator of the weight, wd1. The outcome in both models was DROP which was an indicator of whether a participant dropped out of the study at a given EXIT time (DROP=1 for yes; DROP=0 for no). The *proc logistic* statement models

the log odds that $\text{DROP}=0$.

In the pooled logistic model used to estimate the conditional probabilities for the numerator in wd1, predictors included the time-updated time-specific intercepts (EXIT EXIT1 EXIT2 EXIT3), time-updated indicators of heavy drinking (PDBIN) and injection drug use (INJBIN) pertaining to the preceding six months and collected at the most recent measurement time, as well as the time-fixed common predictors measured at study entry, Z_3 . These time-fixed common predictors were the same as those included in Z_1 and Z_2 . However, product terms between the time-fixed common predictors were not included as predictors in the pooled logistic model. The pooled logistic model outputs the conditional probability that $\text{DROP}=0$ (num3) at each record where the numerator of wd1 is the product of conditional probabilities that $\text{DROP}=0$. These outputted probabilities are saved in the dataset, n3.

In the pooled logistic model used to estimate the conditional probabilities for the denominator in wd1, predictors included the time-updated time-specific intercepts, time-updated indicators of heavy drinking and injection drug use pertaining to the preceding six months and collected at the most recent measurement time, time-fixed common predictors included in the pooled logistic model used to estimate the numerator for wd1, as well as the time-updated common predictors included in L_3 . These time-updated common predictors were the same covariates as those included L_1 and L_2 , but collected at the most recent measurement time. The pooled logistic model outputs the conditional probability that $\text{DROP}=0$ (den3) where the denominator of wd1 is the product of conditional probabilities that $\text{DROP}=0$. These outputted probabilities are saved in the dataset, d3.

In part 1d, two pooled logistic models were fit to ALIVEDATA and used to estimate the

conditional probabilities for the numerator and denominator of the weight, wd2. The outcome in both models was DIED which was an indicator of whether a participant died at a given EXIT time (DIED=1 for yes; DIED=0 for no). The *proc logistic* statement models the log odds that DIED=0. The specification of the predictors included in these pooled logistic regression models were identical to the specifications used to estimate wd1. The pooled logistic model outputs the conditional probability that DIED=0 (num4 and den4) where the numerator and denominator of wd2 is the product of conditional probabilities that DIED=0. These outputted probabilities are saved in the n4 and d4 datasets.

In part 1e, the data sets with the conditional probabilities are merged with ALIVEDATA to form dataset, e. In the data step that follows the merge, the weights wx1, wx2, wd1, and wd2 are obtained by taking the ratio of the products of the conditional probabilities estimated in parts 1a through 1d. The weight, w is obtained from taking the product of wx1, wx2, wd1, and wd2.

In part 2, the *proc phreg* statement is used to fit a weighted Cox model for the joint effect of heavy drinking and injection drug use on HIV acquisition. The indicators for heavy drinking and any injection drug use in the prior six months and collected at the current measurement time were included as predictors in the weighted Cox model along with the product term between heavy drinking and any injection drug use (PDINJ=PDBIN*INJBIN). The time-fixed covariates included in Z_1 , Z_2 , and Z_3 were also included as predictors. The outcome was an indicator of HIV infection at a given exit time (HIV=1 if yes, HIV=0 if no). The *covs* option outputs model parameters with robust standard errors. The statement *weight w*, re-weights the data using the weights, w, estimated in part 1. The *test* statement performs a joint Wald test on the product term represented by PDINJ. The output from this Wald test is labeled *pterm*. *Contrast* statements with the *estimate=exp* option are used to estimate hazard ratios for heavy drinking alone, any

injection drug use alone, and both heavy drinking and any injection drug use.

GLOSSARY OF DATA AND VARIABLES USED IN PROVIDED SAS CODE

ALIVEDATA is the ALIVE data file. The variables included in ALIVEDATA appear in uppercase and are defined as:

- ID – Unique participant identifier
- VISITY – Calendar date when study measurement was taken
- ENTER – Time since study entry for the VISITY of the current record
- ENTER1, ENTER2, ENTER3 – Restricted quadratic spline basis functions for ENTER
- EXIT – Time since study entry corresponding to the VISITY of the subsequent record; for the final record, time since study entry at exit from follow up due to HIV infection or censoring
- EXIT1, EXIT2, EXIT3 – Restricted quadratic spline basis functions for EXIT
- PDBIN – Indicator of whether a participant reported heavy drinking in the prior six months at the current measurement time (PDBIN=1 for yes; PDBIN=0 for no)
- PDBIN1B – Indicator of whether a participant reported heavy drinking in the prior six months at the prior measurement time (PDBIN1B=1 for yes; PDBIN1B=0 for no)
- INJBIN – Indicator of whether a participant reported any drug injections in the prior six months at the current measurement time (INJBIN=1 for yes; INJBIN=0 for no)
- INJBIN1B – Indicator of whether a participant reported any drug injections in the prior six months at the prior measurement time (INJBIN1B=1 for yes; INJBIN1B=0 for no)
- PDINJ – $PDBIN * INJBIN$
- AGE – Age at study entry
- AGE1, AGE2, AGE3 – Restricted quadratic spline basis functions for AGE
- FEMALE – Indicator of female sex (FEMALE=1 for yes; FEMALE=0 for no)

- EDY – Years of education at study entry
- EDY1, EDY2, EDY3 – Restricted quadratic spline basis functions for EDY
- AGEEDY – AGE*EDY
- FEMAGE – FEMALE*AGE
- FEMEDY – FEMALE*EDY
- STI – Indicator for the report of a sexually transmitted infection during the prior six months at the current measurement time
- STI1B – Indicator for the report of a sexually transmitted infection during the prior six months at the prior measurement time
- SEX3CAT – Indicators for the reported number of sexual partners during the prior six months at the current measurement time
- SEX3CAT1B – Indicators for the reported number of sexual partners during the prior six months at the prior measurement time
- MSM – Indicator for the report of male sex with a male during the prior six months at the current measurement time
- MSM1B – Indicator for the report of male sex with a male during the prior six months at the prior measurement time
- COKE – Indicator for the report of cocaine use during the prior six months at the current measurement time
- COKE1B – Indicator for the report of cocaine use during the prior six months at the prior measurement time
- GALL – Indicator for the report of shooting gallery attendance during the prior six months at the current measurement time

- GALL1B – Indicator for the report of shooting gallery attendance during the prior six months at the prior measurement time
- DROP – Indicator of whether a participant dropped out of the study at a given EXIT time (DROP=1 for yes; DROP=0 for no)
- DIED – Indicator of whether a participant died at a given EXIT time (DIED=1 for yes; DIED=0 for no)
- HIV – Indicator of HIV infection at a given EXIT time (HIV=1 for yes; HIV=0 for no)

The data and variables generated from ALIVEDATA appear in lowercase and are defined as:

- num1 – Conditional probability of reporting the level of alcohol consumption that a participant reported at a given measurement time in numerator of wx1
- n1 – Dataset that contains num1
- den1 – Conditional probability of reporting the level of alcohol consumption that a participant reported at a given measurement time in denominator of wx1
- d1 – Dataset that contains den1
- num2 – Conditional probability of reporting the level of injection drug use that a participant reported at a given measurement time in numerator of wx2
- n2 – Dataset that contains num2
- den2 – Conditional probability of reporting the level of injection drug use that a participant reported at a given measurement time in denominator of wx2
- d2 – Dataset that contains den2
- num3 – Conditional probability of a participant not dropping out at a given EXIT time in numerator of wd1

- n3 – Dataset that contains num3
- den3– Conditional probability of a participant not dropping out at a given EXIT time in denominator of wd1
- d3 – Dataset that contains den3
- num4 – Conditional probability of a participant not dying at a given EXIT time in numerator of wd2
- n4 – Dataset that contains num4
- den4– Conditional probability of a participant not dying at a given EXIT time in denominator of wd2
- d4 – Dataset that contains den4
- e – Dataset resulting from merging ALIVEDATA, n1, d1, n2, d2, n3, d3, n4, and d4
- wx1 – Exposure weight for alcohol
- wx2 – Exposure weight for injection drug use
- wx3 – Censoring weight for dropout
- wx4 – Censoring weight for death
- w – Inverse probability-of-exposure-and-censoring weight used to fit joint Cox model

SAS (VERSION 9.2) CODE

/***Part 1: Estimating Stabilized Weight, w;*/

/***Part 1a: estimating conditional probabilities for stabilized weight, wx1 using pooled logistic regression;*/

/*Numerator for wx1;*/

*Sorting records in ALIVEDATA by ID and VISITY;

proc sort data=ALIVEDATA; by ID VISITY; run;

*Modeling the log odds that PDBIN=0 and outputting corresponding probabilities as num1 into n1 dataset;

proc logistic data=ALIVEDATA;

 model PDBIN=ENTER ENTER1 ENTER2 ENTER3 PDBIN1B INJBIN1B AGE AGE1 AGE2 AGE3 FEMALE EDY
 EDY1 EDY2 EDY3 AGEEDY FEMAGE FEMEDY;

 output out=n1(keep=ID VISITY PDBIN num1) p=num1;

run;

*For records where PDBIN=1, reassigning num1 to correspond to the probability that PDBIN=1 in n1 dataset;

data n1;

 set n1;

 if PDBIN=1 then num1=1-num1;

 keep ID VISITY PDBIN num1;

run;

/*Denominator for wx1;*/

*Modeling the log odds that PDBIN=0 and outputting corresponding probabilities as den1 into d1 dataset;

proc logistic data=ALIVEDATA;

 class SEX3CAT1B/param=ref desc;

 model PDBIN=ENTER ENTER1 ENTER2 ENTER3 PDBIN1B INJBIN1B AGE AGE1 AGE2 AGE3 FEMALE EDY
 EDY1 EDY2 EDY3 AGEEDY FEMAGE FEMEDY STI1B SEX3CAT1B MSM1B COKE1B GALL1B;

 output out=d1(keep=ID VISITY PDBIN den1) p=den1;

run;

*For records where PDBIN=1, reassigning den1 to correspond to the probability that PDBIN=1 in d1 dataset;

data d1;

 set d1;

```

        if PDBIN=1 then den1=1-den1;
        keep ID VISITY PDBIN den1;
run;

/**Part 1b: estimating conditional probabilities for stabilized weight, wx2 using pooled logistic regression;** /
/*Numerator for wx2;*/
*Modeling the log odds that INJBIN=0 and outputting corresponding probabilities as num2 into n2 dataset;
proc logistic data=ALIVEDATA;
    model INJBIN=ENTER ENTER1 ENTER2 ENTER3 PDBIN INJBIN1B AGE AGE1 AGE2 AGE3 FEMALE EDY
        EDY1 EDY2 EDY3 AGEEDY FEMAGE FEMEDY;
    output out=n2(keep=ID VISITY INJBIN num2) p=num2;
run;
*For records where INJBIN=1, reassigning num2 to correspond to the probability that INJBIN=1 in n2 dataset;
data n2;
    set n2;
    if INJBIN=1 then num2=1-num2;
    keep ID VISITY INJBIN num2;
run;

/*Denominator for wx2 ;*/
*Modeling the log odds that INJBIN=0 and outputting corresponding probabilities as den2 into d2 dataset;
proc logistic data=ALIVEDATA;
    class SEX3CAT1B/param=ref desc;
    model INJBIN=ENTER ENTER1 ENTER2 ENTER3 PDBIN INJBIN1B AGE AGE1 AGE2 AGE3 FEMALE EDY
        EDY1 EDY2 EDY3 AGEEDY FEMAGE FEMEDY STI1B SEX3CAT1B MSM1B COKE1B GALL1B;
    output out=d2(keep=ID VISITY INJBIN den2) p=den2;
run;
*For records where INJBIN=1, reassigning den2 to correspond to the probability that INJBIN=1 in d2 dataset;
data d2;
    set d2;
    if INJBIN=1 then den2=1-den2;
    keep ID VISITY INJBIN den2;

```

```

run;

/**Part 1c: Estimating conditional probabilities for stabilized weight, wd1 using pooled logistic regression;**/
/*Numerator for wd1;*/
*Modeling the log odds that DROP=0 and outputting corresponding probabilities as num3 into n3 dataset;
proc logistic data=ALIVEDATA;
    model DROP=EXIT EXIT1 EXIT2 EXIT3 PDBIN INJBIN AGE AGE1 AGE2 AGE3 FEMALE EDY
        EDY1 EDY2 EDY3;
    output out=n3(keep=ID VISITY num3) p=num3;
run;

/*Denominator for wd1;*/
*Modeling the log odds that DROP=0 and outputting corresponding probabilities as den3 into d3 dataset;
proc logistic data=ALIVEDATA;
    class SEX3CAT/param=ref desc;
    model DROP=EXIT EXIT1 EXIT2 EXIT3 PDBIN INJBIN AGE AGE1 AGE2 AGE3 FEMALE EDY
        EDY1 EDY2 EDY3 STI SEX3CAT MSM COKE GALL;
    output out=d3(keep= ID VISITY den3) p=den3;
run;

/**Part 1d: estimating conditional probabilities for stabilized weight, wd2 using pooled logistic regression;**/
/*Numerator for wd2;*/
*Modeling the log odds that DIED=0 and outputting corresponding probabilities as num4 into n4 dataset;
proc logistic data=ALIVEDATA;
    model DIED=EXIT EXIT1 EXIT2 EXIT3 PDBIN INJBIN AGE AGE1 AGE2 AGE3 FEMALE EDY
        EDY1 EDY2 EDY3;
    output out=n4(keep= ID VISITY num4) p=num4;
run;

/*Denominator for wd2;*/
*Modeling the log odds that DIED=0 and outputting corresponding probabilities as den4 into d4 dataset;
proc logistic data=ALIVEDATA;

```

```

class SEX3CAT/param=ref desc;
model DIED=EXIT EXIT1 EXIT2 EXIT3 PDBIN INJBIN AGE AGE1 AGE2 AGE3 FEMALE EDY
      EDY1 EDY2 EDY3 STI SEX3CAT MSM COKE GALL;
output out=d4(keep= ID VISITY den4) p=den4;
run;

/**Part 1e: calculating cumulative probabilities for stabilized weights and in turn, w;**/
*Sorting records in ALIVEDATA and all generated datasets by ID and VISITY;
proc sort data=ALIVEDATA; by ID VISITY; run;
proc sort data=n1; by ID VISITY; run;
proc sort data=d1; by ID VISITY; run;
proc sort data=n2; by ID VISITY; run;
proc sort data=d2; by ID VISITY; run;
proc sort data=n3; by ID VISITY; run;
proc sort data=d3; by ID VISITY; run;
proc sort data=n4; by ID VISITY; run;
proc sort data=d4; by ID VISITY; run;

*Merging ALIVEDATA with generated datasets by ID and VISITY;
data e; merge ALIVEDATA n1 d1 n2 d2 n3 d3 n4 d4; by ID VISITY; run;
*Sorting merged dataset, e;
proc sort data=e; by ID VISITY; run;
*Calculating wx1, wx2, wd1, and wd2;
data e;
  set e;
  by ID VISITY;
  retain x1num x1den x2num x2den d1num d1den d2num d2den;
  if first.id then do; x1num=1; x1den=1; x2num=1; x2den=1; d1num=1; d1den=1; d2num=1; d2den=1; end;
  x1num=x1num*num1;
  x1den=x1den*den1;
  wx1=x1num/x1den;
  x2num=x2num*num2;

```

```

x2den=x2den*den2;
wx2=x2num/x2den;
d1num=d1num*num3;
d1den=d1den*den3;
wd1=d1num/d1den;
d2num=d2num*num4;
d2den=d2den*den4;
wd2=d2num/d2den;
run;
*Calculating w;
data e;
    set e;
    w=wx1*wx2*wd1*wd2;
    label num1= den1= num2= den2= num3= den3= num4= den4=;
run;

/****Part 2: Fitting Joint Marginal Structural Cox Proportional Hazards Model;****/

proc phreg data=e covs;
    model (ENTER, EXIT)*HIV(0)=PDBIN INJBIN PDINJ AGE AGE1 AGE2 AGE3 FEMALE EDY
        EDY1 EDY2 EDY3/ties=efron rl;

    weight w;
    pterm: test PDINJ;
    contrast ' PDBIN=1 and INJBIN=0 vs PDBIN =0 and INJBIN=0' PDBIN 1 / estimate=exp;
    contrast ' PDBIN=0 and INJBIN=1 vs PDBIN =0 and INJBIN=0' INJBIN 1 / estimate=exp;
    contrast ' PDBIN=1 and INJBIN=1 vs PDBIN=0 and INJBIN=0' PDBIN 1 INJBIN 1 PDINJ 1 / estimate=exp;
run;

```

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2. Howe CJ, Cole SR, Westreich DJ, Greenland S, Napravnik S, Eron JJ, Jr. Splines for Trend Analysis and Continuous Confounder Control [Research Letter]. *Epidemiology* 2011;**22**(6):874-875.