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Flexible Marginal Structural Models for Estimating the Cumulative Effect of a Time-Dependent Treatment on the Hazard: Reassessing the Cardiovascular Risks of Didanosine Treatment in the Swiss HIV Cohort Study

Yongling XIAO, Michal ABRAHAMOWICZ, Erica E. M. MOODIE, Rainer WEBER, and James YOUNG

The association between antiretroviral treatment and cardiovascular disease (CVD) risk in HIV-positive persons has been the subject of much debate since the Data collection on Adverse events of Anti-HIV Drugs (D:A:D) study reported that recent use of two antiretroviral drugs, abacavir (ABC) and didanosine (DDI), was associated with increased risk. We focus on the potential impact of DDI use, as this drug has not been as studied intensively as ABC. We propose a flexible marginal structural Cox model with weighted cumulative exposure modeling (Cox WCE MSM) to address two key challenges encountered when using observational longitudinal data to assess the adverse effects of medication: (1) the need to model the cumulative effect of a time-dependent treatment and (2) the need to control for time-dependent confounders that also act as mediators of the effect of past treatment. Simulations confirm that the Cox WCE MSM yields accurate estimates of the causal treatment effect given complex exposure effects and time-dependent confounding. We then use the new flexible Cox WCE MSM to assess the association between DDI use and CVD risk in the Swiss HIV Cohort Study. In contrast to the nonsignificant results obtained with conventional parametric Cox MSMs, our new Cox WCE MSM identifies a significant short-term risk increase due to DDI use in the previous year. Supplementary materials for this article are available online.

KEY WORDS: Antiretroviral treatment; Cardiovascular disease; Regression splines; Survival analysis.

1. INTRODUCTION

With the advent of potent antiretroviral (ARV) therapy, the life expectancy of HIV-infected persons has steadily improved, however, incidence of cardiovascular disease (CVD) has increased (Martínez, Larrousse, and Gatell 2009). Indeed, CVD is one of the leading causes of non-HIV-related death among HIV-infected persons (Sackoff et al. 2006). One may wonder if the increased CVD risk is due to ARV therapy itself, or it is simply an unmasking of the illness due to the increased lifespan of HIV-infected individuals?

Recently, investigators from the Data collection on Adverse events of Anti-HIV Drugs (D:A:D) reported an increased risk of myocardial infarction (MI) with recent use of the nucleoside analog reverse transcriptase inhibitors (NRTIs): abacavir (ABC) and didanosine (DDI) (Sabin et al. 2008). Numerous studies have focused on the potential association between ABC and CVD (Bavinger et al. 2013). In this article, we focus on the potential impact of DDI use. In recent meta-analyses, the combination of DDI and lamivudine was found more effective and better tolerated than other common NRTI combinations (Carr and Amin 2009; Chowers et al. 2010). In the guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (accessed October 2013), DDI has been indicated being associated with a number of serious adverse events such as pancreatitis and peripheral neuropathy (PN), however an association between DDI and CVD is more speculative. In the SMART trial (Lundgren et al. 2008a), current DDI use was not associated with major CVD events (OR = 1.06, 95% CI: 0.43–2.58). In contrast, Worm et al. (2010) found that recent DDI exposure was associated with an increased risk of MI (RR = 1.41, 95% CI: 1.09–1.82). A recent case–control study reported that MI risk was not affected by recent DDI use but decreased with increasing duration of past exposure (OR (95% CI) for cumulative exposure: 0.88 (0.77–1.01)) (Lang et al. 2010).

The above discrepancies in findings may partly reflect differences in analytical methods. Indeed, observational studies of drug effects must account for between- and within-subject variation in the temporal patterns of drug use (Abrahamowicz and Tamblyn 2005), and potential confounding by (counter-) indication (Walker et al. 1996). The question of whether it is a disease or its treatment that leads to an increased risk is methodologically challenging.

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In assessing the association between DDI use and CVD risk using longitudinal observational data, one challenge is how to model the history of DDI treatment. This requires assessing whether and how the treatment effects may cumulate over time, including the need to account for potential differences in the impact of the past treatments, received at different times, on the current risk. An inappropriate specification of the relationship between the risk at time t and the treatment history up to t may bias the estimated effects and reduce the power to detect an association (Abrahamowicz, Beauchamp, and Sylvestre 2012). Published studies of the potential impact of DDI treatment on CVD risk relied on simple exposure metrics, such as duration of past use or indicators of current or recent use (Sabin et al. 2008; Lang et al. 2010; Worm et al. 2010). Such metrics impose strong assumptions and ignore variation in the recency or duration of the DDI treatment. However, effects of past drug exposures may cumulate over time and depend on the time since exposure (Csajka and Verotta 2006).

Another challenge in observational studies of the effects of time-dependent (TD) treatments concerns the need to account for relevant TD covariates. Any TD variable that: (1) affects or predicts both the outcome and subsequent treatment changes, and (2) is itself affected by past treatments, will act simultaneously as both a confounder and a mediator of the total treatment effect. Conventional multivariable models are not able to consistently estimate the total causal treatment effect in the presence of a TD confounder which acts also as a mediator of treatment effects (Hernán, Brumback, and Robins 2000; Robins, Hernán, and Brumback 2000). The concern over TD confounding and mediation is important in the context of assessment of DDI impact on CVD risks. Patients experiencing virologic failure on first or subsequent treatment combinations might be more likely to receive DDI, as resistance to DDI develops slowly (Stanford University, HIV Drug Resistance Database 2007). On the other hand, intermittent viral replication as a consequence of virologic failure may increase CVD risk (Lundgren et al. 2008b). However, the use of DDI may also prevent future virologic failures, which could prevent CVD events. Thus, virologic failure may act as both a TD confounder and a mediator of the effect of DDI use on CVD risk.

In this article, we propose a new time-dependent marginal structural Cox model that incorporates weighted cumulative exposure (WCE) modeling to account for both (1) full treatment history, including variations in its duration and timing, and (2) simultaneous TD confounding and mediation. We first validate the proposed model in simulations, and then use it to assess the causal effect of DDI use on the risk of the cardiovascular events in the Swiss HIV Cohort Study.

2. A FLEXIBLE MARGINAL STRUCTURAL COX MODEL WITH WEIGHTED CUMULATIVE EXPOSURE

We propose a new flexible marginal structural Cox model with WCE modeling, which combines the flexible modeling of the cumulative effects of TD treatments (Sylvestre and Abrahamowicz 2009), and the marginal structural Cox model to account for TD confounders affected by past treatments (Hernán, Brumback, and Robins 2000). The WCE approach accounts for past exposure/treatment history in a Cox proportional hazards (PH) model by modeling the cumulative effect as the weighted sum of past exposures, which are assigned different weights depending on the time elapsed since exposure (Abrahamowicz et al. 2006). A flexible extension of this Cox WCE model uses splines to estimate a smooth weight function of arbitrary shape (Sylvestre and Abrahamowicz 2009). In analyses of adverse effects of various medications, the flexible Cox WCE model substantially improved the fit to data, compared to simpler exposure models, and yielded new insights (Sylvestre et al. 2011; Dixon et al. 2012; Abrahamowicz, Beauchamp, and Sylvestre 2012). However, the model does not handle TD variables which may act as both confounders and mediators of the effects of past treatments (Sylvestre and Abrahamowicz 2009).

In the marginal structural Cox model (referred to as Cox MSM), the TD confounders/mediators are controlled for with inverse probability of treatment (IPT) weights (Hernán, Brumback, and Robins 2000). Although the importance of accounting for potential cumulative effects of treatments in longitudinal studies has been recognized in the causal inference literature (Robins 1999; Platt et al. 2013), to date, the proposed Cox MSM and its applications for binary exposures have only considered simple summary metrics of an exposure history (e.g., Hernán, Brumback, and Robins 2000; Westreich et al. 2010; Hernández et al. 2012).

2.1 Cox MSM With WCE Modeling

In the new Cox MSM with WCE modeling (Cox WCE MSM), the hazard at time u is defined as

$$\lambda_{T_{\bar{a}}}(u|V) = \lambda_0(u)\exp(\beta \mathrm{WCE}(u) + \alpha V), \tag{1}$$

where V is the vector of baseline covariates. The WCE(u) is defined as the weighted sum of past treatments over the time window $[u - c, u]$:

$$\mathrm{WCE}(u) = \sum_{t=u-c}^{u} w(u-t)a(t), \tag{2}$$

where $a(t)$ represents either a binary indicator of being treated, or a quantitative measure of treatment intensity or dose at time t, and $u - t$ is the time elapsed since t. In the Cox WCE MSM (Equation (1)), $\lambda_0(u)$ is the baseline hazard for the "reference" population with $V = 0$ and $\bar{a}(t) = 0$ (i.e., never treated). $\lambda_{T_{\bar{a}}}(u|V)$ represents the hazard at time u, had a subject followed, possibly contrary to the fact, the treatment history $\bar{a}$ up to time u, that is, the counterfactual hazard. To model counterfactuals, we use IPT weighting to construct a pseudopopulation (see Section 2.2). β is the causal effect of the WCE, in terms of the log of hazard ratio associated with a unit increase in WCE(u).

Like conventional MSMs, the flexible Cox WCE MSM requires a number of assumptions in order for causal parameters to be identified: (1) at each interval, all confounders of the association between treatment and the outcome have been measured (no unmeasured confounders); (2) the treatment and marginal response models have both been correctly specified; (3) exposure status is not uniquely defined by covariates (positivity assumption); and (4) each person's potential outcome depends only on his exposure, but not on that of others (Robins, Hernán, and Brumback 2000). Assumption (2) implies that the treatment model correctly specifies the dependence of treatment on

confounding variables, while the marginal outcome model correctly specifies how the hazard depends on the exposure and any baseline covariates included in the model.

2.2 Estimation of the Cox WCE MSM

Estimation involves two steps. First, we calculate the IPT weights to construct a pseudo-population in which there is no TD confounding. In the second step, we estimate the weight function for the effect of the TD treatments using cubic regression B-splines in the pseudo-population.

Estimation of IPT Weights. Assuming that the treatment status changes only at discrete times (e.g., clinic visits), one can calculate the IPT weights based on the person–visit data. The subject–visit–specific stabilized IPT weights for subject i are calculated as (Hernán, Brumback, and Robins 2000)

$$w_i^{(s)}(u) = \prod_{k=1}^{m(u)} (P[A(k) = a_i(k) | \overline{A}(k-1) = \overline{a}_i(k-1), V = v_i]) \\ /(P[A(k) = a_i(k) | \overline{A}(k-1) = \overline{a}_i(k-1), \\ \overline{L}(k) = \overline{l}_i(k), V = v_i]), \quad (3)$$

where $m(u)$ is the number of visits up to time u, V denotes baseline covariates, and $\overline{A}(u)$ and $\overline{L}(u)$ denote treatment and covariate history up to u. Stabilization reduces variability in the estimated treatment effects, but even estimators based on stabilized IPT weighs may still suffer from variance inflation due to a few extreme weights (Cole and Hernán 2008). Weight truncation has been shown to reduce variability at the cost of introducing some bias (Cole and Hernán 2008; Xiao, Moodie, and Abrahamowicz 2012).

Flexible Estimation of the WCE Effect. To estimate the weight function in Equation (2) for the cumulative effect of a TD treatment, without imposing a priori constraints on its parametric form, we adapt the approach of Sylvestre and Abrahamowicz (2009), who used cubic regression B-splines (Ramsay 1988). There are several advantages of using cubic regression B-splines functions. First, B-splines are linear in the regression coefficients which permits standard methods of estimation and inference (Wegman and Wright 1983). Second, since each B-spline takes nonzero values over only a limited interval, modifying data in one region will only affect part of the curve, reducing the impact of outliers. Furthermore, the fact that the cubic B-spline function and its first two derivatives are continuous at the knots ensures smooth and clinically plausible estimates for the weight function. Finally, by fixing specific spline coefficients to zero, regression B-splines can be constrained to go to zero smoothly at either boundary of the data range (Ramsay 1988).

Using cubic regression B-splines, the weight function of time since exposure, $u - t$, can be expressed as

$$w(u-t) = \sum_{k=1}^{p} \theta_k B_k(u-t), \quad (4)$$

where $B_k, k = 1, \ldots, p$ represent the p functions in the cubic B-spline basis, and p is equal to the sum of the number of interior knots and the spline order (4 for cubic splines). The θ's are the p coefficients of the B-spline basis, which determine the shape of the weight function and must be estimated from data.

The weight function in (4) is estimated over the user-specified time interval from 0 (current time u) to c time units ago, where c represents the longest time interval over which past treatments may affect current risk. For cubic splines, four exterior knots are placed at each boundary (0 and c). The m interior knots of the spline basis are placed so as to divide the time window $[0; c]$ into $m + 1$ equal subintervals. By substituting the spline function in (4) for weights $w(u - t)$ in Equation (1), we obtain

$$\lambda_{T_{\overline{a}}}(u|V) = \lambda_0(u) \exp\left(\beta \sum_{t=u-c}^{u} \sum_{k=1}^{p} \theta_k B_k(u-t) a(t) + \alpha V\right).$$

Reordering the terms, the above equation can be rewritten as

$$\lambda_{T_{\overline{a}}}(u|V) = \lambda_0(u) \exp\left(\sum_{k=1}^{p} \beta\theta_k \sum_{t=u-c}^{u} B_k(u-t) a(t) + \alpha V\right) \\ = \lambda_0(u) \exp\left(\sum_{k=1}^{p} \gamma_k D_k(u) + \alpha V\right), \quad (5)$$

where $D_k(u) = \sum_{t=u-c}^{u} B_k(u-t) a(t)$, $k = 1, \ldots, p$ are the artificial TD covariates which together represent WCE(u). The advantage of reparameterization is that standard estimation techniques can be applied (Abrahamowicz, MacKenzie, and Esdaile 1996). The terms $\gamma_k = \beta\theta_k$, $k = 1, \ldots, p$ represent the regression coefficients of $D_k(u)$ and can be estimated using standard software for conventional Cox models with TD covariates.

Once γ's have been estimated, the log hazard ratio corresponding to a contrast between any two treatment history patterns, $\overline{a}_1(u)$ and $\overline{a}_0(u)$, can be calculated as

$$\sum_{k=1}^{p} \hat{\gamma}_k \sum_{t=u-c}^{u} B_k(u-t)[a_1(t) - a_0(t)].$$

The coefficient of WCE(u), β in (1), that is, the logHR of being always treated for c days (the longest time interval during which past treatment could affect the current risk) versus never treated, can be reconstructed by substituting $a_1(t) = \{1, \ldots, 1\}$ and $a_0(t) = \{0, \ldots, 0\}$ into the above equation. Thus,

$$\hat{\beta} = \sum_{t=0}^{c} \sum_{k=1}^{p} \hat{\gamma}_k B_k(c-t). \quad (6)$$

Finally, to facilitate comparisons between different analyses, the normalized weight function, with the area under the curve constrained to 1.0, is then calculated as

$$\hat{w}(u-t) = \frac{\sum_{k=1}^{p} \hat{\gamma}_k B_k(u-t)}{\hat{\beta}}. \quad (7)$$

Constrained WCE Models. The weights may be often expected to smoothly decrease to zero at the end of the support interval, implying that the treatment that occurred c days ago has no effect on the current risk (Sylvestre and Abrahamowicz 2009). This is straightforward as imposing $\gamma_p = 0$ in Equation (5) is sufficient to force $w(c) = 0$, while adding the constraint $\gamma_{p-1} = 0$ forces the first derivative of the weight function to equal to 0 at $(u - t) = c$, ensuring that $w(u - t)$ decays *smoothly* to 0 at the end of the time window. Similarly, to add a constraint at the left end of the interval (corresponding to current treatment at $t = u$), one can force both γ_1 and γ_2 to be 0. Such a *left constrained* model may be appropriate in analyses where

the treatment of interest is expected to affect the risk after some latency period.

In some applications, there may be considerable uncertainty regarding (i) the length of the time window c over which past treatment may affect current risk, (ii) the need for constraints at either end of the time window, and (iii) the "optimal" number of interior knots m necessary to ensure adequate flexibility of the estimated weight function while reducing the risk of overfit bias. We recommend estimating alternative models, with 1–3 interior knots, plausible choices for c, and boundary constraints, and then relying on the Bayesian information criterion (BIC) adapted to censored survival data (Schwarz 1978; Volinsky and Raftery 2000), to select the final model. See Appendix A in the online Appendix for a discussion of model selection criteria for Cox WCE MSM.

3. SIMULATION STUDIES

3.1 Data Generation

We adapted the data-generating mechanism of Young et al. (2010) to the WCE context. Event times were generated from the following structural nested accelerated failure time model (Hernán et al. 2005):

$$T_{\overline{0}} = \int_0^{T_{\overline{a}}} \exp[\beta \mathrm{WCE}(u)]du, \tag{8}$$

where $T_{\overline{a}}$ denotes the counterfactual event time under treatment history $\overline{a}$, and $T_{\overline{0}}$ denotes the counterfactual event time under the never-treated regime (i.e., $\overline{a} = \overline{0}$). When event times follow an exponential distribution, the causal effect of the treatment in the Cox MSM $\lambda_{T_{\overline{a}}}(u|V) = \lambda_0(u)\exp(\beta \mathrm{WCE}(u)))$ equals to the effect assumed in the data-generating model (8) (Young et al. 2010).

In simulation, each of $N = 1,000$ subjects had up to $m = 10$ visits equally spaced at 30-day intervals. Details of the data generation are given in Appendix B of the online Appendix. Briefly, we first generated counterfactual event times under the never-treated regime $T_{\overline{0}}$, and baseline values of the TD confounder L, $L(1)$. Next, for each visit $j \in [1, 10]$, we alternated between generating (1) the binary treatment indicator $A(j)$ depending on the previous treatment and current confounder value, and (2) the current $L(j)$ value conditional on the counterfactual event time T_0 and previous values of $A(j-1)$ and $L(j-1)$. Treatment was made to affect risk according to the WCE model (Equation (2)). We considered two alternative true weight functions $w(u-t)$ (bold curves in panels (a) and (b) of Figure (1)), each defined over the time window $[0, 120]$ days. The final event time was simulated conditional on the TD values of the updated WCE and counterfactual event time $T_{\overline{0}}$, using the approach by Young et al. (2010). Subjects were censored at $u = 300$ if they had no event up to that time; no other losses to follow-up were generated. The overall censoring rate was about 30%, implying about 700 observed events per sample.

3.2 Analysis of Simulated Data

For each scenario, we simulated 100 samples. First, stabilized IPT weights, for each subject at each visit, were calculated using Equation (3) and kept constant between the visits. The data were then augmented to person–day data and the artificial TD covariates $D_k(u)$, $k = 1, \ldots, p$ (see Section 2.2) were calculated for each subject at each day. Finally, we fitted the Cox WCE MSM: $\lambda[u|\overline{A}(u)] = \lambda_0(u)\exp(\sum_{k=1}^{p} \gamma_k D_k(u))$, with stabilized IPT weights. We estimated three alternative models with 1–3 interior knots within the prespecified time window $[0, 120]$ and a priori imposed right constraints $\hat{w}(\mathrm{c}) = \hat{w}'(\mathrm{c}) = 0$, $\mathrm{c} = 120$. The BIC was used to identify the best-fitting model. In sensitivity analyses, the models were reestimated with the IPT weights truncated at the 99th percentile of their distribution.

3.3 Simulation Results

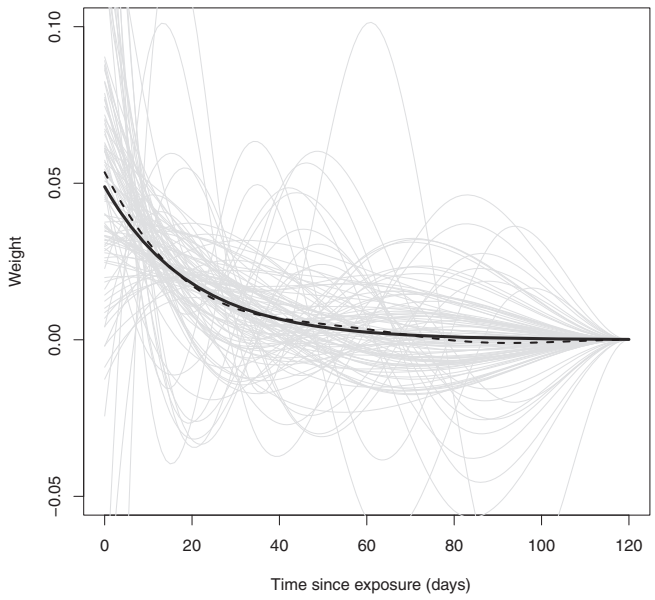
The top panel of Figure 1 presents the estimated weight functions for the two scenarios, using cubic splines with the BIC-selected number of knots. The mean estimates (dashed curves) are very close to the true marginal weight functions (bold curves), although in Scenario 2 the peak is slightly underestimated (Figure 1(b)). The estimates from individual samples show large variability (gray curves). This may partly reflect sampling variance in the BIC-based selection of the number of knots which, in turn, may be related to high IPT weights. Indeed, the highest weights in individual samples range from 14 to 490. In contrast, the 99th percentiles of the sample-specific IPT weights are stable, varying from 3.3 to 4.8. As shown in the bottom two panels of Figure 1, for both scenarios, truncating IPT weights at the 99th percentile of the distribution of IPT weights in each sample dramatically reduced the variability of the estimated weight functions, at the cost of slight increase in the bias for Scenario 2.

For each sample, the cumulative effect of being always treated in the last 120 days was estimated using Equation (6). For both scenarios, the mean $\hat{\beta}$'s were acceptably close to the true β, with the relative biases of only 3.3% and 11.7%, and both 95% CIs included the true β (data not shown). Overall, simulations confirmed that the Cox WCE MSM yielded acceptably accurate estimates of the marginal cumulative treatment effect, in terms of both its strength and the shape of the weight function.

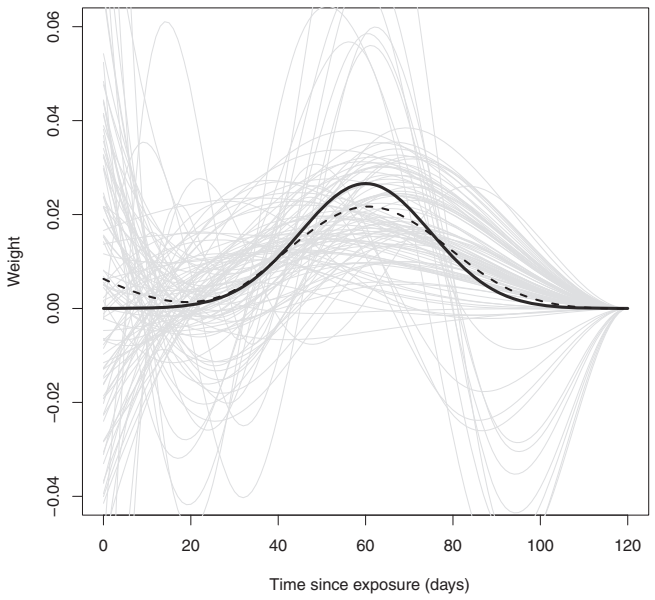
4. ASSESSING THE ASSOCIATION BETWEEN DDI USE AND CVD RISKS

4.1 The Swiss HIV Cohort Study

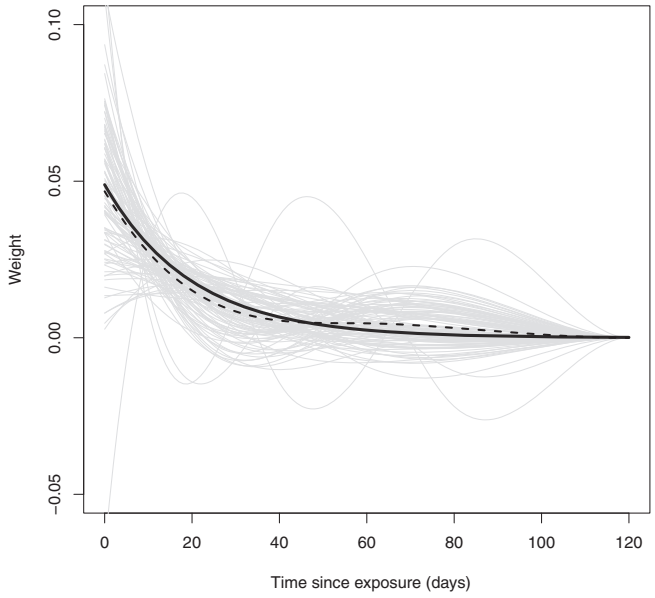
To assess the potential association between DDI use and CVD risk, we reanalyzed data from the SHCS, an ongoing multicenter, prospective observational study of individuals infected with HIV, initiated in 1988 (Swiss HIV Cohort Study 2010). We analyzed all data from April 2000, when CVD risk assessment became routine until October 2012. Demographic, clinical, laboratory, antiretroviral (ART) therapy information, and CVD risk factors were collected at enrolment and at follow-up visits. Each patient's follow-up was divided into one-month periods, and both the treatment and all TD covariates were assumed to remain constant within each period. Time zero was the date of patient's first record after April 2000. Patients were censored at a non-CVD death, the last follow-up date, or October 31, 2012.



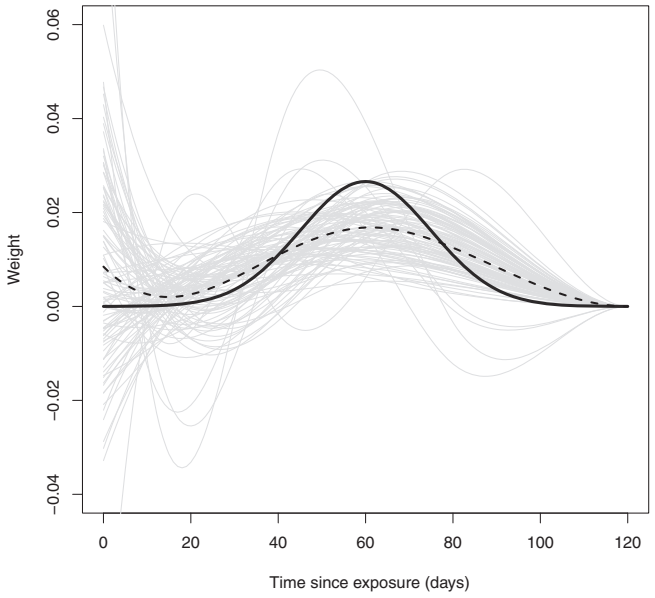
(a) Scenario 1



(b) Scenario 2



(c) Scenario 1, IPT weights truncated



(d) Scenario 2, IPT weights truncated

Figure 1. Estimated BIC-selected marginal weight functions over 100 samples. Columns correspond to Scenarios 1 (left) and 2 (right). The top row corresponds to Cox MSM with WCE modeling using untruncated IPT weights, while the bottom row shows estimated curves from Cox MSM with WCE modeling with IPT weights truncated at the 99th percentile. In each panel, the dashed curve is the pointwise mean of the estimated individual weight functions from 100 samples, shown in gray curves. The true marginal weight function is represented by the solid dark curve.

A total of 11,625 patients were followed for a median of 6.7 years (IQR: 2.8–11.3). There were 3109 (26.7%) patients exposed to DDI, with a median exposure of 26.8 months (IQR: 9.1–55.6), including 2418 (20.8%) subjects already exposed to DDI prior to their first CVD risk assessment, and 691 (5.9%) who started DDI during follow-up. During follow-up, 350 (3.0%) patients developed the composite CVD event, defined, as in D:A:D analyses, as the first occurrence of MI, CVD death or an invasive CVD procedure (Sabin et al. 2008). As in the D:A:D analyses, month was used as the unit of time in Equations (1) and (2) (Sabin et al. 2008).

4.2 Estimated Models

Treatment Models. Measured TD covariates included the number of previously failed regimens, indicators of hepatitis infection (chronic B or C), fat loss, diabetes, nervous system toxicity, gastrointestinal toxicity, pregnancy, stage of HIV infection (A, B, or C), and current use of three ARV drugs (zalcitabine, stavudine, and tenofovir) (Young, Klein, and Ledergerber 2011). Because some of these TD variables may lie on a causal pathway between the decision to initiate, continue or interrupt the use of DDI and the

development of a CVD event, all analyses reported below use MSMs (Hernán, Brumback, and Robins 2000).

Stabilized IPT weights were constructed using Equation (3). The probabilities of receiving the observed DDI treatment at each one-month interval were estimated using alternative logistic regression models, depending on whether the patient (i) has not yet initiated DDI (*new users*) or (ii) has been previously exposed to DDI (*ever users*). Both models for the denominator included the baseline covariates (age at baseline, sex, ethnicity, education, and HIV transmission group) and the above TD variables, updated at each month. The models in the numerator of Equation (3) included only the baseline covariates. For the ever users, we added an indicator for DDI use in the previous month in both the denominator and the numerator. Details of the IPT weights calculation are described in the online Appendix C. Since censoring was mainly administrative and including inverse probability of censoring weights (IPCW) did not change the main results (data not shown), all the MSMs in this article were estimated using the IPT weights only. In addition, to reduce the impact of extremely high weights, we truncated the IPT weights at the 99th percentile of their distribution across all person–months of follow-up.

Outcome Models. Because of the uncertainty about the way that past and current DDI exposure might affect CVD risk, we considered alternative parameterizations of Cox MSMs and we compared their fit to data (Abrahamowicz, Beauchamp, and Sylvestre 2012). All Cox MSMs adjusted for all baseline covariates and used the same truncated stabilized IPT weights (described above). We first fit four simpler parametric Cox MSMs. Models 1–3 used the same exposure metrics for DDI as in the D:A:D analyses (Sabin et al. 2008), and were nested, with each consecutive model adding one additional DDI-related TD variable (updated at each month of follow-up). Model 1 included only the total duration of past DDI use; Model 2 added a binary TD indicator of any "recent DDI use" within the last 6 months; and Model 3 additionally included a TD indicator of any past exposure (at least 6 months ago). Finally, Model 2A used separate TD indicators of any use in (i) the last month, and (ii) 1–6 months ago.

In addition, we used the proposed flexible Cox WCE MSM to estimate the potential cumulative effect of past DDI use. Because of uncertainty regarding for how long past DDI exposure might still affect current CVD risk, we initially considered alternative time windows of c=48 and c=30 months. In preliminary analyses, the weight function estimated with the 48-month window showed overfit bias and numerical instability in the right tail, while their weights estimated for exposures in the past 30 months agreed well with the estimates obtained with the shorter 30-month window (Figure D.2 in the online Appendix). Thus, in our main Cox WCE MSM analyses, the time window was limited to the past 30 months. Nine alternative Cox WCE MSMs were estimated with c=30 months, with different combinations of 1–3 interior knots, and weight functions constrained at both ends of the time window, unconstrained, or right-constrained (see Section 2.2). The optimal WCE MSM was then identified using BIC and the corresponding weight function was calculated by multiplying the estimated normalized weight function (Equation (7)) and the estimated coefficient for WCE (Equation (6)). The 95% pointwise confidence bounds were constructed using the variance–covariance matrix of the regression coefficients for the artificial TD covariates, which together represent the estimated weight function (see Equation (5)).

Details on goodness-of-fit comparisons, assessment of the proportional hazards assumption, and the corresponding results for the SHCS analysis are described in Appendices E and F of the online Appendix.

4.3 Results

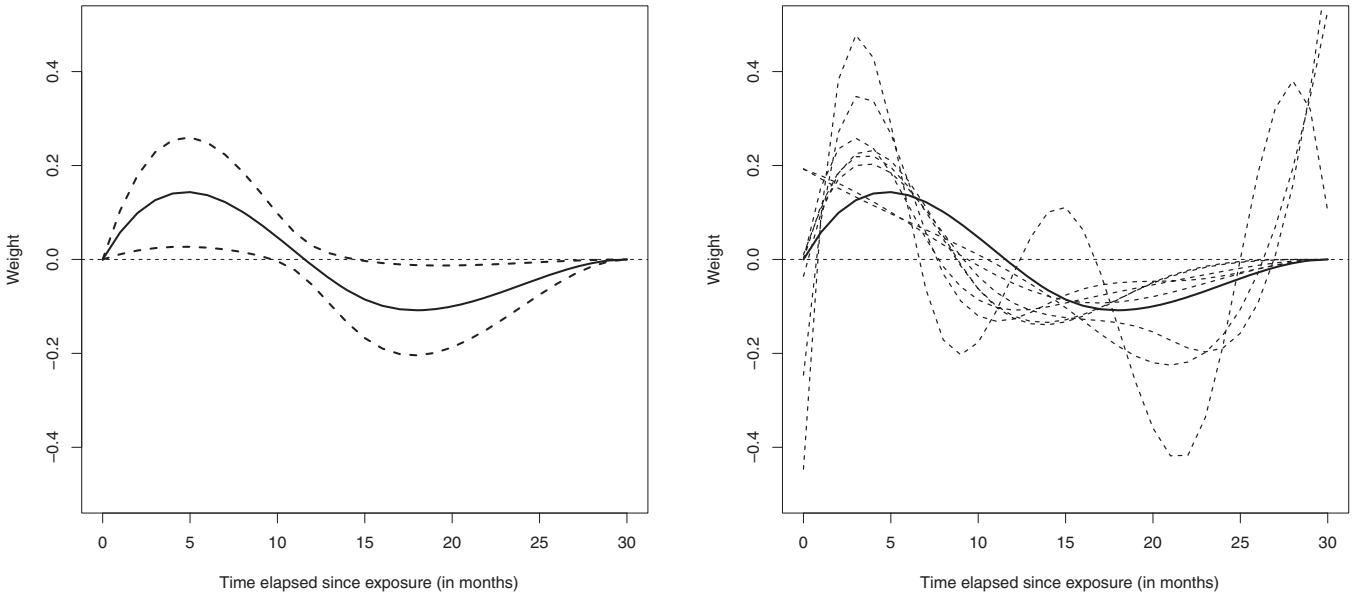
The stabilized IPT weights had a mean of 1.35 and a maximum of 7309. After truncation at the 99th percentile, the maximum weight was reduced to 4.7, with a mean of 1.04. In all the four parametric MSMs (Models 1–3 and 2A), for all TD variables representing DDI exposure, 95% confidence intervals include HR=1.0 (Table 1). Moreover, the deviances of all parametric Models 1–3 and 2A (Table E.2 in the online Appendix) are only marginally lower than the deviance of the null MSM that adjusts for the same covariates but excludes any effects of DDI and, thus, reduces degrees of freedom (df) by 1–3. Thus, all four conventional parametric MSMs consistently indicate the lack of an association between DDI use and CVD risk. However, the validity of this conclusion depends on the parameterization of DDI exposure in these parametric models being correct.

Among alternative Cox WCE MSMs with a 30-month window, a parsimonious model with one interior knot and a weight function constrained to zero at both ends of the time window had the lowest BIC and quasi-likelihood information criterion (Platt et al. 2013). The weight function estimated by the BIC-selected WCE MSM is shown in the left panel of Figure 2. The weight

Table 1. Hazard ratios and 95% confidence intervals for the effects of DDI exposure on the risk of a composite cardiovascular event in the SHCS cohort, estimated with parametric Cox MSMs*

	Model 1	Model 2	Model 2A	Model 3
Cumulative use (per year)	1.04 (0.95,1.13)	1.02 (0.92,1.12)	1.01 (0.92, 1.12)	1.04 (0.93, 1.16)
Recent exposure (within last 6 months)		1.23 (0.68,2.21)		1.02 (0.49, 2.10)
Current exposure			1.27 (0.48, 3.38)	
Past exposure within 1–6 months			1.03 (0.39, 2.69)	
Past exposure more than 6 months ago				0.81 (0.54, 1.21)

NOTE: *All MSMs adjusted for age at baseline, sex, ethnicity, education, HIV transmission group, as well as the baseline values of the TD covariates including calendar year, the number of previously failed regimens, indicators of hepatitis infection (chronic B or C), fat loss, diabetes, nervous system toxicity, gastrointestinal toxicity, pregnancy, previous reported categories of HIV infection (A, B, or C), and current use of three ARV drugs (zalcitabine, stavudine, and tenofovir). See Online Appendix C.1 for details of IPT weights estimation.



(a) BIC-selected optimal Cox WCE MSM (b) Nine alternative Cox WCE MSMs

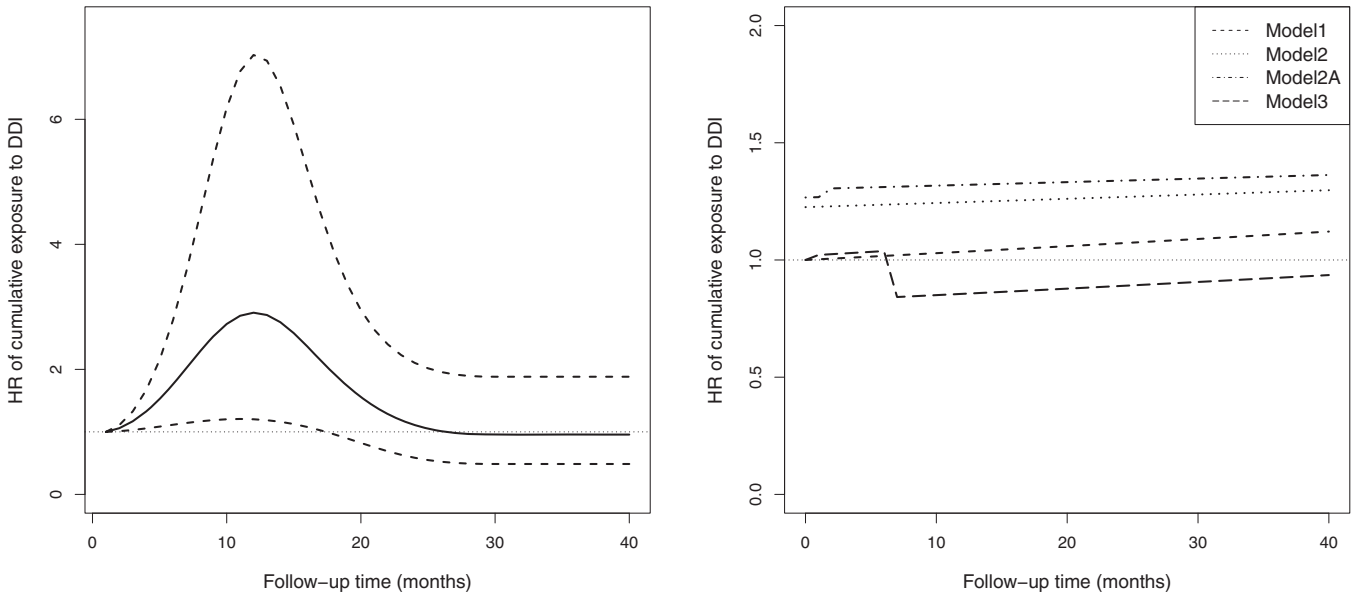
Figure 2. The left panel is the estimated weight function of the cumulative effect of DDI on the cardiovascular risk and its 95% pointwise confidence bands using the BIC-selected Cox WCE MSM. The right panel shows the weight functions estimated using all nine alternative Cox WCE MSMs, which differed in the choice of the number of interior knots and the boundary constraints in estimating the spline function.

function suggests *dual* effects of past DDI use on the current hazard of CVD events. Weights assigned to DDI exposures in the last year are positive, indicating increased risk, with the highest impact due to exposures that occurred about 3–6 months ago. In contrast, DDI use in the more distant past, between one and two years ago, is assigned *negative* weights, implying *reduced* CVD risk. The corresponding 95% pointwise confidence bands, over both time intervals, often exclude 0 (Figure 2), suggesting that both the short-term risk increase and the longer-term protective effect are statistically significant. Similar dual effects were revealed by most of the alternative WCE MSMs using a 30-month window, even if some unconstrained models show considerable overfit bias (the right panel of Figure 2), and by all Cox WCE MSMs using a 48-month window (online Appendix Figure D.2).

Interestingly, the dual effect of DDI exposure, suggested by our WCE MSM estimates, is generally consistent with the point estimates of the parametric MSMs: Model 2 suggests risk increase with recent DDI use, while Model 3 suggests past exposure may have a protective effect (Table 1). However, in the parametric MSMs, none of the effects of DDI exposure are significant. This may be due to a combination of (i) the crude categorization of the time since exposure, and (ii) some overlap between effects captured by binary indicators of DDI use in specific periods and total duration of past DDI exposure. With respect to (i), the nonmonotone weight function estimated in our WCE MSMs indicates that the effect of "past exposure" varies largely depending on its timing: from a risk increase for exposures up to 12 months ago, to a risk reduction for 12–24 months ago, to lack of effect for DDI use more than 2 years ago. Parametric Model 3 defines "past exposure" as any use more than 6 months ago and, thus, imposes the restriction that DDI use in any of these three subintervals must have the *same* effect, regardless of its timing and duration. On the other hand, the inclusion of total duration of past use in all parametric MSMs 1–3 implies that the risk must systematically either increase or decrease with increasing duration, which excludes the possibility of a dual effect. By avoiding such restrictive assumptions, the flexible WCE MSM fits the data much better than conventional MSMs (see online Appendix: Table E.2) and provides new insights about possibly complex mechanisms that may link past and recent DDI use with CVD risk.

The dual effect of past DDI use on CVD risk was unexpected and, thus, must be interpreted with caution. Although the finding seems robust with respect to the choice of knots and time window, it may reflect some confounding bias if, for example, DDI use is correlated with changes in unmeasured CVD risk factors. However, the dual effect may also reflect a truly complex combination of direct and indirect effects of DDI exposure. For example, the risk of peripheral neuropathy (PN) peaks in the first 3 months of DDI use and then subsides (Arenas-Pinto et al. 2008), while immunosuppression in advanced HIV infection is also associated with an increased risk of PN (Ghosh, Chandran, and Jansen 2012). Hence, DDI could have a dual effect on PN, with a short-term risk of drug-induced neuropathy but a long-term protective effect, as immunosuppression abates with increasing duration of continued effective therapy. If so, then DDI may have a similar dual effect on other forms of neuropathy, such as the cardiovascular autonomic neuropathy associated with sudden MI in diabetic patients (Kuehl and Stevens 2012). This possible explanation needs to be investigated in future, but our example illustrates how WCE modeling can lead to new, testable hypotheses about complex causal pathways linking drug use with clinical outcomes.

To further explore the implications of a dual effect of past DDI use, Figure 3 compares how the cumulative effect of being



(a) BIC-selected Cox WCE MSM (b) Four parametric Cox MSMs

Figure 3. The left panel shows the total cumulative effect (HR) of being always treated with DDI (vs. never treated) as a function of treatment duration estimating by the BIC-selected Cox WCE model, with the 95% pointwise confidence bounds. The right panel shows the total cumulative effects as a function of treatment duration estimated by the four parametric Cox MSMs, separately.

always treated (vs. never being treated), estimated with different models, changes with increasing treatment duration. Consistent with the estimated weight function (Figure 2), Figure 3(a) shows that, according to the BIC-selected WCE MSM, CVD risk gradually increases during the first year of uninterrupted DDI treatment. One year after treatment initiation, continuous DDI users have more than twice the CVD risk of never-users (HR=2.91, 95% CI: 1.20–7.03). However, if the DDI use continues beyond the first year, the risk gradually decreases and by about 2 years after the treatment initiation it does not differ from the subjects who never used DDI (HR=0.96, 95% CI: 0.47–1.88).

Figure 3(a) highlights the statistically significant short-term cumulative effect of recent DDI use, that may result in a more than doubling of the CVD risk after about one year of continuous treatment. This important short-term risk increase was not detected by any of the four conventional parametric MSMs (see Figure 3(b)). Each of these simpler MSMs imposed a priori certain dose–response relationship, such as monotonic changes in risks with increasing DDI use (Models 1, 2, and 2A), with possible jumps at specific, arbitrary time points (Models 2, 2A, and 3). These restrictive assumptions seem incompatible with the complex relationship between DDI use and CVD risk (see Figure 3(a)), resulting in weak cumulative effect estimates using conventional MSMs (see Figure 3(b)).

5. DISCUSSION

The new flexible Cox WCE MSM simultaneously addresses two analytical challenges of observational longitudinal studies: (i) modeling the cumulative effect of a time-dependent (TD) treatment/exposure and (ii) controlling for TD confounders which also act as mediators of the effect of past treatments. Specifically, the model uses (i) cubic regression B-splines for flexible modeling of the weight function describing how the effects of past treatments cumulate over time (Sylvestre and Abrahamowicz 2009), and (ii) IPT weighting to control for the TD confounding/mediating variables (Hernán, Brumback, and Robins 2000). The fact that the Cox WCE MSM can be fitted using standard software for a TD Cox model, by adding artificial TD covariates and IPT weights, facilitates its use in applications.

In simulations, the proposed flexible Cox WCE MSM yielded acceptably accurate estimates of the marginal causal treatment effect and of the weight function. However, the weight function estimates had large variability. Truncation of the IPT weights at the 99th percentile of their distribution dramatically reduced the variability of the weight functions with only a slightly increased bias.

In the SHCS analyses, we estimated the effect of past DDI use on current CVD risk using alternative Cox MSMs. Results of all four conventional MSMs, with DDI exposure parameterized as in the previous studies (Sabin et al. 2008; Worm et al. 2010), consistently suggested a lack of an association between DDI use and CVD risk. The Cox WCE MSM substantially improved model fit over all four conventional MSMs, which reflects their inability to capture complex exposure effects. Without a priori assuming any specific form of the weight function, the BIC-selected Cox WCE MSM suggests that past DDI use may have dual effects: DDI use in the past 12 months increases the current CVD risk, while DDI use in the more distant past is associated with reduced CVD risk. The corresponding 95% confidence bands for the estimated weight function over both time intervals often exclude 0, suggesting that the dual effects are unlikely to reflect merely sampling error, in contrast to the null results of all conventional MSMs. The dual effect was robust to different choices of the number of knots, the time window and boundary constraints. In spite of the dual effect, continuous users of DDI

are never protected against CVD risk: with increasing treatment duration, the early risk increase is eventually balanced out by potential indirect benefits of previous use, so that long-term users have risks very similar to never-users. The flexible WCE modeling detected a statistically significant doubling of the CVD risk after about a year of continuous treatment, which was not identified by any of the conventional models.

The Cox WCE MSM may be of interest in other analyses of the effects of time-varying treatments or exposures, especially in the case of little a priori knowledge regarding how exposure history affect current hazard and concerns about TD confounders/mediators. In our opinion, the former concern is best addressed by fitting several clinically plausible models, including both the proposed Cox WCE MSM and more conventional MSMs, and then using goodness-of-fit criteria to identify the model(s) most consistent with the data (Abrahamowicz, Beauchamp, and Sylvestre 2012). The DDI analyses illustrate how the results of different models can be jointly interpreted while taking into account the differences in the underlying assumptions. The flexible WCE MSM, which avoids restrictive assumptions of conventional models, is able to accurately model a large variety of possibly complex exposure–risk associations. In the case of relatively simple relationships, for example, limited to the acute effect of exposure in the last few days, goodness-of-fit criteria will likely indicate that the additional degrees of freedoms required by the WCE model are not warranted, suggesting simpler models such as current exposure are sufficient (Abrahamowicz, Beauchamp, and Sylvestre 2012).

Further research is necessary to address remaining challenges. The proposed flexible Cox WCE MSM should be extended to test the proportional hazards assumption which implies that the estimated cumulative treatment effect remains constant during the follow-up (Abrahamowicz and MacKenzie 2007). Furthermore, methods to deal with unobserved confounding in simpler MSM analyses (Brumback et al. 2004) or instrumental variables approaches, developed specifically for studies of adverse effects of treatments (Brookhart et al. 2006), should be adapted to flexible MSM analyses of time-to-event data. Finally, there is a need to validate goodness-of-fit criteria for the comparisons of weighted likelihoods for nonnested MSMs that involve IPT weights.

The analysis of the SHCS data has some limitations. First, if we knew the date of subject's seroconversion after exposure to HIV virus, it would define a more clinically meaningful time zero than the date of a patient's first record after April 2000, when the CVD risk assessments became part of routine follow-up. Second, 20.8% of the DDI ever-users began use before April 2000. Because these prevalent DDI users were slightly sicker than those who were DDI naïve, their inclusion could lead to an overestimation of the DDI–CVD association. However, we believe that with the proper modeling of the IPT weights separately for new and past DDI users (see online Appendix C), such potential selection biases have been well controlled.

As in all observational data analyses, we relied on the untestable assumption of no unmeasured confounders. However, unobserved confounders will affect all alternative models and thus are unlikely to have a major impact on the model comparison using goodness of fit. In addition, to reduce the risk of model misspecification which could bias causal effect estimates (Robins and Hernán 2008), our treatment models included all the measured potential confounders identified based on prior knowledge. Our flexible WCE modeling substantially reduces the risk of a serious misspecification of the exposure–response relationship, compared to conventional models which rely on simple exposure indicators. Finally, while we suggested a possible reason for the dual effect of DDI exposure, this finding has to be confirmed in independent analyses of other HIV-positive populations. The apparent protective effect of DDI use 1–2 years ago might reflect a depletion of susceptibles if most patients prone to adverse events discontinue the drug after only a short time.

The flexible Cox WCE MSM provides new insights that may reconcile inconsistent earlier findings of the effect of DDI use on CVD risk. The model allows the effects of past use to smoothly change over time, avoiding clinically implausible jumps imposed by the conventional models at arbitrarily chosen times (e.g., one or six months after exposure). Further, the suggestion of potential dual effect of past DDI use on CVD risk may help generate new hypotheses regarding the underlying mechanism(s). Most importantly, the flexible analyses revealed a clinically important, two-fold increase in CVD risks associated with uninterrupted DDI use in the past year, which was not detected by any of the conventional models. We anticipate that this new flexible Cox WCE MSM may help disentangle complex effects of TD treatments in different settings, and stimulate further methodological developments in the challenging but societally important field of research on the adverse effects of medication.

SUPPLEMENTARY MATERIALS

Section A discusses details of BIC-based selection of the best-fitting, that is, minimum BIC, WCE model, among the alternative models with different number of knots, time windows and constraints. Section B describes in detail the methods and the assumptions used to generate the data analyzed in our simulations. Section C provides information on the estimation of the treatment model for the application, in the Swiss HIV Cohort study (SHCS), including estimation of the IPT weights, and their distribution. Section D, and specifically Figure D2, present results of sensitivity analyses, and compares the weight function for the effects of past and recent DDI use, obtained with alternative WCE MSM models, whereas section E compares the fit of the WCE MSM with the simpler parametric MSM's, using different goodness-of-fit criteria. Section F presents both the approximate method used to assess if the PH assumption does hold for the WCE MSM model estimated for the SHCS application, and the results of these analyses. Finally, section G provides the R code used to implement WCE MSM in the SHCS analyses.

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